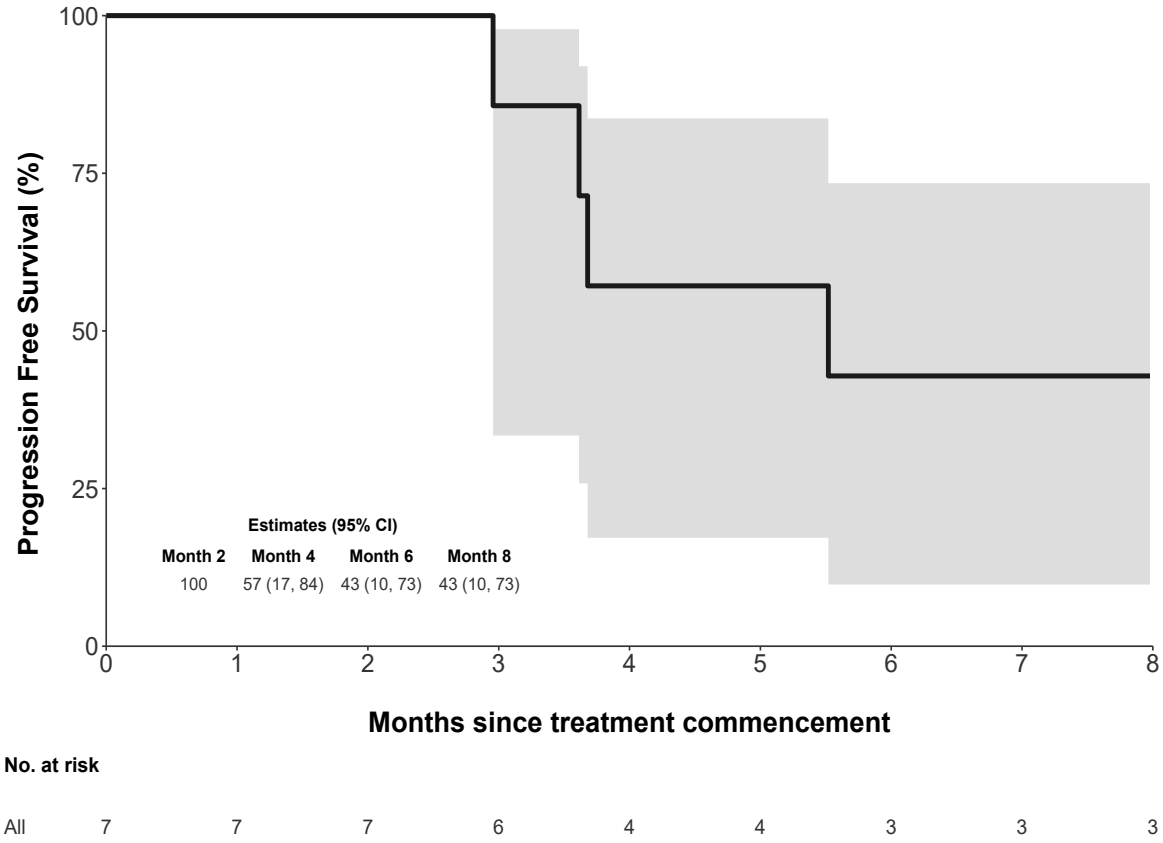
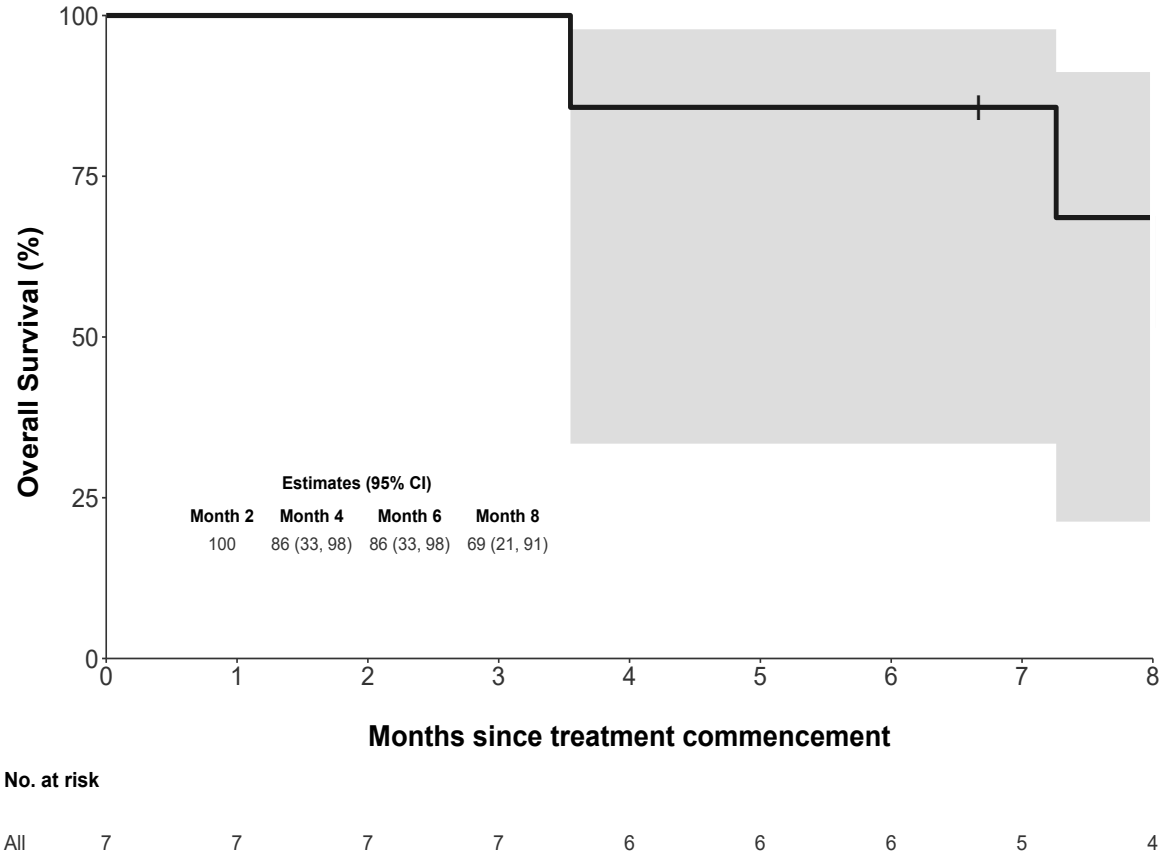
**A Phase Ib/II Trial of combined BRAF and EGFR inhibition in *BRAF* V600E positive metastatic colorectal cancer and other cancers: The EVICT (Erlotinib and Vemurafenib In Combination Trial) Study**

Lavinia Tan, Ben Tran, Jeanne Tie, Ben Markman, Sumi Ananda, Niall C. Tebbutt, Michael Michael, Emma Link, Stephen Q. Wong, Sushma Chandrashekar, Jerick Guinto, David Ritchie, Rachel Koldej, Benjamin J. Solomon, Grant A. McArthur, Rodney J. Hicks, Peter Gibbs, Sarah-Jane Dawson and Jayesh Desai

**SUPLEMENTARY APPENDIX**

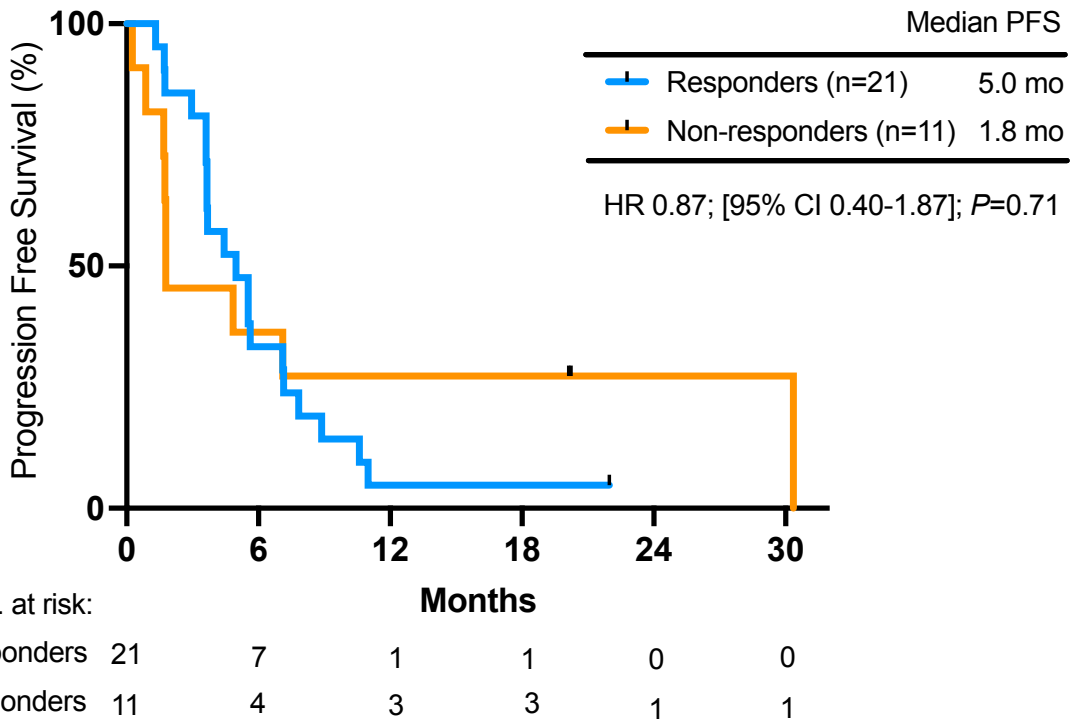



**Supplementary Figure S1.** Kaplan-Meier estimate of progression-free survival (PFS) for non-CRC patients (n=7). The shaded areas represent 95% CI.

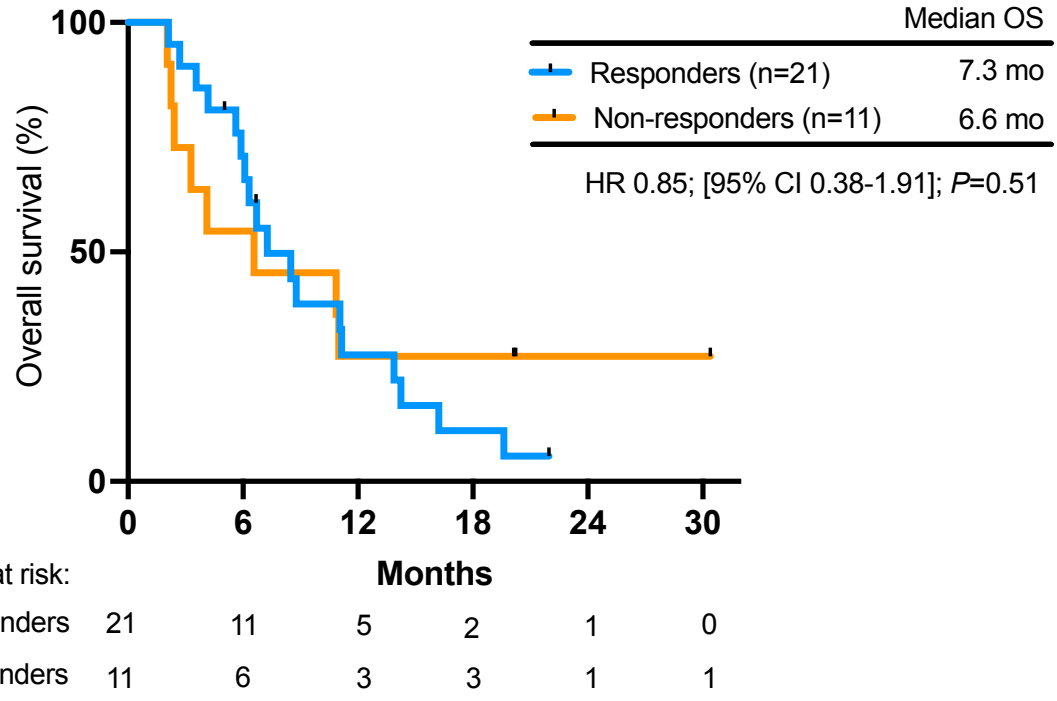



**Supplementary Figure S2**. Kaplan-Meier estimate of overall survival (OS) for non-CRC patients (n=7). The shaded areas represent 95% CI.

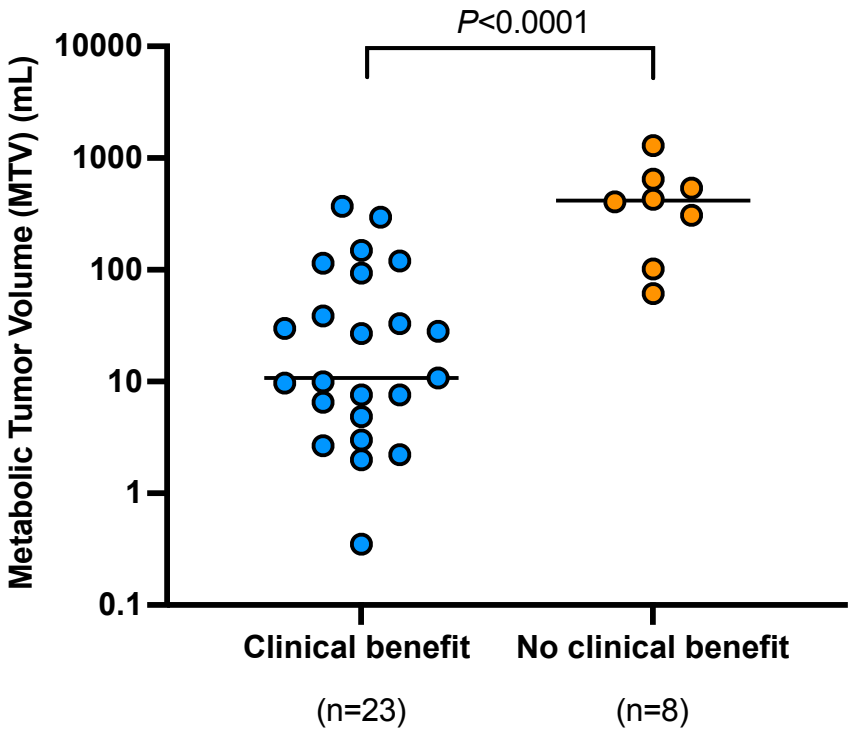
A)


Median PFS
Responders (n=21) 5.0 mo
Non-responders (n=11) 1.8 mo
HR 0.87; [95% CI 0.40-1.87]; P=0.71
Progression Free Survival (%)
100
50
0
0
6
12
18
24
30
Months
No. at risk:
Responders 21 7 1 1 0 0
Non-responders 11 4 3 3 1 1

B)

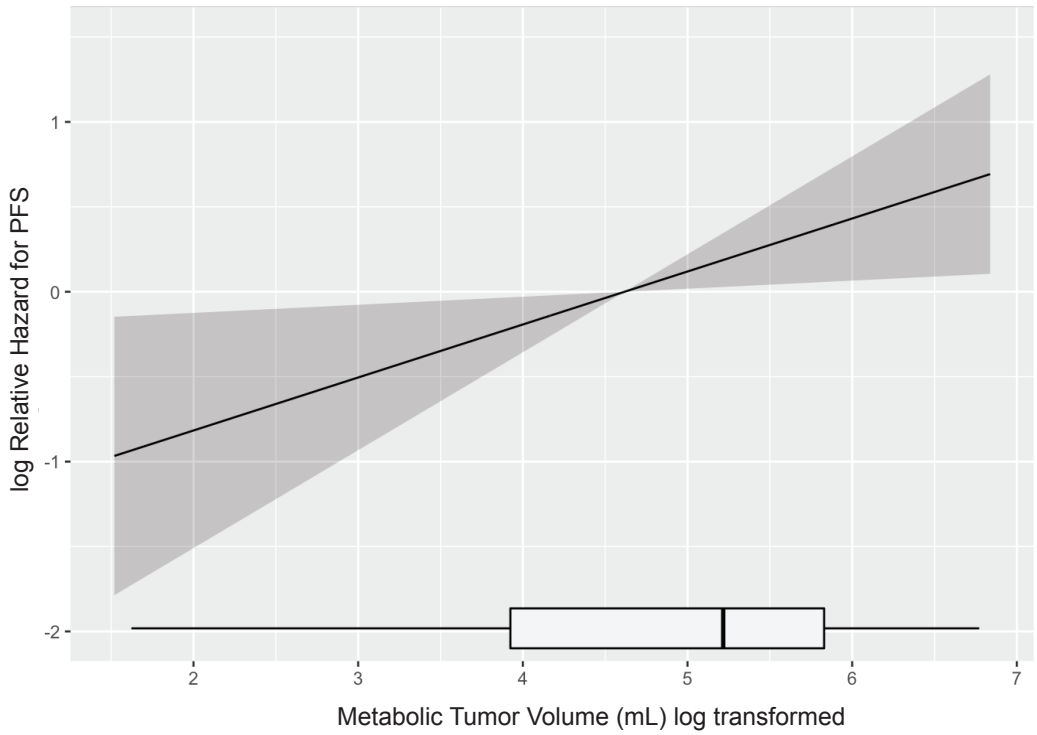

Median OS
Responders (n=21) 7.3 mo
Non-responders (n=11) 6.6 mo
HR 0.85; [95% CI 0.38-1.91]; P=0.51
Overall survival (%)
100
50
0
0
6
12
18
24
30
Months
No. at risk:
Responders 21 11 5 2 1 0
Non-responders 11 6 3 3 1 1

**Supplementary Figure S3.** Kaplan-Meier estimate of A) PFS and B) OS for 32 patients who underwent paired FDG-PET scan at baseline and after 4 weeks of therapy stratified by metabolic response.

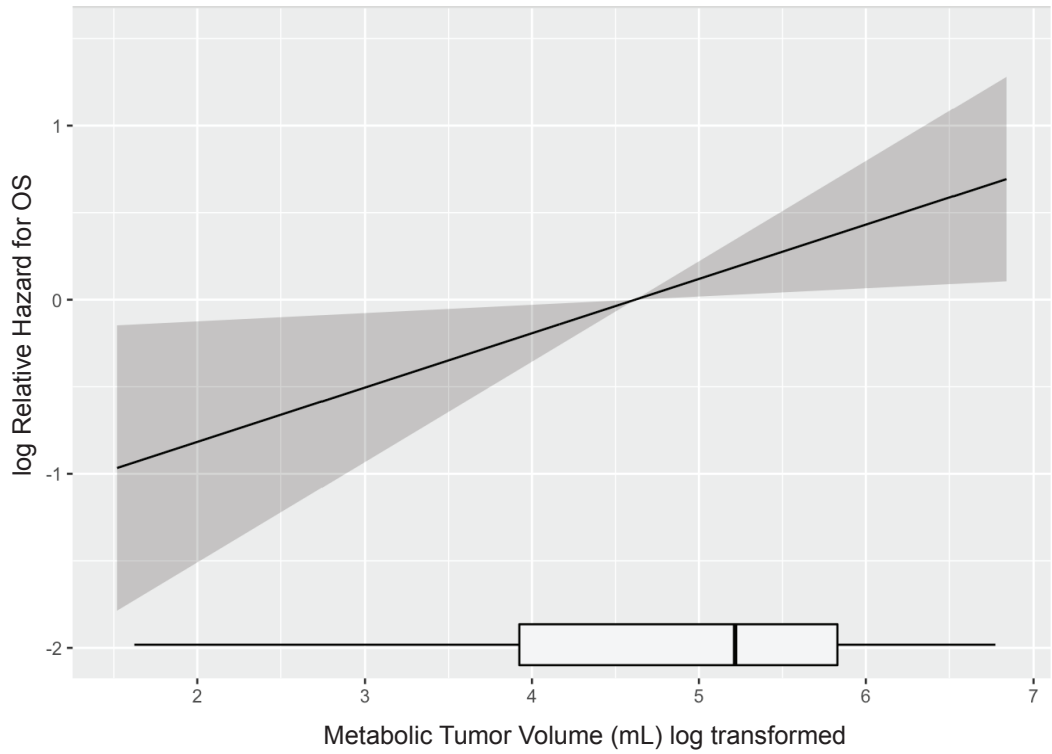



**Supplementary Figure S4.** Metabolic tumor volume (MTV) (mL) at baseline according to clinical benefit rate.

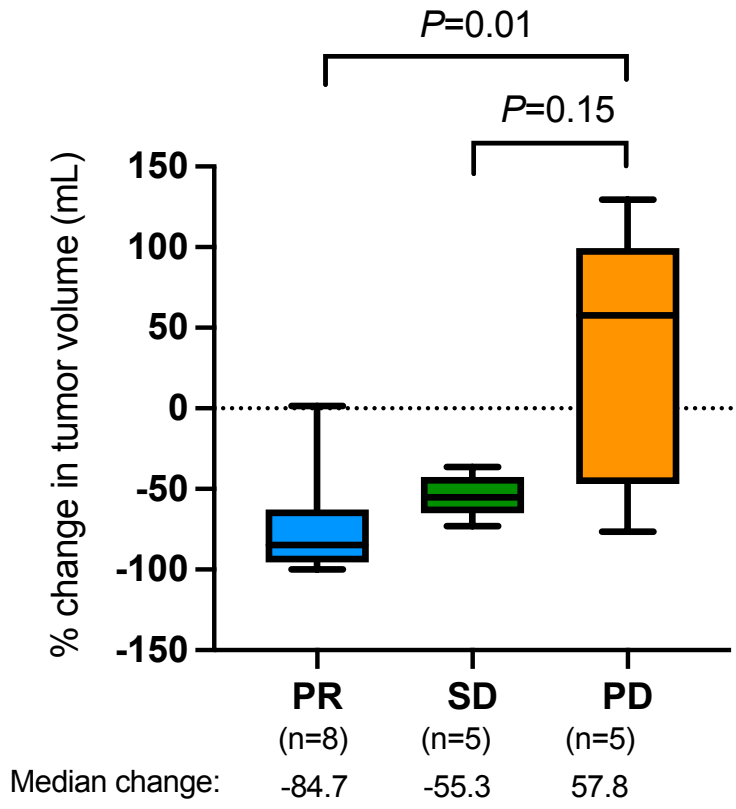
A)


log Relative Hazard for PFS
1
0
-1
-2
2
3
4
5
6
7
Metabolic Tumor Volume (mL) log transformed

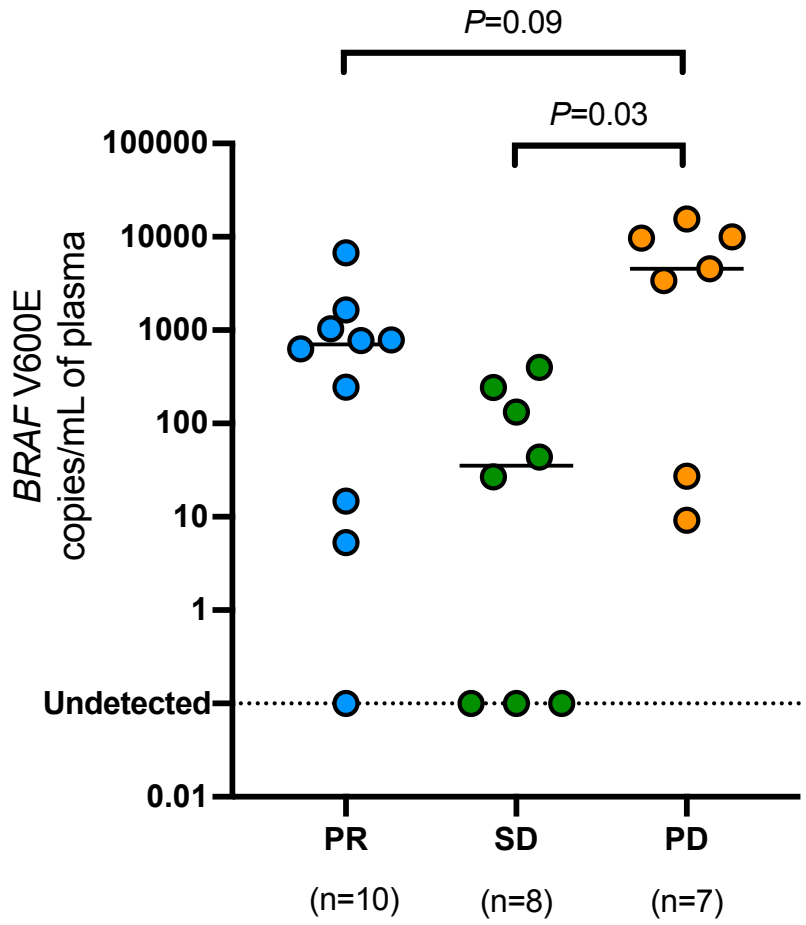
B)


log Relative Hazard for OS
1
0
-1
-2
2
3
4
5
6
7
Metabolic Tumor Volume (mL) log transformed

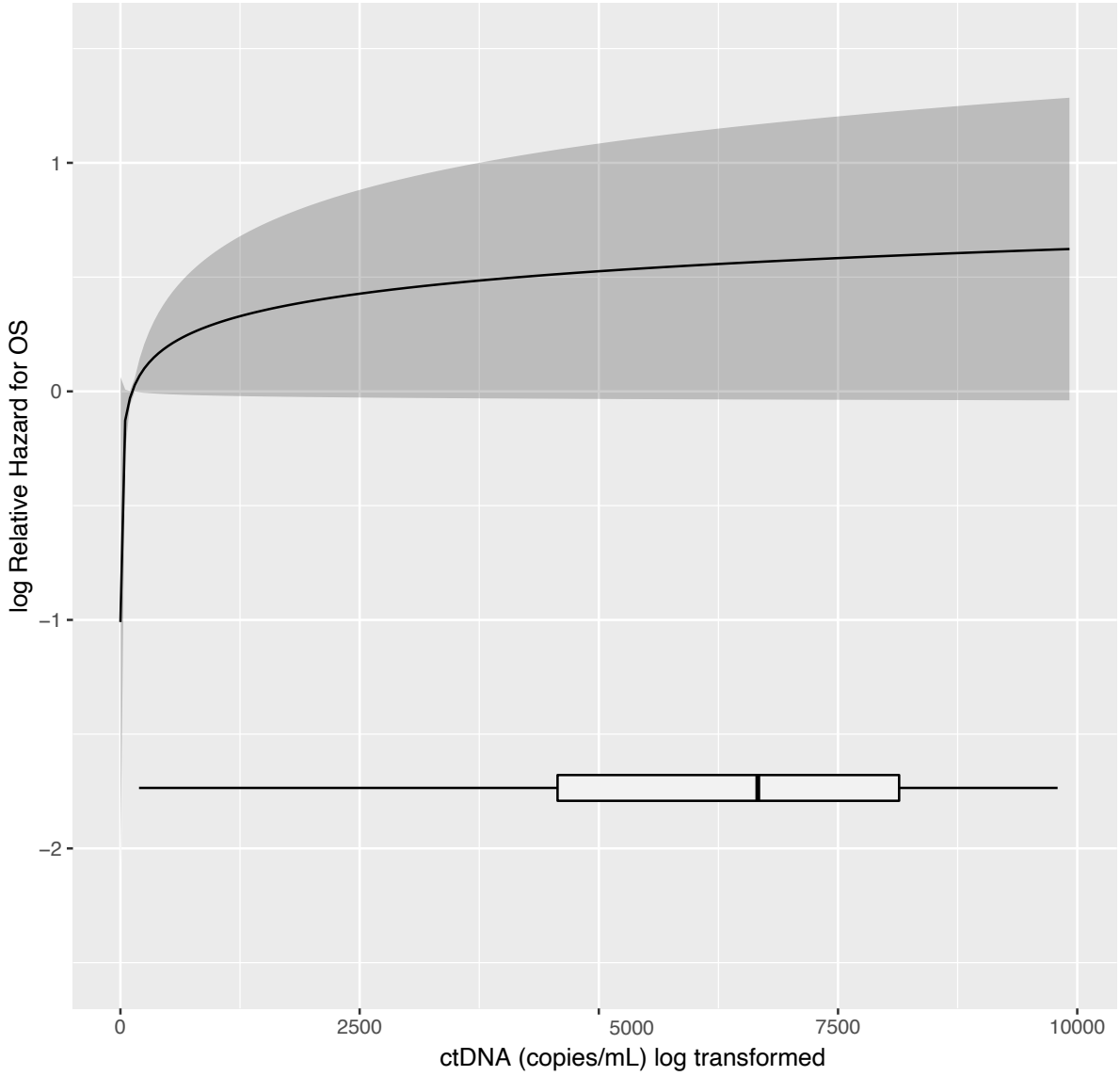
**Supplementary Figure S5.** Linear Cox regression model showing the association between baseline metabolic tumor volume (MTV) (mL) as assessed by FDG-PET with (A) PFS and (B) OS (95% CI represented by shading)



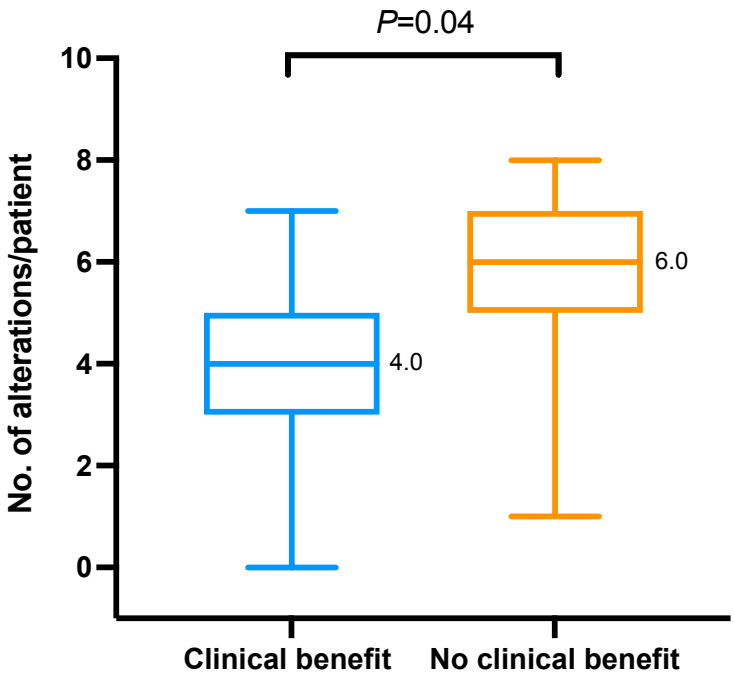

**Supplementary Figure S6.** Percentage change in metabolic tumor volume (MTV) (mL) at 4 weeks for patients achieving PR, SD, or PD. P values represent PR vs. PD and SD vs. PD by two-tailed t test.



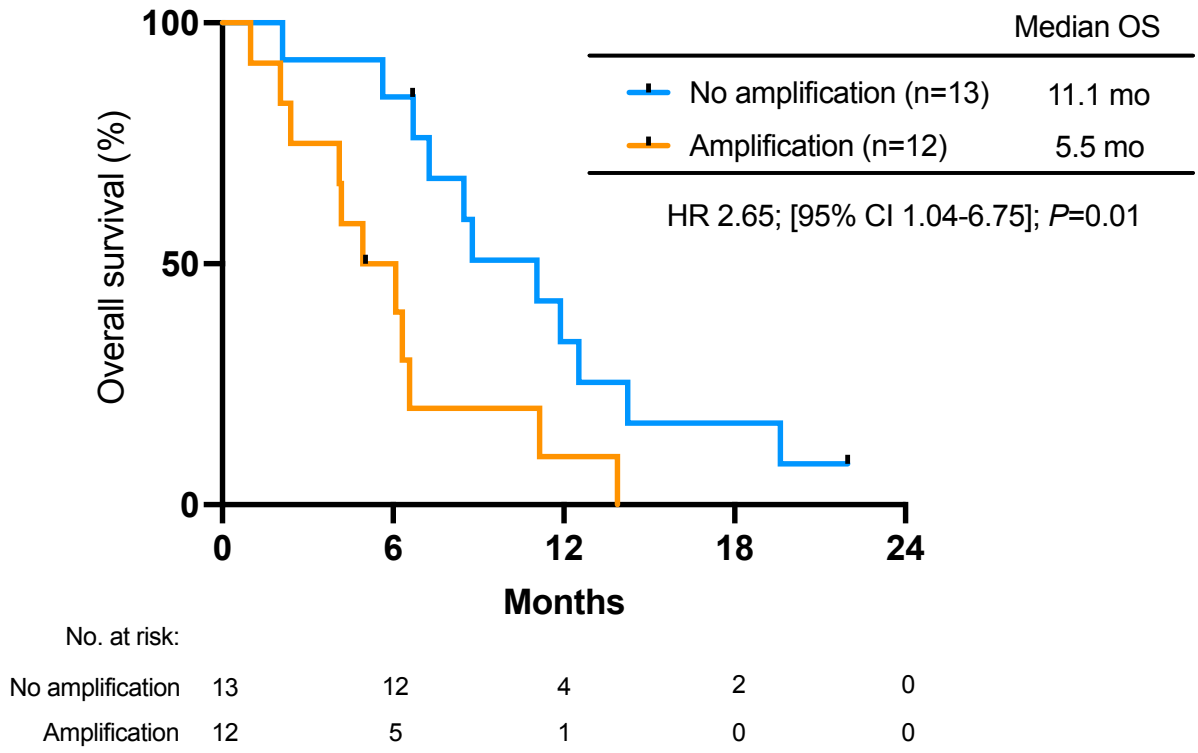

**Supplementary Figure S7.** Baseline ctDNA levels (copies/mL) according to best confirmed overall response as assessed by RECIST v1.1.



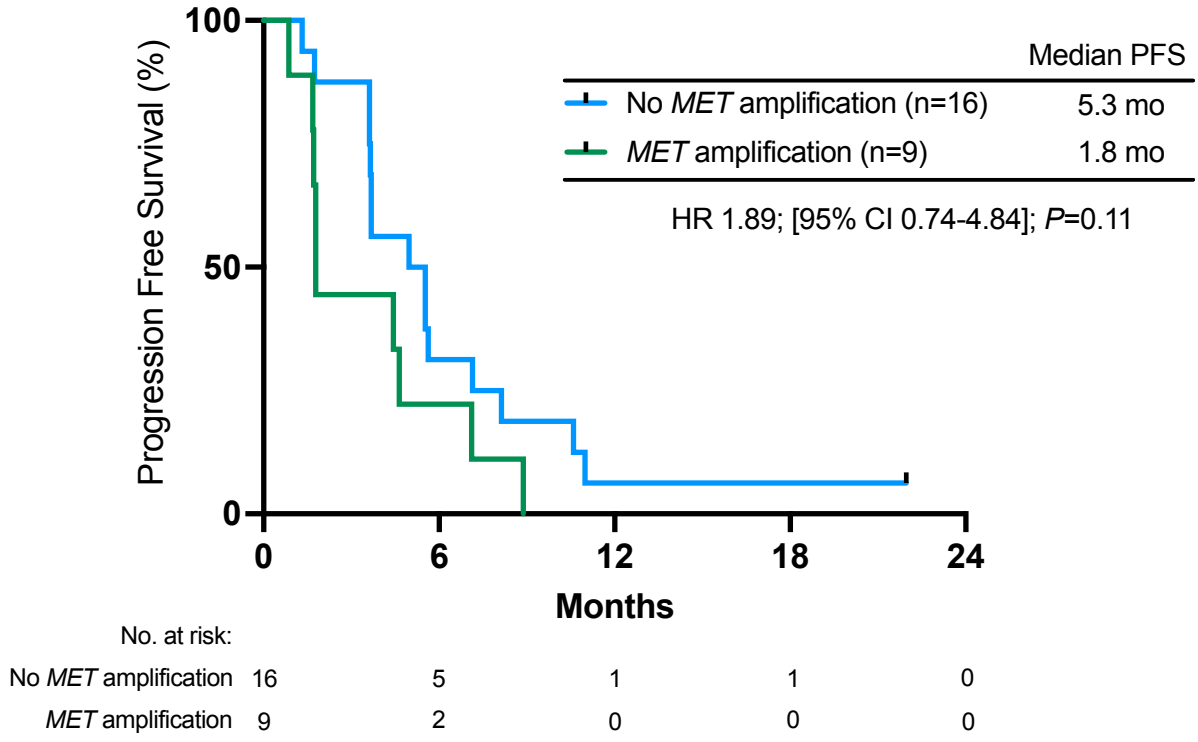

**Supplementary Figure S8.** Linear Cox regression model showing the association between ctDNA copies/mL (as assessed by ddPCR) and overall survival (95% CI represented by shading)




**Supplementary Figure S9.** Median number of detectable genetic alterations (SNVs, indels, amplifications) per patient in mCRC cohort (n=21) stratified according to clinical benefit rate. The box-whisker graph shows the minimum, maximum and median (middle line; value shown)

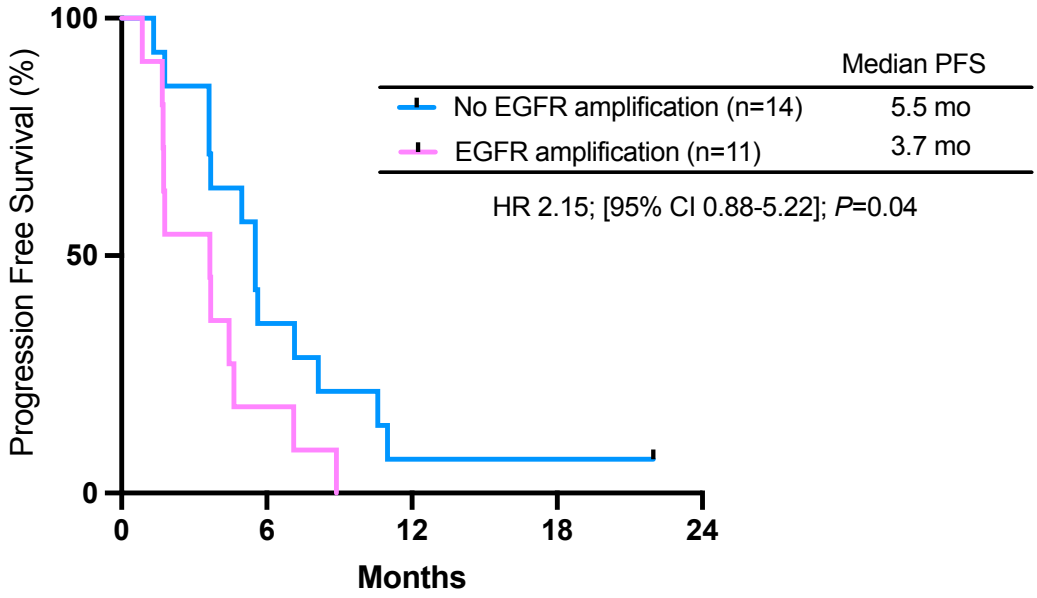



**Supplementary Figure S10.** Kaplan-Meier estimate of OS for patients (n=25) with a detectable amplification(s) versus no amplification in baseline plasma. Amplification is defined as the presence of any amplification in *EGFR*, *MET* and/or *ERRB2*.



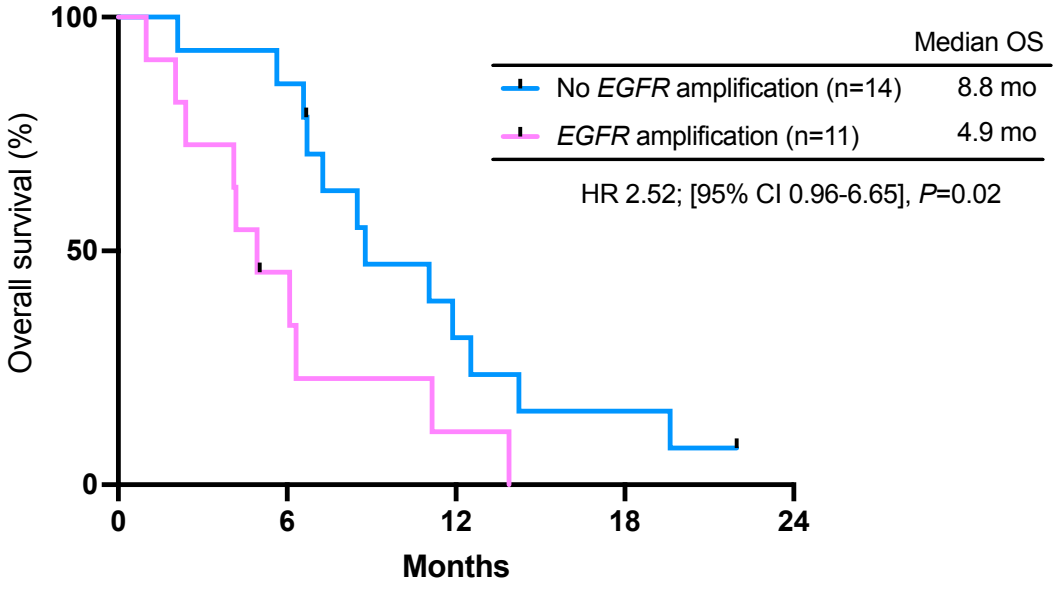

**Supplementary Figure S11.** Kaplan-Meier estimate of PFS for patients (n=25) with a detectable *MET* amplification versus no *MET* amplification in baseline plasma.

A)



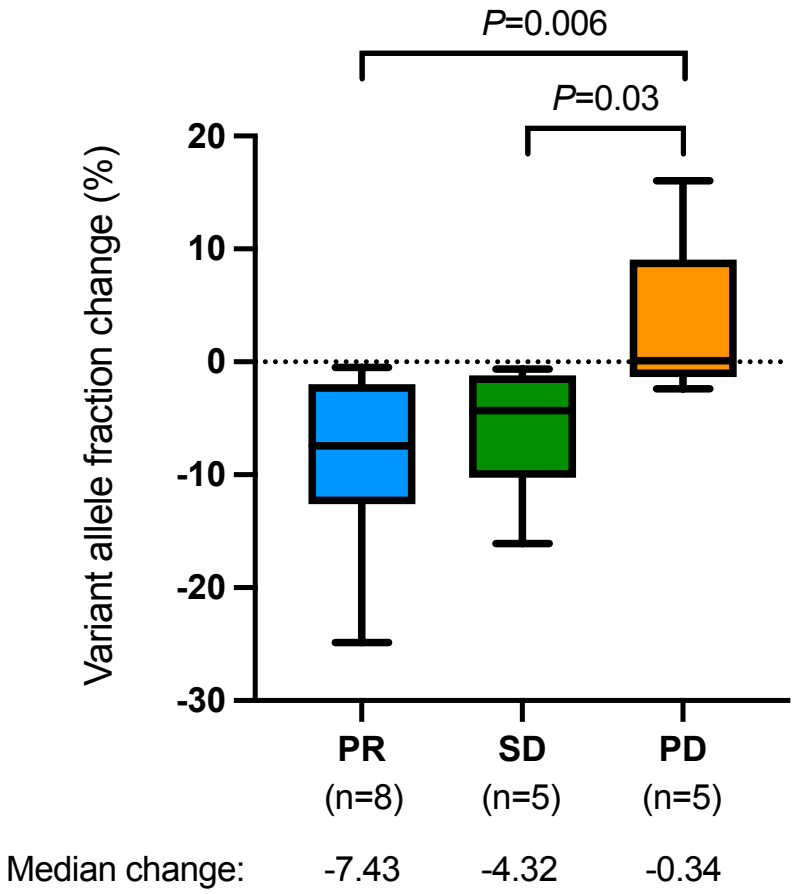

| No. at risk: | | | | | |
|---|---|---|---|---|---|
| No *EGFR* amplification: | 14 | 5 | 2 | 1 | 0 |
| *EGFR* amplification: | 11 | 2 | 0 | 0 | 0 |

B)

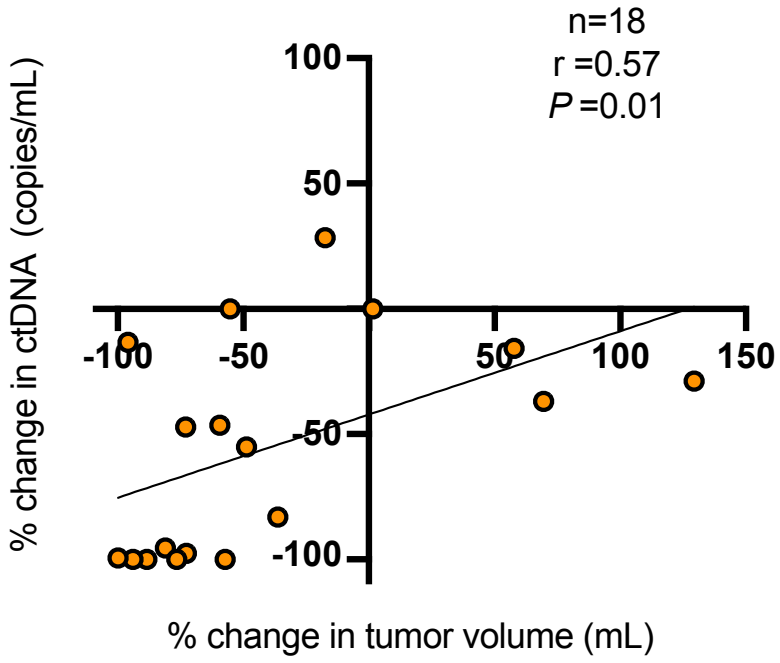



| No. at risk: | | | | | |
|---|---|---|---|---|---|
| No *EGFR* amplification: | 14 | 12 | 4 | 2 | 0 |
| *EGFR* amplification: | 10 | 4 | 1 | 0 | 0 |

**Supplementary Figure S12.** Kaplan-Meier estimate of A) PFS and B) OS for patients (n=25) with a detectable *EGFR* amplification versus no *EGFR* amplification in baseline plasma.

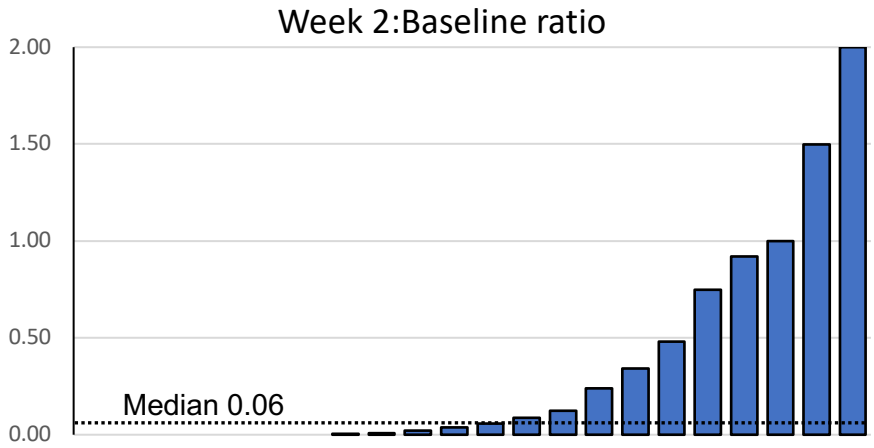



**Supplementary Figure S13.** Percentage change in *BRAF* V600E VAF at 4 weeks for patients achieving PR, SD, or PD. P values represent PR vs. PD and SD vs. PD by two-tailed t test.

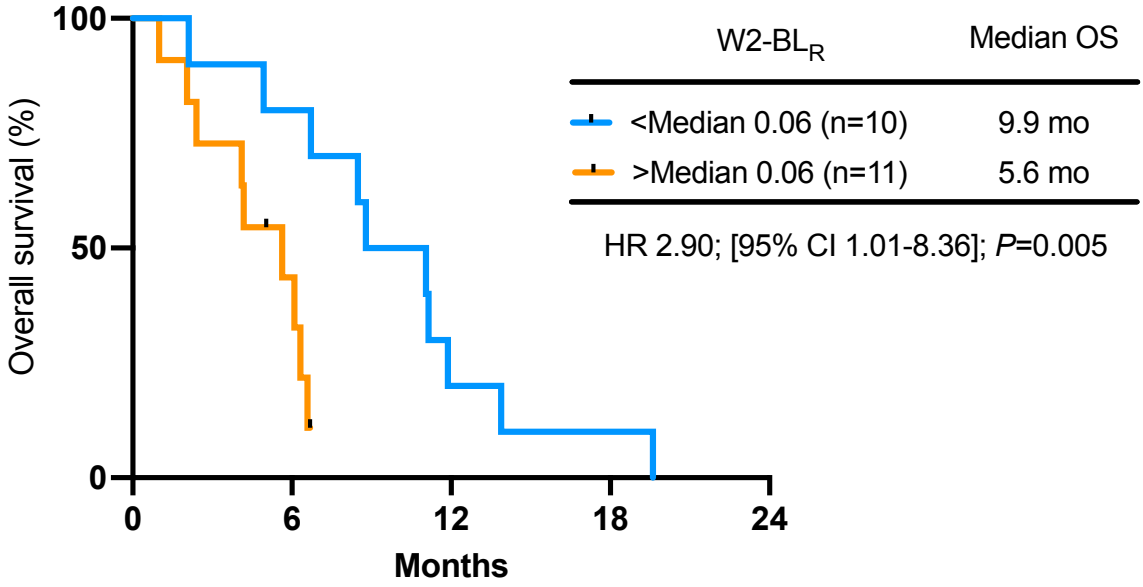



**Supplementary Figure S14.** Correlation between % change in ctDNA copies/mL and % change in tumor volume as assessed by FDG-PET at 4 weeks. Analysis was performed using Spearman rank correlation.

**A)**



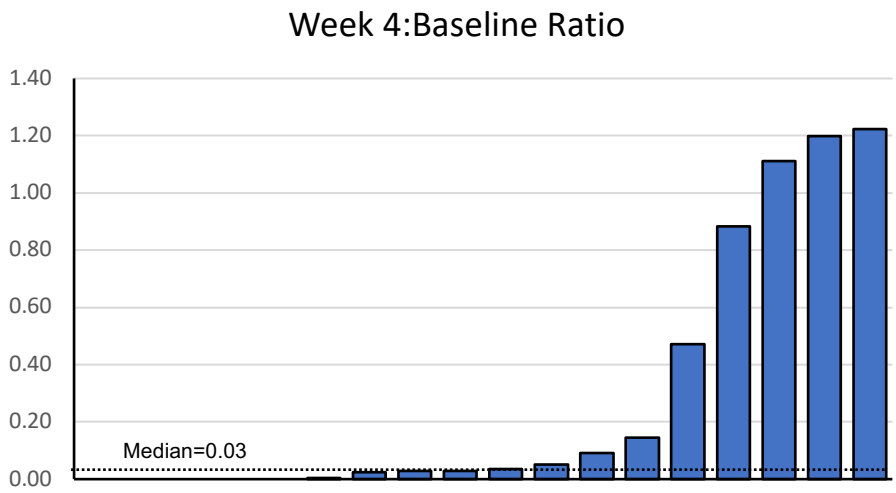

**B)**



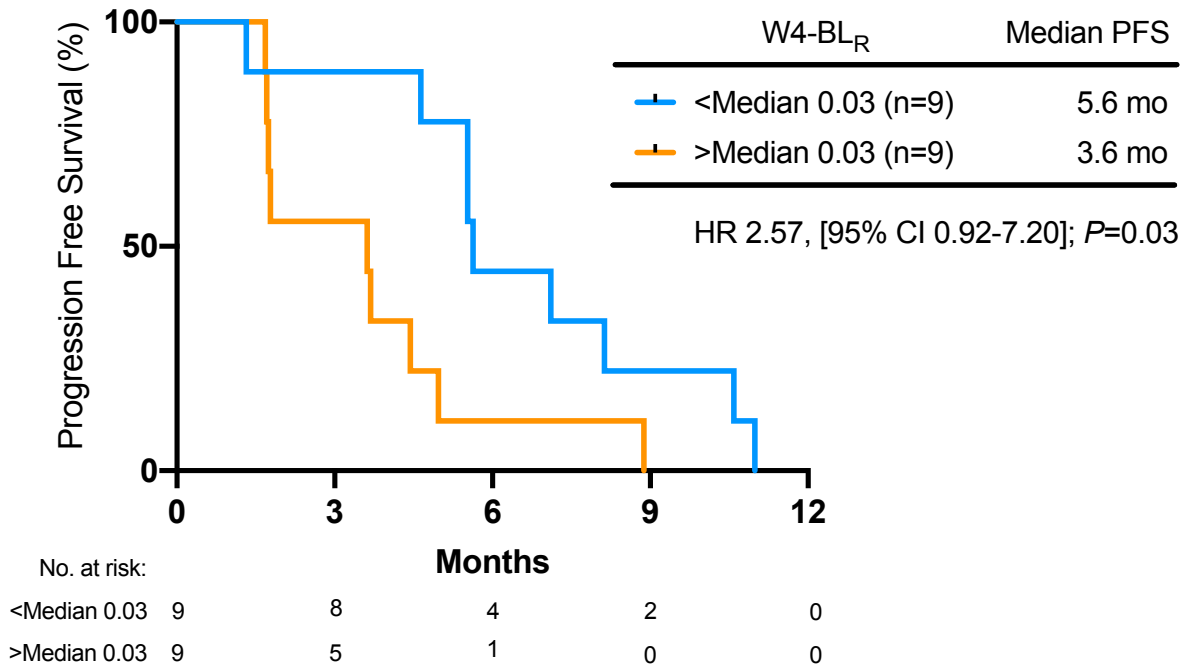

| No. at risk: | | | | | |
|---|---|---|---|---|---|
| <Median 0.06 | 10 | 8 | 2 | 1 | 0 |
| >Median 0.06 | 11 | 4 | 0 | 0 | 0 |

**Supplementary Figure S15.** Ratio of mutation abundance (VAF) on treatment at week 2 relative to baseline. (A) Median ratio (B) Kaplan-Meier estimate of OS for patients (n=21) stratified by week 2-baseline ratio (W2-$BL_R$).

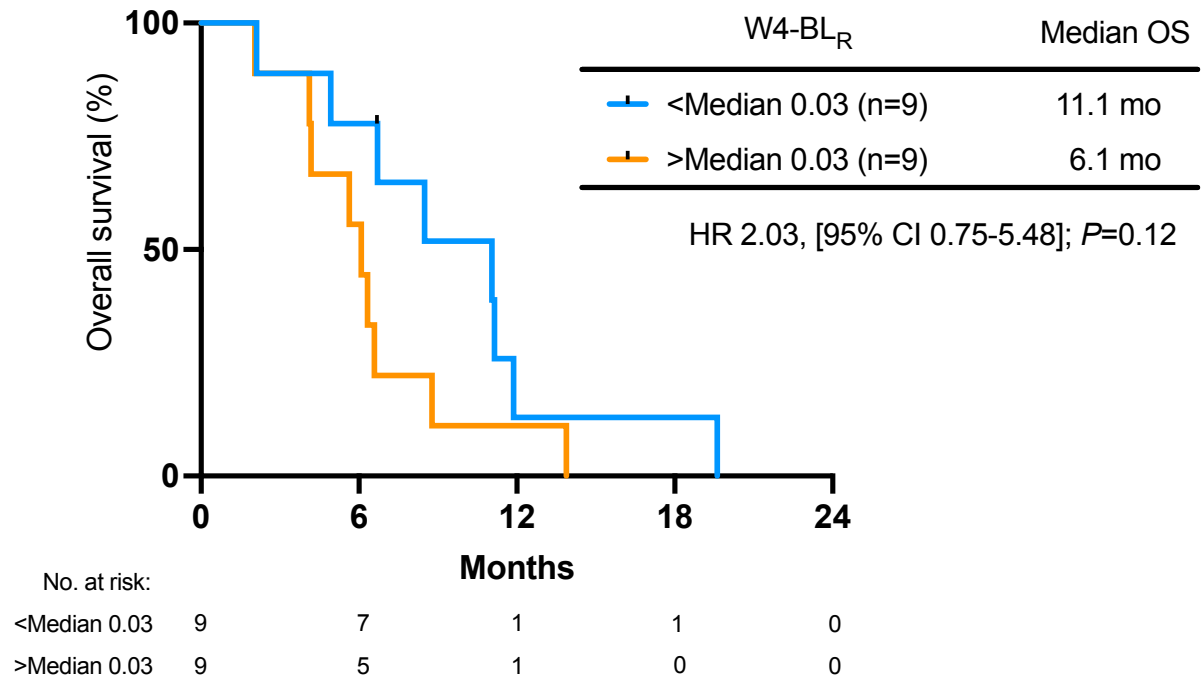
**A)**


Week 4:Baseline Ratio
1.40
1.20
1.00
0.80
0.60
0.40
0.20
0.00
Median=0.03

**B)**


Progression Free Survival (%)
100
50
0
0
3
6
9
12
Months
W4-BL$_R$
Median PFS
<Median 0.03 (n=9)
5.6 mo
>Median 0.03 (n=9)
3.6 mo
HR 2.57, [95% CI 0.92-7.20]; P=0.03
No. at risk:
<Median 0.03 9 8 4 2 0
>Median 0.03 9 5 1 0 0

C)




**Supplementary Fig. S16**. Ratio of mutation abundance (VAF) on treatment at week 4 relative to baseline. (A) Median ratio (B) Kaplan-Meier estimate of PFS and (C) OS for patients (n=18) stratified by week 4-baseline ratio (W4-BL$_R$).

**Supplementary Table S1.** List of genes from AVENIO ctDNA panel

| Gene | Seq Target | SNV | Indel‡ | Fusion§ | CNV§ |
|---|---|---|---|---|---|
| ABL1 | Selected regions | • | | | |
| AKT1 | Selected regions | • | | | |
| AKT2 | Selected regions | • | | | |
| ALK | Selected regions | • | • | • | |
| APC | Selected regions | • | • | | |
| AR | All coding regions | • | | | |
| ARAF | Selected regions | • | | | |
| BRAF | Selected regions | • | • | | |
| BRCA1 | All coding regions | • | | | |
| BRCA2 | All coding regions | • | | | |
| CCND1 | All coding regions | • | | | |
| CCND2 | All coding regions | • | | | |
| CCND3 | All coding regions | • | | | |
| CD274 | All coding regions | • | | | |
| CDK4 | All coding regions | • | | | |
| CDK6 | Selected regions | • | | | |
| CDKN2A | All coding regions | • | | | |
| CSF1R | Selected regions | • | | | |
| CTNNB1 | Selected regions | • | • | | |
| DDR2 | Selected regions | • | | | |
| DPYD | Selected regions | • | | | |
| EGFR | All coding regions | • | • | | • |
| ERRB2 | All coding regions | • | • | | • |
| ESR1 | All coding regions | • | | | |
| EZH2 | Selected regions | • | | | |
| FBXW7 | All coding regions | • | | | |
| FGFR1 | Selected regions | • | | | |
| FGFR2 | Selected regions | • | | • | |
| FGFR3 | Selected regions | • | | • | |
| FLT1 | Selected regions | • | | | |
| FLT3 | Selected regions | • | | | |
| FLT4 | Selected regions | • | | | |
| GATA3 | Selected regions | • | | | |
| GNA11 | Selected regions | • | | | |
| GNAQ | Selected regions | • | | | |
| GNAS | Selected regions | • | | | |
| IDH1 | Selected regions | • | | | |
| IDH2 | Selected regions | • | | | |
| JAK2 | Selected regions | • | | | |
| JAK3 | Selected regions | • | | | |
| KDR | Selected regions | • | | | |
| KEAP1 | All coding regions | • | | | |
| KIT | Selected regions | • | • | | |
| KRAS | All coding regions | • | | | |
| MAP2K1 | Selected regions | • | | | |
| MAP2K2 | Selected regions | • | | | |
| MET | All coding regions | • | • | | • |

| | | | | | |
|---|---|---|---|---|---|
| MLH1 | All coding regions | • | | | |
| M2H2 | All coding regions | • | | | |
| MSH6 | All coding regions | • | | | |
| MTOR | Selected regions | • | | | |
| NF2 | All coding regions | • | | | |
| NFE2L2 | Selected regions | • | | | |
| NRAS | Selected regions | • | | | |
| NTRK1 | Selected regions | • | | • | |
| PDCD1LG2 | All coding regions | • | | | |
| PDGFRA | Selected regions | • | | | |
| PDGFRB | Selected regions | • | | | |
| PIK3CA | Selected regions | • | • | | |
| PIK3R1 | Selected regions | • | | | |
| PMS2 | All coding regions | • | | | |
| PTCH1 | Selected regions | • | | | |
| PTEN | All coding regions | • | • | | |
| RAF1 | Selected regions | • | | | |
| RB1 | All coding regions | • | | | |
| RET | Selected regions | • | | • | |
| RNF43 | Selected regions | • | | | |
| ROS1 | Selected regions | • | | • | |
| SMAD4 | All coding regions | • | | | |
| SMO | All coding regions | • | | | |
| STK11 | All coding regions | • | | | |
| TP53 | All coding regions | • | | | |
| TERT Promoter | Selected regions | • | | | |
| TSC1 | Selected regions | • | • | | |
| TSC2 | Selected regions | • | | | |
| UGT1A1 | Selected regions | • | | | |
| VHL | All coding regions | • | • | | |

All coding regions are based on the longest transcript from Ensembl build 82.
‡ Indels are limited to variants in a pre-specified list of positions, referred to as “Loci of Interest”, except for EGFR exon 19 long deletions, EGFR exon 20 long insertions and MET long insertions, which are not restricted to a pre-defined set of Indels.

§ Detection of Fusions and CNVs are limited to variants in a pre-specified list of positions, referred to as “Loci of Interest” in the AVENIO analysis software.

**Supplementary Table S2.** Quantitative and qualitative ctDNA response criteria

| Criteria | Group | Week 2 | | | Week 4 | | |
|---|---|---|---|---|---|---|---|
| | | N | Median PFS, Months | *P* | N | Median PFS, Months | *P* |
| Qualitative response criteria | G1 | 15 | 3.7 | 0.05 | 14 | 4.5 | 0.18 |
| | G2 | 6 | 6.9 | | 4 | 8.1 | |
| | G3 | 4 | 5.4 | | 3 | 3.7 | |
| Quantitative response criteria | CCR | 4 | 8.1 | <0.0001 | 5 | 7.1 | 0.05 |
| | CPR | 8 | 3.7 | | 3 | 4.4 | |
| | CSD | 8 | 4.8 | | 9 | 4.6 | |
| | CPD | 1 | 0.9 | | 1 | 1.7 | |
| | CND | 4 | 5.4 | | 3 | 3.7 | |

Abbreviations: CCR, ctDNA complete response; CPR, ctDNA partial response; CSD, ctDNA stable disease; CPD, ctDNA progressive disease; CND, ctDNA nonmeasurable

**Appendix 1.** EVICT Study Protocol

Peter MacCallum Cancer Centre

| | |
|---|---|
| **FULL TITLE** | **A Phase I/II Trial of the combination of BRAF and EGFR inhibition in BRAF V600E mutant metastatic colorectal, advanced or metastatic lung adenocarcinoma and other cancers: The EViCT (Erlotinib and Vemurafenib In Combination Trial) Study** |
| **SHORT TITLE** | **The EViCT (Erlotinib and Vemurafenib In Combination Trial) Study** |
| **PROTOCOL NUMBER** | **2014.019** |
| **ROCHE STUDY NUMBER** | **ML28737** |
| **VERSION NUMBER** | Final version 2.0 |
| **DATE OF PROTOCOL** | 05 March 2014 |
| **SPONSOR** | Peter MacCallum Cancer Centre<br>St Andrews Place<br>East Melbourne VIC 3002 Australia |
| **STUDY CHAIR** | Dr Jayesh Desai<br>Royal Melbourne Hospital/Peter MacCallum Cancer Centre<br>c/o Department of Medical Oncology<br>Royal Melbourne Hospital<br>Grattan St, Parkville VIC Australia, 3050 |
| **PROTOCOL AUTHORS** | Jayesh Desai, Thao Le, Marnie Collins<br>Grant Mcarthur, Paul Waring |

# PROTOCOL HISTORY

| Version No | Date | Reason |
|---|---|---|
| 1.0 | 23 December 2013 | |
| 2.0 | 05 March 2014 | Minor corrections of table 6 (Schedule of assessments) to be consistent with body text of the protocol. |

# PROTOCOL AUTHORISATION PAGE

**A Phase I/II Trial of the combination of BRAF and EGFR inhibition in BRAF V600E mutant metastatic colorectal, advanced or metastatic lung adenocarcinoma and other cancers: The EViCT (Erlotinib and Vemurafenib In Combination Trial) Study**

| | |
|---|---|
| PROTOCOL NUMBER | |
| FINAL VERSION NUMBER | Version 2.0 |
| DATE OF PROTOCOL | 05 March 2014 |
| STUDY CHAIR | Dr Jayesh Desai |
| SIGNATURE | |
| DATE SIGNED | |
| SPONSOR | Peter MacCallum Cancer Centre<br>St Andrews Place<br>East Melbourne VIC 3002 Australia |
| SPONSOR REPRESENTATIVE | Peter MacCallum Cancer Centre<br>Locked Bag # 1, A'Beckett St<br>Melbourne 8006 Australia |
| SIGNATURE | |
| DATE SIGNED | |

Note: Original and signed document held by the Centre for Biostatistics and Clinical Trials on behalf of the Sponsor

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| **Pharmacody-namic study details** | Prof Paul Waring | See above | See above | See above |
| **Drug support** | Dr Christine Operschall Birke | Project Manager - Supported Studies Roche Products Pty | Tel: +61 2 9454 9341 | christine.operschall_birke @roche.com |

| | | | | |
|---|---|---|---|---|
| | | Limited | | |
| **SAE reporting** | EVICT Clinical Trial Manager (BaCT) | | See Section 9.2.2 | |
| **SAE Reviewers** | Dr Jayesh Desai<br>Prof Grant McArthur<br>A/Prof Ben Solomon | See above | See above | See above |
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# TABLE OF CONTENTS

## LIST OF TABLES



## LIST OF FIGURES

# PROTOCOL SYNOPSIS

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|---|---|
| **Study Title** | **A Phase I/II Trial of the combination of BRAF and EGFR inhibition in BRAF V600E mutant metastatic colorectal, advanced or metastatic lung adenocarcinoma and other cancers: The EViCT (Erlotinib and Vemurafenib In Combination Trial) Study** |
| **Development Phase** | Phase I/II |
| **Indication** | BRAF V600E mutant advanced or metastatic cancers |
| **Study Drugs** | Erlotinib and vemurafenib |
| **Study Overview** | This study will include 2 parts:<br>• Phase I Lead-In Phase: Dose Escalation/de-escalation in BRAF V600E mutant metastatic colorectal cancer (mCRC) patients to determine the maximum tolerated dose to be used in Phase II<br>• Phase II: Dose Expansion Phase which includes<br>o BRAF V600E mutant mCRC Expansion Cohort and<br>o Exploratory Expansion Cohort (for BRAF V600E mutant non CRC, with a focus on lung adenocarcinoma) |
| **Number of Subjects/Sites** | It is expected the study will accrue up to 46 BRAF V600E mutant metastatic CRC (mCRC) patients (including 6-18 patients in the Lead-In Phase and a maximum of 18 additional patients in the Expansion Phase) and approximately 10 BRAF V600E mutant advanced or metastatic non-colorectal cancer patients in the exploratory cohort of the Expansion Phase.<br>This study will be available to all CTA sites, with the expectation that approximately 8 sites will open. |
| **Study Duration** | Recruitment is expected to take place over 2 years from activation. Patients will remain on treatment until disease progression after which time they will be followed for survival only. The expected time to progression is 6 months and the expected additional survival time is 12 months; patients may therefore be followed for a minimum of approximately 18 months and the total study duration is expected to be 3.5 years. |
| **End of Study** | Study closure will occur when all patients have been followed for up to 18 months after treatment commencement or when all patients have progressed, died, or withdrawn consent, whichever occurs first. |
| **Hypothesis** | It is hypothesised that the combination treatment of vemurafenib and erlotinib will be safe and will show a sufficient level of activity in patients with BRAF V600E mutant advanced or metastatic cancers to warrant further investigation in later phase trials. |
| **Study Objectives** | **Primary:**<br><u>Phase I Lead-In Phase</u><br>• To determine the safety of the combination of vemurafenib and erlotinib in the first 4 weeks of treatment in BRAF V600E mutant metastatic CRC and |

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| | identify the dosing regimen to be evaluated in Phase II.<br>Phase II Dose Expansion<br>• To evaluate the clinical efficacy of the combination of vemurafenib and erlotinib in BRAF V600E mutant metastatic CRC as measured by the proportion of patients achieving a complete or partial response (CR or PR) within the first 24 weeks of treatment.<br>**Secondary:**<br>• To evaluate the clinical efficacy of the combination of vemurafenib and erlotinib in BRAF V600E mutant advanced or metastatic cancers (lung adenocarcinoma and other) as measured by the proportion of patients achieving a complete or partial response (CR or PR) within the first 24 weeks of treatment.<br>• To evaluate other measures of clinical efficacy of the combination of vemurafenib and erlotinib in the two patient groups (mCRC, lung adenocarcinoma and other) including: the clinical benefit rate at 16 weeks after treatment commencement (CR, PR and SD), time to progression, progression-free survival and overall survival.<br>• To determine the safety of the combination of vemurafenib and erlotinib over the course of treatment within each of the two patient groups (mCRC, lung adenocarcinoma and other).<br>**Exploratory:**<br>• To explore the pharmacodynamic effects of BRAF/EGFR inhibition using pre-treatment, 4 weeks and on progression disease FDG-PET in each patient group (optional for patients with cancer other than CRC and lung adenocarcinoma).<br>• To explore the pharmacodynamic effects of BRAF/EGFR inhibition using paired pre-treatment and day 14 tumour biopsies (optional) or hair follicle plucks (optional) in each patient group and how these correlate with response.<br>• To evaluate circulating biomarkers and their correlation with response including<br>o Changes in circulating tumour DNA (ctDNA),<br>o Changes in serum cytokine/chemokine microRNA profiles and in immune function in PBMCs; with BRAF/EGFR inhibition and how these correlate with response. |
| **Study Endpoints** | **Primary:**<br>Phase I Lead-In Phase<br>• The incidence of dose-limiting toxicities reported within the first 4 weeks of treatment with the combination of vemurafenib and erlotinib. Dose-limiting toxicities are defined in Section 3.1.1.2.<br>Phase II Dose Expansion |

- The achievement of a complete response (CR) or partial response (PR) as defined by Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 within the first 24 weeks of treatment with the combination of vemurafenib and erlotinib.

**Secondary:**

Secondary endpoints of interest include the following:

- Clinical benefit as defined by: (i) achievement of a complete or partial response (CR or PR) during the first 16 weeks of treatment with the combination of vemurafenib and erlotinib; or (ii) maintenance of stable disease (SD) until 16 weeks after commencement of treatment according to RECIST v1.1 guidelines.
- Time to progression measured from the date of commencement of treatment with the combination of vemurafenib and erlotinib until disease progression. Time to progression for patients who die without prior disease progression will be censored at the date of death. Patients who have not progressed or died by the study close-out date will be censored at this date. Patients who are not known to have progressed or died and who are lost to follow-up before the close-date will be censored at the date they were last known to be alive and progression-free.
- Progression-free survival (PFS) measured from the date of commencement of treatment with the combination of vemurafenib and erlotinib until disease progression or death prior to progression from any cause. Patients who have not progressed or died by the study close-out date will have their progression-free survival time censored at this date. Patients who are not known to have progressed or died and who are lost to follow-up before the close-out date will have their progression-free survival time censored at the date they are last known to be alive and progression-free.
- Overall survival (OS) measured from the date of commencement of treatment with the combination of vemurafenib and erlotinib until death from any cause. Patients who have not died by the study close-out date will have their overall survival time censored at this date. Patients who are not known to have died and who are lost to follow-up before the close-out date will have their overall survival time censored at the date they were last known to be alive.
- Frequency and worst grade of adverse events according to CTCAE v4.03, withdrawal due to unacceptable toxicity.

**Exploratory**:

<u>Functional Imaging:</u>

Target inhibition will be evaluated with FDG-PET. Scans performed pre-treatment, 4 weeks and at disease progression in all patient groups (compulsory for CRC and lung adenocarcinoma patients and optional for other cancer patients)

<u>Tumour Tissue:</u>

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| | 1) Archival Tissue (In all patients)<br>a. Analysis of mutations in related pathways including PIK3CA, PTEN, KRAS and NRAS for all plus EGFR for lung adenocarcinoma.<br>b. Microsatellite instability and / or mismatch repair proficiency by IHC.<br>c. Expression determined by IHC including EGFR, epiregulin and, amphiregulin. Copy number analysis by ISH, including EGFR.<br>2) Paired tumour Biopsy Cohort (optional, in selected patients): at pre-treatment, 14 days and at disease progression will be conducted. Pharmacodynamic biomarker assays for pathway activation/inhibition including pEGFR, pAKT, pS6, pPRAS40, pERK by IHC using validated antibodies and where possible by other methods (eg. Western blot, reverse phase protein array, multiple reaction monitoring) will be performed.<br>3) Paired Eyebrow hair follicle plucks (optional, in selected patients): eyebrow hair follicles will be plucked pre-treatment and on Day 14. Assays for pathway activation/inhibition including pEGFR, pAKT, pS6, pPRAS40, pERK by IHC using validated antibodies and where possible by other methods (eg. Western, reverse phase protein arrays, multiple reaction monitoring) will be performed.<br><u>Circulating Biomarkers</u><br>Blood will be collected baseline, Week 2, 4, 8 and then every 8 weeks thereafter and at disease progression for the purposes of evaluating changes in circulating biomarkers including ctDNA, cytokines and chemokines; with BRAF/EGFR inhibition and how these correlate with response. |
| **Study Design** | An initial Lead-In Phase/Phase I will be conducted to establish the safety of the combination treatment of vemurafenib and erlotinib in patients with BRAF V600E metastatic CRC prior to the Dose Expansion Phase/Phase II.<br>**Lead-In Phase**<br>There will be 3 dose levels:<br>• Dose level D-1 = erlotinib (100 mg/day) and vemurafenib (720 mg b.i.d)<br>• Dose level D1 = erlotinib (100 mg/day) and vemurafenib (960 mg b.i.d)<br>• Dose level D2 = erlotinib (150 mg/day) and vemurafenib (960 mg b.i.d)<br>The first dose to be evaluated will be dose level D1 and dose escalation (to dose level D2) or de-escalation (to dose level D-1) will be implemented using a standard 3+3 design (see Schema 2). Dose escalation/de-escalation decisions will be made by the Safety Monitoring Committee (SMC).<br>Dose Limiting Toxicities (DLTs) will be monitored over the first four weeks of treatment in a series of cohorts of 3 patients. After each cohort of 3 patients completes the DLT observation period, a clinical synthesis of the available toxicity information (including DLTs, adverse events that are not DLTs, and adverse events post the DLT observation period), will be reviewed by the Safety Monitoring Committee (SMC) (see Section 8.3) and will be used to determine the dose regimen for the next cohort of 3 patients at a Lead-In Phase |

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| | meeting/teleconference.<br><br>DLT-evaluable patients will be defined as all eligible patients registered in the Lead-In Phase who commence treatment with the combined regimen at the dose level to which they were accrued and who either: (i) experience a DLT during the observation period; or (ii) receive at least 21 days of treatment during the observation period (28 days) without experiencing a DLT. Patients who do not receive at least 21 days of treatment during the observation period (28 days) for reasons other than treatment-related toxicity, cease treatment or withdraw from the study for reasons unrelated to study treatment prior to completion of the DLT observation period will not be evaluable and will therefore be replaced in that cohort. If any patient in any phase experiences a DLT, erlotinib and/or vemurafenib will be ceased for that patient until the toxicity has reduced to grade < 1 or baseline. Erlotinib and/or vemurafenib will then resume for that patient at 1 dose level lower than the previous dose after discussion with the Study Chair (see Section 5.4). Patients treated in Dose Level -1 with such toxicities will need to be discussed with the Study Chair.<br><br>Following the 4 week DLT-observation period, patients not experiencing a DLT will continue with treatment until disease progression after which time they will be followed for survival only.<br><br>**Expansion Phase**<br><br>Once the maximum tolerated dose (MTD) is defined in Phase I, the Expansion Phase/Phase II will commence in the mCRC cohort using a Simon optimal two-stage design, with 9 patients recruited to the first stage and a possible additional 15 patients recruited to the second stage.<br><br>Evaluable patients for the Expansion Phase will be defined as all registered, eligible patients who commence treatment with the combined regimen of vemurafenib and erlotinib at the MTD defined in the Lead-In Phase. The 6 patients treated with the MTD in the Lead-In Phase will also comprise the first 6 patients in the mCRC expansion cohort.<br><br>A non-CRC exploratory expansion cohort will be enrolled on the study in parallel in a single stage. Evaluable patients will be defined as all registered, eligible patients who commence treatment with the combined regimen of vemurafenib and erlotinib at the MTD defined in the Lead-In Phase.<br><br>Patients in both cohorts of the Expansion Phase will remain on treatment until disease progression or unacceptable toxicity after which time they will be followed for survival only. The expected time to progression is 6 months and the expected additional survival time is 12 months; therefore each patient is expected to be on study for approximately 18 months. |
| **Eligibility Criteria (Inclusion and Exclusion)** | **Inclusion Criteria**<br><br>1. Male or female patients ≥ 18 years of age at the time of study entry<br><br>2. All patients must have histological or cytological confirmed metastatic colorectal cancer with a BRAF V600E mutation of their primary cancer or related metastases. Patients with other tumour types with a proven BRAF V600E mutation can be considered for enrolment into the Expansion Phase |

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| | exploratory cohort with the permission of the Study Chair.<br><br>3. Patients with BRAF V600E mCRC are permitted to have had a maximum of 2-lines of therapy for metastatic disease. A maintenance strategy post 1st-line treatment is not considered as an additional line of therapy, nor is rechallenge with oxaliplatin. Patients with lung adenocarcinoma are required to have received prior treatment with a platinum doublet. There is no requirement for previous treatment for other tumour types.<br><br>4. All patients must have measurable disease per RECIST 1.1 criteria (see Appendix 5).<br><br>5. A tumour paraffin tissue block or 20 - 30 unstained slides from the tumour tissue block must be available for the purpose of biomarker analyses. Obtaining archived tumour material or unstained slides from an archived tumour block will suffice to meet this requirement. The availability of the tumour tissue block must be confirmed at screening for a patient to be considered eligible. If no tissue block and fewer than 20 unstained slides are available, eligibility must be confirmed with the Study Chair or delegate.<br><br>6. ECOG performance status 0 to 1 inclusive (see Appendix 1).<br><br>7. Participants must have adequate organ and marrow function as defined below:<br><br>• Absolute neutrophil count ≥ 1.5 x $10^9$/L<br>• Platelets ≥ 100 x $10^9$/L<br>• ALT and AST ≤ 2.5 x upper limit of normal (ULN), or ≤ 5 x ULN if liver metastases are present<br>• Total serum bilirubin ≤ 1.5 x ULN<br>• Serum creatinine ≤ 1.5 x ULN, **or** creatinine clearance > 50ml/min<br><br>8. Participants must be suitable for oral drug administration.<br><br>9. Life expectancy > 3 months.<br><br>10. Female patients of childbearing potential (see below) must:<br><br>a) Be on highly effective contraception. Highly effective contraception methods include:<br><br>• total abstinence, or<br>• sterilisation (see below), or<br>• combination of any two of the following (a+b, or a+c, or b+c):<br>○ Use of oral, injected or implanted hormonal methods of contraception. Hormonal contraceptives include any marketed contraceptive agent that includes an oestrogen and/or a progestin.<br>○ Placement of an intrauterine device (IUD)<br>○ Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/cream/ vaginal suppository |

b) Have a negative serum or urine pregnancy test performed within the 7 days before start of treatment.

c) Highly effective contraception for females of child bearing potential must be maintained throughout the study and for 6 months after study drug discontinuation.

11. Female patients **not** of child-bearing potential. Women are considered **not** of child bearing potential if they have had either:

    - 12 months of natural (spontaneous) amenorrhoea with an appropriate clinical profile (eg. age appropriate, history of vasomotor symptoms), or
    - A surgical bilateral oophorectomy (with or without hysterectomy), or
    - Tubal ligation at least 6 weeks ago.

    In the case of unilateral oophorectomy alone, a woman is considered not of child-bearing potential *only* once the reproductive status has been confirmed by follow up hormone level assessment.

12. Sexually active males must use a condom during intercourse while taking the drug and for 6 months after stopping treatment and should not father a child in this period. A condom is required to be used also by vasectomised men in order to prevent delivery of the drug via seminal fluid.

13. Absence of any psychological, familial or sociological condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before trial entry.

14. Ability to understand and the willingness to sign a written informed consent. Before study entry, written informed consent must be obtained from patient prior to performing any study-related procedures.

**Exclusion criteria**

1. Active CNS lesions are excluded (i.e. those with radiographically unstable, symptomatic lesions). Patients treated with stereotactic therapy or surgery are eligible if patient remains without evidence of disease progression within the CNS for ≥ 1 month. Previous whole brain radiotherapy is not allowed with the exception of patients who have had definitive resection or stereotactic therapy of all radiologically detectable parenchymal lesions.

2. History of or known spinal cord compression, or carcinomatous meningitis.

3. Patients who have had any systemic cytotoxic/biologic or investigational therapies within 4 weeks prior to study entry or who have not recovered from the side effects of such earlier therapy.

4. Previous malignancies within the past 5 years are excluded except for adequately treated carcinoma in-situ of the cervix. Isolated elevation in PSA in the absence of radiographic evidence of metastatic prostate cancer is allowed.

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| | 5. Participants who have had radiotherapy and/or major surgery within 2 weeks prior to study entry.<br>6. Anticipated or concurrent use of any other anti-cancer therapies or study agents.<br>7. Clinical significant cardiac disease including any of the following:<br>a. unstable angina,<br>b. symptomatic or otherwise uncontrolled arrhythmia requiring medication (does not include stable, lone atrial fibrillation),<br>c. QTcF > 480 msecs (See Appendix 2 for Fridericia's correction formula) or a history of congenital long QT syndrome,<br>d. uncontrolled hypertension,<br>e. symptomatic congestive heart failure (NYHA II, III, IV, See Appendix 3),<br>f. myocardial infarction ≤ 6 months prior to first study treatment,<br>g. serious uncontrolled cardiac arrhythmia.<br>8. Patients with active uncontrolled infection.<br>9. Known history of human immunodeficiency virus (HIV) infection.<br>10. Known history of active hepatitis B or C.<br>11. Other severe, acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration, or may interfere with the interpretation of study results, which in the judgment of the investigator would make the patient inappropriate for entry into this study.<br>12. Patients who are receiving treatment with medications known to be strong CYP3A4 inhibitors within 7 days before starting treatment with erlotinib and vemurafenib or strong inducers of CYP3A4 within 14 days before starting treatment with erlotinib and vemurafenib.<br>A comprehensive list of inhibitors, inducers and substrates may be found at http://medicine.iupui.edu/flockhart/table.htm.<br>13. Nursing (lactating) women.<br>14. Severe hypersensitivity to any of the study drugs, study drug classes, or excipients in the formulation of either erlotinib or vemurafenib (see section 5).<br>15. Patients with EGFR mutant lung adenocarcinoma. |
| **Study Procedures**<br>See Table 6 | • Identification and consent of patient as potential participant.<br>• Screening investigations will occur between Day -28 to -1 followed by patient registration if found eligible (for details see Section 6.3).<br>• Safety assessments (Physical examination, haematology and biochemistry) and performance status will be conducted at: screening, Week 1, 2, 4, 6, 8, 12, 16, 20, 24 and every 8 weeks thereafter until 28 days after end of |

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| | treatment (see Section 6.7.1). ECG will be performed at: screening, Week 2, 4, 8, 12, 24 and every 8 weeks thereafter until 28 days after end of treatment. Skin examination should be performed ideally by a dermatologist with the intention of finding of any side effects associated with the use of vemurafenib such as cuSCC, rash, and photosensitivity at: screening, Week 4, 8, 16, 24 and every 8 weeks thereafter until 28 days after end of treatment.<br>• Assessment of tumour response (CR, PR, SD or PD) will occur at Week 8, 16, 24 and every 8 weeks thereafter until evidence of disease progression or until patient withdrawal for other reasons (see Section 6.7.2).<br>• FDG-PET (optional in patients with cancers other than CRC and lung adenocarcinoma) and tumour biopsies (optional in all patients) at screening, Week 4 and at progressive disease (see Section 6.7.3).<br>• Blood sample for exploratory biomarkers including ctDNA, cytokines and chemokines will be collected baseline, Week 2, 4, 8 and then every 8 weeks thereafter and at disease progression.<br>• Optional fresh tumour sample obtained from accessible metastatic site (eg liver biopsy, fine needle aspirates) for pharmacodynamics biomarker studies. Samples may be taken pre-treatment, at Day 14 (Week 2), and at disease progression<br>• Optional paired eyebrow hair follicle plucks taken pre-treatment and at Day 14 for pharmacodynamics biomarker studies.<br>• End of Treatment Visit is to be performed when disease progression, intolerable toxicity, withdrawal of consent for protocol specified procedures, or discontinuation from the study for any other reason has occurred (see Section 6.5).<br>• Follow-Up Visits for assessments of toxicities, response and survival (see Section 6.6). |
| **Sample Size Determination** | **Phase I Lead-In Phase:**<br>The Lead-In Phase will involve a standard 3+3 design; only one dose escalation and one dose de-escalation will be considered if required. A maximum of 6 evaluable patients will be enrolled at each dose level therefore the sample size will be between 6 and 18 evaluable patients.<br><br>**Phase II Dose Expansion:**<br>Simon's optimal two-stage design will be implemented for the mCRC patient cohort in the Expansion Phase. Non-CRC patients will be enrolled in an exploratory cohort of the Expansion Phase which will run in parallel. It is expected that approximately 10 patients will be enrolled into this exploratory cohort.<br>For the mCRC patient cohort which is of primary interest, the study is designed to distinguish a favourable true response rate (CR or PR) within the first 24 weeks of treatment of ≥ 20% from a null (uninteresting) rate of ≤ 5% and will allow early stopping if there is no strong evidence suggesting that the |

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| | treatment combination of vemurafenib and erlotinib is active.<br><br>The required sample size for the mCRC expansion cohort is a maximum of 24 patients, of whom the first 6 patients will be those treated with the MTD in the Lead-In Phase. In the first stage of the Expansion Phase, if 0 of the first 9 evaluable patients (including the 6 patients treated with the MTD in the Lead-In Phase) achieve a CR or PR within the first 24 weeks of treatment, the mCRC expansion cohort may not proceed to the second stage. Otherwise, the mCRC expansion cohort will proceed to the second stage and accrue an additional 15 evaluable patients for a total of 24 evaluable patients. The treatment combination of vemurafenib and erlotinib will be considered active at the end of the second stage if 3 or more patients achieve a CR or PR within the first 24 weeks of treatment. These calculations are based on a significance level of 0.10 and power of 0.80.<br><br>The probability of the cohort stopping early at the end of the first stage is 63% if the true response rate is 5%. At the end of the study, the probability of declaring the treatment combination active in the cohort given a true response rate of 5% (null hypothesis) is 10%. The probability of declaring the treatment combination active in the cohort given a true response rate of 20% (alternate hypothesis) is 80%. |
| **Statistical Analysis** | All patients registered on the trial will be accounted for in reports of trial outcomes. Baseline patient characteristics will be summarised by cohort (dose level cohorts in the Lead-In Phase and cancer type cohorts in the Expansion Phase) using descriptive statistics and will be reported for continuous variables as number of patients, mean, median, minimum and maximum; and for categorical variables as counts and percentages.<br><br>For the Lead-In Phase, analysis will be focused primarily on adverse events, particularly DLTs reported in the DLT observation period. These will be tabulated descriptively for each dose level cohort separately.<br><br>The majority of the statistical analysis to be performed for this study will take place at the completion of the Expansion Phase.<br><br>**Analysis of the primary endpoint for the Expansion Phase**<br><br>The proportion of patients achieving a CR or PR within the first 24 weeks of treatment will be estimated separately for each cancer type cohort (mCRC and non-CRC) together with 95% confidence intervals (95% CIs) calculated based on exact values of the binomial distribution. The estimates will be calculated for each cohort using the evaluable patient population as defined previously.<br><br>If the observed response rate is high enough to warrant an investigation of associations between patient characteristics and response, exploratory binary logistic regression analyses will be performed. Patient prognostic factors considered will include age, sex, disease characteristics, performance status and previous treatment history.<br><br>**Analysis of secondary endpoints for the Expansion Phase**<br><br>The proportion of patients experiencing clinical benefit lasting until 16 weeks |

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| | after commencement of treatment and corresponding 95% CI will be calculated separately for each cancer type cohort using the evaluable patient populations. Exploratory binary logistic regression analyses investigating associations between patient characteristics and clinical benefit will also be performed if the observed clinical benefit rate is high enough to warrant further investigation.<br><br>The incidence and worst grade of toxicities/adverse events, clinically important new or changed laboratory results and other safety data will be summarised in detail using descriptive statistics for each cancer type cohort. All patients who commenced treatment with vemurafenib and erlotinib will be included in this analysis.<br><br>Time-to-event secondary endpoints of time to progression, progression-free survival and overall survival will be estimated for each cohort separately using the Kaplan-Meier product limit method; annual rates will be calculated along with 95% CIs. The association of patient prognostic factors and time-to-event endpoints will be assessed using the log-rank test and Cox proportional hazards regression models where appropriate. |

# ABBREVIATIONS

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| ADR | Adverse drug reaction |
| AE | Adverse Event |
| ALT (SGPT) | Alanine Aminotransferase (Serum glutamic-pyruvic transaminase) |
| ANC | Absolute Neutrophil Count |
| AST (SGOT) | Aspartate Aminotransferase (Serum glutamic-oxaloacetic transaminase) |
| BaCT | Centre for Biostatistics and Clinical Trials |
| b.i.d | bis in die (Twice a Day) |
| BP | Blood Pressure |
| CI | Confidence interval |
| CR | Complete Response (RECIST Criteria) |
| CRC | Colorectal Cancer |
| CRF | Case Report/Record Form |
| CSR | Case Study Report |
| cuSCC | cutaneous Squamous Cell Carcinoma |
| CT | Computed Tomography |
| ctDNA | Circulating tumour (mutant) DNA |
| CTCAE | Common Toxicity Criteria for Adverse Events |
| CTN | Clinical Trial Notification |
| CYP | Cytochrome P |
| DLT | Dose Limiting Toxicity |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| EGFR | Epidermal Growth Factor Receptor |
| EORTC | European Organisation for Research and Treatment of Cancer |
| EOT | End of Treatment |
| FDG-PET | Fluoro-Deoxy-Glucose-Positron Emission Tomography |
| GCP | Good Clinical Practice |
| Hb | Haemoglobin |
| HR | Heart rate |
| HREC | Human Research Ethics Committee |
| i.v. | Intravenous(ly) |
| IB | Investigator (Drug) Brochure |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonization |
| IEC | Independent Ethics Committee |
| IHC | Immunohistochemistry |
| IRB | Institutional Review Board |
| LDH | Lactate Dehydrogenase |

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| LFT | Liver Function Test |
| LLN | Lower Limit of Normal |
| mCRC | Metastatic Colorectal Cancer |
| MTD | Maximum Tolerated Dose |
| NHMRC | National Health and Medical Research Council Registered Product |
| NSCLC | Non-Small Cell Lung Cancer |
| OD or QD | Once a day or quaque die |
| OS | Overall Survival |
| PBMC | Peripheral Blood Mononuclear Cell |
| PD | Progression of Disease |
| PFS | Progression Free Survival |
| PK | Pharmacokinetics |
| PR | Partial Response (RECIST Criteria) |
| PS | Performance Status |
| RECIST | Response Evaluation Criteria in Solid Tumours |
| SAE | Serious Adverse Event |
| SD | Stable Disease (RECIST Criteria) |
| SMC | Safety Monitoring Committee |
| SOP | Standard Operating Procedure |
| SUSAR | Suspected Unexpected Serious Adverse Drug Reaction |
| TGA | Therapeutic Goods Administration |
| UAE | Unexpected Adverse Event |
| ULN | Upper Limit of Normal |
| WBC | White Blood Cells |

# 1 BACKGROUND INFORMATION

## *1.1 Overview of disease pathogenesis, epidemiology and current treatment*

Colorectal cancer (CRC) is the 2nd leading cause of cancer-related death in the Western population and results in approximately 50,000 deaths annually in the United States (Siegel, 2011). The incidence and mortality has decreased from 1999-2006, which is attributed to improvements in surgical and adjuvant therapy as well as increasing use of screening methods leading to earlier detection. About 20% of patients present with metastatic colorectal cancer (mCRC) and untreated, this group has a median overall survival (OS) of 7 months (Gray, 1980) and with therapy, a 5-year survival rate of 10% (Sanoff et al, 2008).

Approximately 8-12% of patients with metastatic CRCs, and 1.5-2.8% of patients with lung adenocarcinomas, possess the BRAF V600E mutation (Maughan et al, 2011; Souglakos et al, 2009; Bokemeyer et al, 2012; Tveit et al, 2012; Richman et al, 2009; Tran et al, 2011; Yokota et al, 2011; Tie et al, 2011; Sanchez –Torres et al 2013). Approximately 90% of all identified BRAF mutations that occur in human cancer are a T1799A transversion mutation in exon 15, which results in a V600E amino acid substitution (Wan et al, 2004). The V600E mutation accounts for approximately 90% of all activating BRAF mutations in melanoma, >99% in CRC and approximately 55-65% in NSCLC. BRAF mutations are mutually exclusive of RAS mutations. The V600E mutation appears to mimic regulatory phosphorylation and increases BRAF activity approximately 10-fold as compared to wild-type (Davies et al, 2002). Accumulating data demonstrate that the presence of a BRAF- mutation is a poor prognostic factor in CRC, with BRAF-mutation positive CRC demonstrating a more aggressive natural history than either KRAS mutant or KRAS/BRAF wild-type CRC, with a lower overall response rate, reduced progression-free and overall survival (Di Nicolantonio et al, 2008; Laurent-Puig et al, 2009; Maughan et al, 2011; Souglakos et al, 2009; Bokemeyer et al, 2012; Tveit et al, 2012; Richman et al, 2009; Tran et al, 2011; Yokota et al, 2011; Tie et al, 2011). Thus, in these patients, there is a critical need for the development of agents that effectively target this pathway in mCRC.

Efforts to target BRAF-mutant CRC with BRAF inhibitors and MEK inhibitors as monotherapies have not been successful to date (Falchook et al, 2012; Kopetz et al, 2010). The highly selective BRAF inhibitor, vemurafenib (PLX4032), has shown some clinical activity in BRAF mutant mCRC (1/19 partial response and 4 minor responses, median progression free survival 3.7 months) (Kopetz et al 2010). Although there were hints of activity in this heavily pre-treated population, it was clear that there were other factors modifying response to vemurafenib, particularly when put in the context of the ~80% response rate seen in the V600E melanoma population. Unfortunately, there were no prospective translational substudies (such as matched biopsies or functional imaging) conducted in this or other trials of mCRC treated with a BRAF inhibitor to allow us to better understand what the in-vivo resistance mechanisms were.

## *1.2 Overview of vemurafenib*

Vemurafenib is a low molecular weight, orally available, inhibitor of oncogenic BRAF kinase, and is currently approved in many countries for the treatment of BRAF V600 malignant melanoma.

The inhibitory concentration (IC50) of vemurafenib for BRAFV600E kinase is 10 nM. It is 2-fold less potent against CRAF (16 nM) and almost 5-fold less potent against BRAF wild type (39 nM). In a panel of 58 kinases, vemurafenib had an IC50 <1 μM for only 1 kinase (BRK kinase) outside the BRAF family. Also, vemurafenib was screened against 63 receptors in 8 different families. At 10 μM,

vemurafenib showed marginal activity (20% to 24% inhibition) against 4 receptors and was inactive against the other 59 targets.

*In vitro* assessments suggest that the combination therapy of vemurafenib with a MEK inhibitor may restore the sensitivity of vemurafenib resistant tumours to vemurafenib therapy by re-establishing the blockade of the RAF-MEK-ERK pathway.

In several mouse xenograft models of *BRAF*V600E-expressing melanoma (LOX, Colo829 and A375), vemurafenib treatment caused partial or complete tumour regression and improved animal survival in a dose-dependent manner.

The investigator should refer to the RO5185426 (PLX4032); Zelboraf (Vemurafenib) Investigator's Brochure [Roche, Ninth version, January 2013] for detailed information regarding ongoing clinical studies, pharmacokinetics in the target disease populations, as well as observed safety and efficacy findings.

Clinical data show consistent efficacy of vemurafenib as measured by several, pre-defined endpoints in both previously treated and untreated patients with metastatic melanoma positive for the *BRAF*$^{V600}$ mutation identified by the companion diagnostic (Cobas) test. In metastatic CRC, only 1 of 20 evaluable patients in the CRC extension cohort of PLX06-02 experienced a partial response. Seven patients (35.0%) had stable disease and 11 patients (55.0%) had progressive disease. In the Phase I dose escalation cohort of PLX06-02, 3 patients with metastatic thyroid cancer were enrolled and treated. All 3 patients had tumours of papillary histology, and though screening for the V600 BRAF mutation was not required for study entry in the dose escalation cohort, all 3 patients had *BRAF*$^{V600}$ mutation-positive tumours.

Across studies with vemurafenib (NO25026, NP22657 and NP25163), the most common reported treatment-related AEs were rash, arthralgia, fatigue, photosensitivity, liver function abnormalities and QT interval prolongation.

The AE profile of vemurafenib in 21 patients with metastatic CRC treated in the extension phase of PLX06-02 is similar to that observed in patients with metastatic melanoma. All patients experienced at least one AE, the most common (reported in ≥ 30% of patients) of which were fatigue (57.1%), hyperglycemia (42.9%), arthralgia (38.1%), diarrhea (38.1%), hyperbilirubinemia (33.3%), nausea (33.3%), photosensitivity reaction (33.3%), rash (33.3%), and vomiting (33.3%). Grade ≥ 3 study-drug-related AEs were reported in 61.9% of patients, the most common of which was cuSCC (23.8%). Eleven (52.4%) patients had their study treatment interrupted and 4 (19.0%) had at least one dose reduction. Adverse events that led to dose interruption and/or modification for the CRC patients were similar to those reported for patients in the melanoma extension cohort. No CRC patients experienced an AE that led to vemurafenib treatment discontinuation.

A complete safety summary for all ongoing studies is provided in the RO5185426 (PLX4032); Zelboraf (Vemurafenib) Investigator's Brochure [Roche, Ninth version, January 2013]. Please also reference Section 5.4 for additional information on the safety profile and the Intergrated Summary of Safety Information.

## *1.3 Overview of erlotinib*

Tarceva™ (erlotinib hydrochloride; previously known as OSI-774) is an orally active antitumor agent developed for the treatment of non-small cell lung cancer (NSCLC), pancreatic cancer and other solid tumours.

Erlotinib acts through direct and reversible inhibition of the human epidermal growth factor receptor 1/epidermal growth factor receptor (HER1/EGFR, hereafter referred to as EGFR) tyrosine kinase. Erlotinib inhibits human EGFR tyrosine kinase with a 50% inhibitory concentration (IC50) of 2 nM in an in vitro enzyme assay and reduces EGFR autophosphorylation in intact tumour cells with an IC50 of 20. EGFR is overexpressed in a significant proportion of epithelium-derived carcinomas. Erlotinib inhibits the epidermal growth factor (EGF)-dependent proliferation of cells at nanomolar concentrations and blocks cell cycle progression at the G1 phase.

The investigator should refer to the Tarceva™ (erlotinib) ASP5901 Investigator Brochure [Roche, Edition 17, March 2013] for detailed information regarding ongoing clinical studies, pharmacokinetics in the target disease populations, as well as observed safety and efficacy findings.

For single-agent erlotinib, the most common adverse reactions (> 20%) in maintenance treatment were rash-like events and diarrhoea. In second-line NSCLC the most common adverse events (AE) (>20%) were rash, diarrhoea, anorexia, fatigue, dyspnoea, cough, nausea, infection and vomiting. When erlotinib was evaluated in combination with gemcitabine for the treatment of pancreatic cancer, the most common adverse reactions (> 20%) were fatigue, rash, nausea, anorexia, diarrhoea, abdominal pain, vomiting, weight decrease, infection, oedema, pyrexia, constipation, bone pain, dyspnoea, stomatitis and myalgia. In general, patients receiving erlotinib in combination with chemotherapy agents have experienced the same types of AEs as observed with each agent alone.

Laboratory abnormalities are observed infrequently with erlotinib as a single agent. These abnormalities primarily involve changes in liver function tests, including elevation of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and/or bilirubin. These same abnormalities have occasionally been observed in patients receiving erlotinib and concomitant gemcitabine, as well as in patients receiving erlotinib concurrently with carboplatin and paclitaxel. A study comparing the pharmacokinetics of erlotinib in patients with moderately impaired hepatic function with patients with normal hepatic function showed no significant difference in exposure, suggesting that no dose modification is necessary for moderately hepatic-impaired patients.

## *1.4 Rationale*

### 1.4.1 Study Rationale

Recent preclinical studies from Corcoran et al. (2012a) and Prahallad et al. (2012) have shown that BRAF inhibition causes a rapid feedback activation of EGFR that supports continued proliferation of BRAF mutant CRC tumour cells via other pathways, particularly the PI3KCA/AKT pathway. These can be effectively treated by the combination of vemurafenib with anti-EGFR agents such as the small-molecule kinase inhibitor erlotinib, or the monoclonal antibody cetuximab. These reports suggest that activation of EGFR may explain the limited therapeutic effect of BRAF inhibitor monotherapy in patients with BRAF mutant metastatic colorectal cancer. However, these findings confirm that BRAF mutation is a therapeutic target in mCRC strengthening the importance of evaluating the clinical activity of new selective and potent BRAF inhibitors in combination with other targeted agents that inhibit EGFR.

The Bernards group (Prahallad et al, 2012) conducted a detailed exploration of the mechanisms of resistance to vemurafenib in BRAF mutant cell lines using a shRNA screening approach, followed by *in-vitro* combination studies. They showed that ERK, which is normally activated (pERK) in BRAF mutant tumours, regulates production of a phosphatase (CD25c) that in turn negatively regulates

EGFR signalling. Inhibition of pERK with vemurafenib stops that negative regulatory process, leading to rapid activation of EGFR, and therefore continued cell proliferation via multiple other downstream pathways. Interestingly, EGFR activation was not seen in melanoma cell-lines treated with vemurafenib, using the same experimental approach, providing further evidence that BRAF mutant CRC is functionally different to melanoma. The use of an EGFR inhibitor with vemurafenib effectively abrogated this resistance mechanism. In these studies, both EGFR antibodies (cetuximab) and small molecules (erlotinib) proved effective as combinations indicating that the activation of the EGFR pathway was ligand-dependent. In a clinical context, erlotinib is a standard of care for the treatment of NSCLC in EGFR mutant tumours in the first line, and in EGFR untested tumours in second and third line, whilst cetuximab remains a standard of care in KRAS WT metastatic CRC. Although erlotinib has not been extensively trialled in CRC, early studies with erlotinib have shown some level of activity, especially KRAS wild-type tumours in combination with cetuximab (DUX), but given the successful development of cetuximab and panitumumab this was not taken forward in any meaningful way. Of note, these studies were conducted in the era prior to our understanding of the importance of KRAS mutations as a negative prognostic marker and the presence of EGFR ligands as positive predictive markers. Erlotinib oral administration also confers an advantage in a combination trial with another oral agent given the ease of administration for patients. Given this background, it would be reasonable to use erlotinib as the EGFR inhibitor in this planned combination trial. Of note, other combination trials are being planned internationally, combining BRAF inhibitors (including vemurafenib or dabrafenib) with cetuximab. These data will collectively provide important guidance on the clinical activity of such combinations.

Clinically, Corcoran et al (2012b) have provided additional data suggesting that response to BRAF inhibitors in mCRC could be modulated by other factors. The combination of the BRAF inhibitor dabrafenib (GSK2118436) and MEK inhibitor, trametinib (GSK1120212), was reported to have anti-tumour activity in patients with BRAF mutant mCRC (3/26 partial response and 4 minor responses; Corcoran et al 2012b). However, this level of anti-tumour activity needs to be put into perspective when compared to results in melanoma [significant tumour shrinkage (confirmed response rates of >50%), prolonged progression free survival and improvements in overall survival; (Chapman et al, 2011; Flaherty et al, 2012; Hauschild et al, 2012), and it is unlikely that these results will prove compelling enough to test the BRAK/MEK inhibitor combination in a larger clinical trial.

Reinforcing its role as an oncogene, lung-specific expression of V600E BRAF in mice leads to the development of lung cancers with bronchioalveolar carcinoma features similar to those observed in patients. Deinduction of transgene expression led to dramatic tumor regression, paralleled by dramatic dephosphorylation of ERK1/2, implying a dependency of BRAF-mutant lung tumors on the MAPK pathway. The growth of these tumors was dependent on persistent oncogene expression, suggesting that mutant BRAF may also be necessary for maintenance (Ji et al, 2007). BRAF V600E – mutant, but not other BRAF mutant, adenocarcinoma cell lines were selectively sensitive to MEK inhibition leading to apoptosis, but were resistant to EGFR inhibition (Pratilas et al, 2008). There are single case reports of patients with BRAF V600E mutant lung adenocarcinoma with clinical and metabolic response to vemurafenib (Gautschi et al, 2012, Peters et al, 2013).

The EViCT study is therefore designed to test the hypothesis that the combination of a BRAF inhibitor (vemurafenib) with an EGFR inhibitor (erlotinib) will result in clinically meaningful anti-tumour activity for metastatic BRAF-mutant CRC. This study will include the evaluation of the safety of the combination, as well as a preliminary assessment of clinical activity.

### 1.4.2 Dose Rationale

This study will evaluate the safety and efficacy of the doublet vemurafenib/erlotinib combination in subjects with BRAF V600E mutant metastatic or advanced tumours. Lead-In Phase includes a 3+3 dose escalation that will identify tolerable combination doses for the combination in metastatic CRC. The safety and efficacy of the tolerable combination dose will be evaluated in the Dose Expansion Phase.

### 1.4.3 Potential for Drug-Drug Interactions

Based on *in vitro* data, vemurafenib is a substrate of CYP3A4. Results from an *in vivo* drug-drug interaction study in patients with cancer demonstrated that vemurafenib is a moderate CYP1A2 inhibitor, a weak CYP2D6 inhibitor and a CYP3A4 inducer. Erlotinib is metabolized in the liver primarily by CYP3A4 and to a lesser extent by CYP1A2, and the pulmonary isoform CYP1A1. Hence, there is a potential for increased erlotinib exposure when administered concomitantly with vemurafenib due to CYP3A4 induction. Therefore, erlotinib starting dose will be 100 mg daily, which is lower than the recommended monotherapy dose in NSCLC (see section 1.4.5). Vemurafenib is not expected to affect erlotinib clearance; neither via inhibition of the target-mediated clearance pathway nor through inhibition of protein catabolism. Although BRAF inhibitors have been demonstrated to activate the EGFR pathway, this activation is believed to be mediated by increased phosphorylation of EGFR (Prahallad et al 2012). In summary, there is a low expectation of clinically relevant pharmacokinetic drug-drug interactions between vemurafenib and erlotinib.

### 1.4.4 Potential for Overlapping Toxicities

The safety profile of both vemurafenib and erlotinib is well characterized. Rash, fatigue, diarrhoea, nausea and vomiting are common adverse reactions (greater than 20% of patients) observed after administration of either vemurafenib or erlotinib. However, diarrhoea is the only potentially severe toxicity seen with either agent. Although skin rash is a potentially severe toxicity seen with either agent, the type of rash seen is actually very different, and although this will need to be monitored closely, is unlikely to be truly overlapping and therefore additive in its severity. In addition, there is a potential small risk for dry skin, erythema, palmar-plantar erythrodysesthesia, folliculitis, musculoskeletal pain, weakness, weight loss, fever, back pain, dizziness, constipation, GGT increase, bilirubin increase and creatinine increase both with vemurafenib and erlotinib.

Overlapping toxicities for the proposed dual combination may potentially be dose-limiting and will be monitored according to Section 3.1.1 and Section 6.7.1.

### 1.4.5 Rationale for starting dose and regimen selection

#### Phase I Lead-In phase

The maximum tolerated dose (MTD)/recommended Phase 2 regimen of vemurafenib plus erlotinib will be defined first in Lead-In phase. The starting dose for the dual combination study drugs is 960 mg twice daily (BID) for vemurafenib and 100 mg daily for erlotinib. Vemurafenib starting dose is the clinically recommended dose for unresectable stage IIIC or stage IV metastatic melanoma positive for a BRAF V600 mutation. Erlotinib starting dose is the recommended dose for pancreatic cancer in combination with gemcitabine, which is lower than the recommended monotherapy dose in NSCLC. These doses are clinically active with manageable toxicity with prolonged dosing and the potential

for overlapping toxicities appears relatively low. However, if unexpected toxicities are observed in dose level D1, subjects will be enrolled in dose level D-1, in which the dose of vemurafenib will be reduced to 720 mg BID. (Additional details regarding dose escalation are provided in Section 3.1.1.1).

#### Phase II Dose Expansion phase

The optimal safe dose combination defined in the Lead-In phase will be brought forward into the Dose Expansion phase. This will likely be the maximal dose from the Lead-In phase for the combination, although a lower dose combination may be selected if significant delayed or prolonged toxicities require frequent dose modifications. In the Dose Expansion phase, approximately 24 subjects with BRAF-mutation V600E positive metastatic CRC (including the 6 subjects enrolled at this dose in Lead-In phase) will be enrolled to confirm safety and to generate signals of activity.

### *1.5 EVICT and metastatic or/advanced lung adenocarcinoma and other tumours with BRAF V600E mutation*

Since advanced-stage NSCLC is currently considered an incurable disease for which standard chemotherapy provides marginal improvement in overall survival at the expense of substantial morbidity and mortality, and because of the case reports of clinical benefit in patients with BRAF V600E mutant lung adenocarcinoma (Gautschi et al 2012, Peters et al 2013), we will also include 10 BRAF V600E mutant advanced or metastatic lung adenocarcinoma or non-colorectal cancer patients in the exploratory cohort of the Dose Expansion phase in order to explore the safety and clinical efficacy of the combination.

This study will therefore provide an opportunity to explore, albeit in a limited capacity, the activity of this combination in other cancer types with the BRAF V600E mutation.

# 2 TRIAL OBJECTIVES AND ENDPOINTS

## *2.1 Hypothesis*

It is hypothesised that the combination treatment of vemurafenib and erlotinib will be safe and will show a sufficient level of activity in patients with BRAF V600E mutant advanced or metastatic cancers to warrant further investigation in later phase trials.

## *2.2 Objectives*

### 2.2.1 Primary Objectives

**Phase I Lead-In Phase**

- To determine the safety of the combination of vemurafenib and erlotinib in the first 4 weeks of treatment in BRAF V600E mutant metastatic CRC and identify the dosing regimen to be evaluated in Phase II.

**Phase II Dose Expansion**

- To evaluate the clinical efficacy of the combination of vemurafenib and erlotinib in BRAF V600E mutant metastatic CRC as measured by the proportion of patients achieving a complete or partial response (CR or PR) within the first 24 weeks of treatment.

### 2.2.2 Secondary Objectives

- To evaluate the clinical efficacy of the combination of vemurafenib and erlotinib in BRAF V600E mutant advanced or metastatic cancers (lung adenocarcinoma and other) as measured by the proportion of patients achieving a complete or partial response (CR or PR) within the first 24 weeks of treatment.
- To evaluate other measures of clinical efficacy of the combination of vemurafenib and erlotinib in the two patient groups (mCRC, lung adenocarcinoma and other) including: the clinical benefit rate at 16 weeks after treatment commencement (CR, PR and SD), time to progression, progression-free survival and overall survival.
- To determine the safety of the combination of vemurafenib and erlotinib over the course of treatment within each of the two patient groups (mCRC, lung adenocarcinoma and other).

### 2.2.3 Exploratory Objectives

- To explore the pharmacodynamic effects of BRAF/EGFR inhibition using pre-treatment, 4 weeks and on progression disease FDG-PET in each patient group (optional for patients with cancer other than CRC and lung adenocarcinoma).
- To explore the pharmacodynamic effects of BRAF/EGFR inhibition using (optional) paired tumour biopsies (pre-treatment and 14 days) or hair follicle plucks in each patient group (optional).
- To evaluate changes in circulating biomarkers including ctDNA, serum chemokine/cytokine mRNA profiles and immune function in PBMCs; with BRAF/EGFR inhibition and how these correlate with response.

## *2.3 Endpoints*

### 2.3.1 Primary Endpoint

**Phase I Lead-In Phase**

- The incidence of dose-limiting toxicities reported within the first 4 weeks of treatment with the combination of vemurafenib and erlotinib. Dose-limiting toxicities are defined in Section 3.1.1.2.

**Phase II Dose Expansion**

- The achievement of a complete response (CR) or partial response (PR) as defined by Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 within the first 24 weeks of treatment with the combination of vemurafenib and erlotinib.

### 2.3.2 Secondary Endpoints

Secondary endpoints of interest include the following:

- Clinical benefit as defined by: (i) achievement of a complete or partial response (CR or PR) during the first 16 weeks of treatment with the combination of vemurafenib and erlotinib; or (ii) maintenance of stable disease (SD) until 16 weeks after commencement of treatment according to RECIST v1.1 guidelines.
- Time to progression measured from the date of commencement of treatment with the combination of vemurafenib and erlotinib until disease progression. Time to progression for patients who die without prior disease progression will be censored at the date of death. Patients who have not progressed or died by the study close-out date will be censored at this date. Patients who are not known to have progressed or died and who are lost to follow-up before the close-date will be censored at the date they were last known to be alive and progression-free.
- Progression-free survival (PFS) measured from the date of commencement of treatment with the combination of vemurafenib and erlotinib until disease progression or death prior to progression from any cause. Patients who have not progressed or died by the study close-out date will have their progression-free survival time censored at this date. Patients who are not known to have progressed or died and who are lost to follow-up before the close-out date will have their progression-free survival time censored at the date they are last known to be alive and progression-free.
- Overall survival (OS) measured from the date of commencement of treatment with the combination of vemurafenib and erlotinib until death from any cause. Patients who have not died by the study close-out date will have their overall survival time censored at this date. Patients who are not known to have died and who are lost to follow-up before the close-out date will have their overall survival time censored at the date they were last known to be alive.
- Frequency and worst grade of adverse events according to CTCAE v4.03, withdrawal due to unacceptable toxicity.

A summary of the time to event endpoint definitions is provided in the table below.

| Endpoint | Relevant patient subset | Start date | Event(s) | Censoring events* |
|---|---|---|---|---|
| Time to progression | All patients who commence treatment | Date of treatment commencement | Progression | Death from any cause |
| Progression-free survival | All patients who commence treatment | Date of treatment commencement | Progression<br>Death from any cause | None |
| Overall survival | All patients who commence treatment | Date of treatment commencement | Death from any cause | None |

** in addition to the close-out date, withdrawal of consent and loss to follow-up.*

A study close-out date will be determined at the time of analysis in order to minimise the bias in reporting of time to event endpoints. This will generally be taken to be the earliest of the dates of last contact of the patients who are still alive and being followed-up. Thus with the exception of any patients who have been lost to follow-up, the status of all patients in the study should be known at this date.

### 2.3.3 Exploratory Endpoints

#### 2.3.3.1 Imaging Studies

Target inhibition will be evaluated with fluoro-deoxy-glucose-positron emission tomography (FDG-PET). Scans performed pre-treatment, at 4 weeks and at disease progression in all patient groups (compulsory for CRC and lung adenocarcinoma patients and optional for other cancer patients).

#### 2.3.3.2 Exploratory Tissue Studies

Tumour Tissue:

1) Archival Tissue (In all patients)
    - Analysis of mutations in related pathways including PIK3CA, PTEN, KRAS and NRAS
    - Microsatellite instability or MMR status
    - Expression determined by IHC including EGFR, copy number by ISH
2) Paired Biopsy Cohort (optional, in selected patients): biopsies at pre-treatment, 14 days (2 weeks) and at disease progression will be conducted. Assays for pathway activation/inhibition including pEGFR, pAKT, pS6, pPRAS40, pERK by IHC using validated antibodies and where possible by other methods (eg. Western, reverse phase protein arrays, multiple reaction monitoring) will be performed.
3) Paired Eyebrow hair follicle plucks (optional, in selected patients): eyebrow hair follicles will be plucked pre-treatment and on Day 14. Assays for pathway activation/inhibition including pEGFR, pAKT, pS6, pPRAS40, pERK by IHC using validated antibodies and where possible by other

methods (eg. Western, reverse phase protein arrays, multiple reaction monitoring) will be performed.

Circulating Biomarkers

Blood will be collected baseline, Week 2, 4, 8 and then every 8 weeks thereafter and at disease progression for the purposes of evaluating changes in circulating biomarkers including:

- Circulating Tumour DNA (ctDNA).
- Serum samples will be analysed for their microRNA profile using Nanostring and their cytokine/chemokine profile using Cytometric Bead Array.
- PBMCs will be analysed using flow cytometry and in vitro assays for the effect of treatment on the patient's immune profile and immune function.
- BRAF/EGFR inhibition and how these correlate with response.

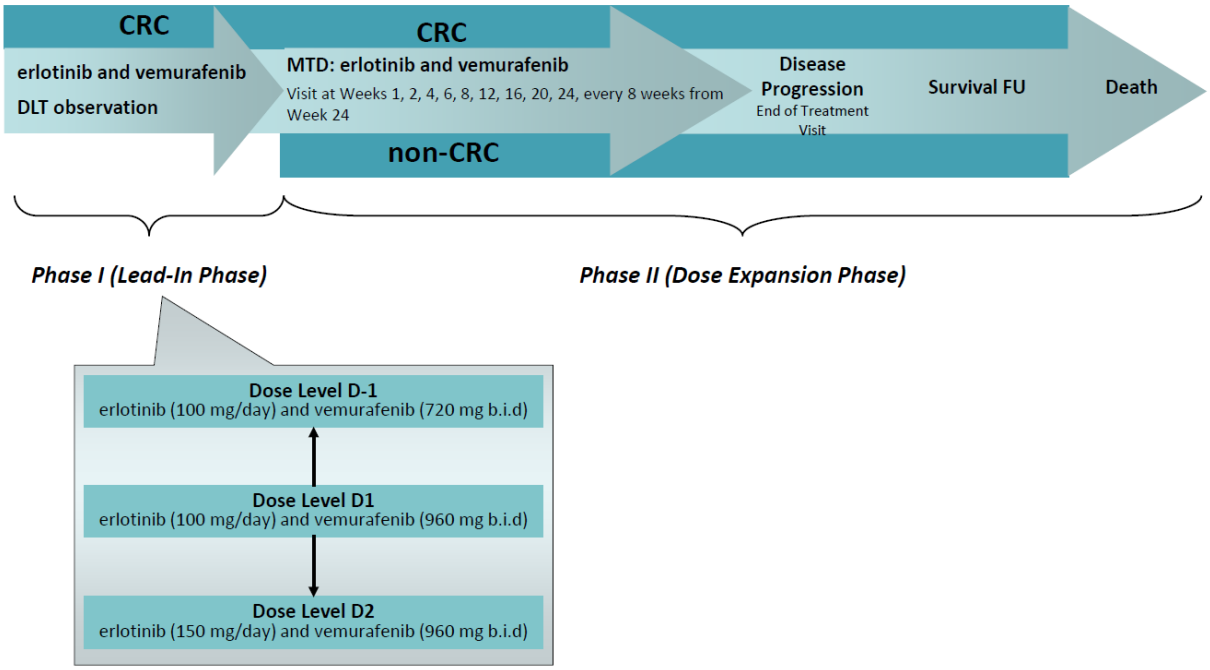
# 3 TRIAL DESIGN

## *3.1 Design*

The study will investigate the safety and efficacy of the combination treatment of vemurafenib and erlotinib in BRAF V600E mutant metastatic tumours. There will be two phases of the study, a Lead-In Phase and an Expansion Phase. The initial Lead-In Phase) will be conducted to establish the safety of the combination treatment of vemurafenib and erlotinib in patients with BRAF V600E mutant metastatic CRC. The Expansion Phase will commence after the Maximum Tolerated Dose (MTD) has been determined in order to investigate the efficacy of the combination treatment in patients with BRAF V600E mutant metastatic CRC and also in an exploratory cohort of patients with BRAF V600E mutant metastatic/advanced cancers (lung adenocarcinoma and other).

A diagram of the study design is provided in Schema 1.

**Schema 1: Overview of the Study**




### 3.1.1 Phase I Lead-In Phase

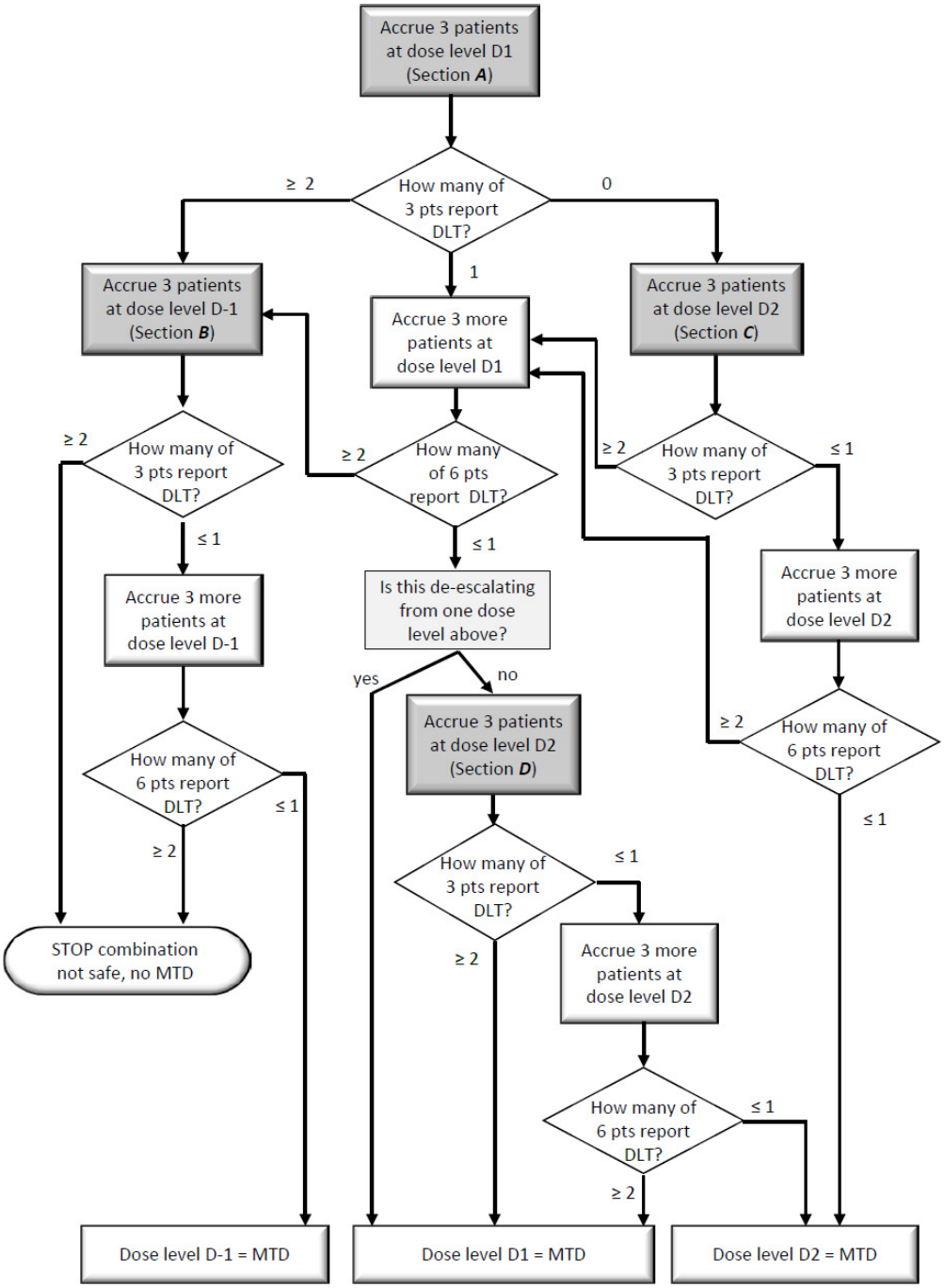
Only patients with BRAF V600E mutant metastatic CRC will be considered in the Phase I Lead-In Phase. The first dose to be evaluated will be Dose level 1 (960mg b.i.d and erlotinib (100 mg/day)).

A series of cohorts of 3 patients will be treated with both agents and observed for toxicity for a minimum of 4 weeks. This will be defined as the Dose Limiting Toxicity (DLT) observation period.

After each cohort of 3 patients completes the DLT observation period, a clinical synthesis of the available toxicity information (including DLTs, adverse events that are not DLTs, and adverse events post the DLT observation period), will be reviewed by the Safety Monitoring Committee (SMC) (see Section 8.3) and will be used to determine the dose regimen for the next cohort of 3 patients at a Lead-In Phase teleconference. Further details of the criteria for the Lead-In Phase and the determination of the MTD are provided in Schema 2 and Section 3.1.1.1.

Following the 4 week DLT-observation period, patients not experiencing a DLT will continue with treatment until disease progression after which time they will be followed for survival only.

**Schema 2: Phase I Dose Escalation/De-escalation**



#### 3.1.1.1 Dose Escalation/De-escalation:

The following (and Schema 2) describes the dose escalation and de-escalation rules that are to be applied in this study.

***A) For patients enrolled at dose level D1 (erlotinib (100 mg/day) and vemurafenib (960 mg b.i.d))***

- If 0/3 patients report a DLT within the observation period then a second cohort will be opened at dose level D2 starting immediately (see ***Section C*** below).
- If 1/3 patients report a DLT within the observation period then a further 3 patients will be enrolled at the current dose level D1.
  - If 1/6 patients report a DLT within the observation period then a new pilot cohort of three patients will be enrolled at dose level D2 (see ***Section D*** below).
  - If ≥2/6 patients report a DLT within the observation period then a new pilot cohort of three patients will be enrolled at dose level D-1 (see ***Section B*** below).
- If ≥2/3 patients report a DLT within the observation period then a new pilot cohort of three patients will be enrolled at dose level D-1 (see ***Section B*** below).

***B) For patients enrolled at dose level D-1 (erlotinib (100 mg/day) and vemurafenib (720 mg b.i.d))***

- If ≤1/3 patients report a DLT within the observation period then a further 3 patients will be enrolled at the current dose level D-1.
  - If ≤1/6 patients report a DLT within the observation period then the current dose level (D-1) will be declared the MTD and the Phase II Expansion Phase of the study will commence at dose level D-1.
  - If ≥2/6 patients report a DLT within the observation period then the study will be stopped and no MTD will be confirmed.
- If ≥2/3 patients report a DLT within the observation period then the study will be stopped and no MTD will be confirmed.

***C) For patients enrolled at dose level D2 (erlotinib (150 mg/day) and vemurafenib (960 mg b.i.d))***

- If ≤1/3 patients report a DLT within the observation period then a further 3 patients will be enrolled to the current dose level D2.
  - If ≤1/6 patients report a DLT within the observation period then the current dose level D2 will be declared the MTD and the Phase II Expansion Phase of the study will commence at dose level D2.
  - If ≥2/6 patients report a DLT within the observation period then a further 3 patients will be enrolled at dose level D1.
    - If ≤1/6 patients report a DLT within the observation period then the current dose level D1 will be declared the MTD and the Phase II Expansion Phase of the study will commence at dose level D1.
    - If ≥2/6 patients report a DLT within the observation period then a new pilot cohort of

three patients will be enrolled at dose level D-1 (see ***Section B*** above).

- If ≥2/3 patients report a DLT within the observation period then a further 3 patients will be enrolled at dose level D1.
  - If ≤1/6 patients report a DLT within the observation period then the current dose level D1 will be declared the MTD and the Phase II Expansion Phase of the study will commence at dose level D1.
  - If ≥2/6 patients report a DLT within the observation period then a new pilot cohort of three patients will be enrolled at dose level D-1 (see ***Section B*** above).

***D) For patients enrolled at dose level D2 (erlotinib (150 mg/day) and vemurafenib (960 mg b.i.d))and this is escalation from dose level D1***

- If ≤1/3 patients report a DLT within the observation period then a further 3 patients will be enrolled to the current dose level D2.
  - If ≤1/6 patients report a DLT within the observation period then the current dose level D2 will be declared the MTD and the Phase II Expansion Phase of the study will commence at dose level D2.
  - If ≥2/6 patients report a DLT within the observation period then the dose level D1 will be declared the MTD and the Phase II Expansion Phase of the study will commence at dose level D1.
- If ≥2/3 patients report a DLT within the observation period then the dose level D1 will be declared the MTD and the Phase II Expansion Phase of the study will commence at dose level D1.

#### 3.1.1.2 Dose-Limiting Toxicity

Clinically relevant toxicities will be those assessed as unrelated to disease, disease progression, intercurrent illness, or concomitant medications. These will be evaluated according to CTCAE v4.03.

A dose-limiting toxicity (DLT) is defined as an adverse event or abnormal laboratory value assessed ***as unrelated to*** disease progression, intercurrent illness, or concomitant medications but considered by the investigator ***to be related to study treatment*** that meets any of the following criteria in Table 1.

For the purpose of dose escalation/de-escalation decisions, only DLTs occurring during the DLT assessment window (Days 1 through 28) will be considered.

#### 3.1.1.3 Definition of DLT-evaluable patients

DLT-evaluable patients will be defined as all eligible patients registered in the Lead-In Phase who commence treatment with the combined regimen at the dose level to which they were accrued and who either: (i) experiences a DLT during the observation period; or (ii) receives at least 21 days of treatment during the observation period (28 days) without experiencing a DLT. Patients who do not receive at least 21 days of treatment during the observation period (28 days) for reasons other than treatment related toxicity, cease treatment or withdraw from the study for reasons unrelated to study treatment prior to completion of the DLT observation period will not be evaluable and will therefore be replaced in that cohort.

#### 3.1.1.4 Maximum Tolerated Dose

The MTD is defined to be the highest dose level for which no more than 1 of the 6 treated patients in the first 28 days of protocol treatment exhibits a DLT.

There will be no intrapatient dose escalation.

### 3.1.2 Phase II Dose Expansion

Once the MTD combination has been determined in the Lead-in Phase, two expansion cohorts will open in parallel as follows:

a) mCRC Expansion Cohort

b) non-CRC Exploratory Expansion Cohort which includes the following patient populations:

- Advanced/metastatic lung adenocarcinoma with a documented BRAF V600E mutation and EGFR and KRAS wild type
- Metastatic Thyroid Cancer with a documented BRAF V600 mutation
- Any other metastatic malignancy with a documented BRAF V600E mutation following discussion with and approval from the Safety Monitoring Committee (SMC)

The MTD determined in Lead-In Phase will be used in the Phase II Dose Expansion.

**Table 1 Criteria for defining dose-limiting toxicities**

| Organ system | Any of the following criteria |
|---|---|
| **Cardiac** | Grade ≥ 3 QTc prolonged (QTc ≥ 501ms) |
| **Digestive** | Gastrointestinal perforation<br>Grade 3 diarrhea lasting for ≥ 48 hours despite the use of optimal anti-diarrhoea therapy |
| **Hepatic** | Grade ≥ 3 total bilirubin or hepatic transaminase (ALT or AST) |
| **Haematology** | Grade ≥ 3 febrile neutropenia |
| | Grade ≥ 4 neutropenia |
| | Grade ≥ 4 thrombocytopenia |
| | Grade ≥ 4 anemia |
| **Skin** | Grade ≥ 3 Steven-Johnson syndrome<br>Grade 4 toxic epidermal necrolysis |
| **Other adverse events** | Other grade ≥ 3 non-hematologic, non-hepatic organ toxicity, excluding the following:<br>○ Grade 3 nausea or vomiting, that resolves to Grade ≤ 1 within 7 days of appropriate supportive therapy.<br>○ Grade 3 rash that resolves to Grade ≤ 2 within 7 days with appropriate supportive therapy.<br>○ Grade 3 photosensitivity that resolves to Grade ≤ 2 within 7 days with appropriate supportive therapy.<br>○ Grade ≥ 3 fatigue that resolves to Grade ≤ 2 within 7 days<br>○ Grade ≥ 3 uricemia that resolves to Grade ≤ 2 within 7 days<br><br>Note:<br>An AE must be clinically significant to be defined as a DLT: study drug-related fever, alkaline phosphatise elevation, electrolyte abnormalities (including K, NA, Cl, HCO3, Mg, Ca, PO4) will not be considered a DLT unless clinically significant.<br>Grade 3 cuSCC is a well described on-target effect of BRAF inhibitors including vemurafenib and will not be considered a DLT. |
| *CTCAE version 4.03 will be used for all grading. The toxicity grades for laboratory parameters most relevant to this study are summarized in Appendix 4.*<br>*Patients may receive supportive care as per local institutional guidelines.* | |

All DLTs must be reported by completing the Trial DLT form and FAXING it to the Trial Centre (BaCT, +61 3 9656 1420) ***within 24 hours*** of knowledge.

#### 3.1.2.1 CRC Expansion Cohort

The mCRC expansion cohort will follow Simon's optimal two-stage design. The study is designed to distinguish a favourable response rate of ≥ 20% from a null (uninteresting) rate of ≤ 5% and will allow early stopping if there is no strong evidence suggesting that the treatment combination of vemurafenib and erlotinib is active.

##### 3.1.2.1.1 Definition of evaluable patients

Evaluable patients will be defined as all registered, eligible patients who commence treatment with the combined regimen of vemurafenib and erlotinib at the MTD defined in the Lead-In Phase. The 6 patients treated with the MTD in the Lead-In Phase will also comprise the first 6 patients in the mCRC expansion cohort.

#### 3.1.2.2 Non-CRC Exploratory Expansion Cohort

The non-CRC exploratory expansion cohort will be enrolled on the study in a single stage. Evaluable patients will be defined as all registered, eligible patients who commence treatment with the combined regimen of vemurafenib and erlotinib at the MTD defined in the Lead-In Phase.

Patients in both cohorts of the Expansion Phase will remain on treatment until disease progression after which time they will be followed for survival only. The expected time to progression is 6 months and the expected additional survival time is 12 months; therefore each patient is expected to be on study for approximately 18 months.

There will also be an **exploratory substudy** of patients (CRC and non CRC) who have disease available for matched pre and post-treatment biopsies to enable analysis of key regulators of the BRAF and EGFR signalling pathway inhibited by erlotinib/vemurafenib combination. This subgroup will allow for matched biopsies on selected patients, but not solely limited to entry criteria and therefore not necessarily affecting the efficacy outcomes.

### *3.2 Total Participant Accrual*

The estimated sample size for the trial is:

- 6 – 18 mCRC patients in the Lead-In Phase and up to 18 additional mRC patients in the Expansion Phase that bring up to 24-36 mCRC patients for the whole study
- 10 metastatic non-colorectal cancer patients in the exploratory cohort of the Expansion Phase with a focus on patients with advanced/metastatic lung adenocarcinoma.

Recruitment to the two cohorts will run in parallel when the Expansion Phase commences. Patients will be recruited from 8 sites with an overall expected accrual rate of 2 patients per month. The recruitment period is therefore expected to be approximately 24 months.

## 4 PARTICIPANT SELECTION

Patients may be included in the trial (**either Phase I or Phase II**) only if they meet all of the following inclusion and exclusion criteria. No exceptions, waivers or exemptions will be granted.

### *4.1 Inclusion Criteria*

1. Male or female patients ≥ 18 years of age at the time of study entry.
2. All patients must have histological or cytological confirmed metastatic colorectal cancer with a BRAF V600E mutation of their primary cancer or related metastases. Patients with other tumour

types with a proven BRAF V600E mutation can be considered for enrolment into the Expansion Phase exploratory cohort with the permission of the Study Chair.

3. Patients with BRAF V600E mCRC are permitted to have had a maximum of 2-lines of therapy for metastatic disease. A maintenance strategy post 1st-line treatment is not considered as an additional line of therapy, nor is rechallenge with oxaliplatin. Patients with lung adenocarcinoma are required to have received prior treatment with a platinum doublet. There is no requirement for previous treatment for other tumour types.
4. All patients must have measurable disease per RECIST 1.1 criteria (see Appendix 5).
5. A tumour paraffin tissue block or 20 - 30 unstained slides from the tumour tissue block must be available for the purpose of biomarker and predictive marker analyses. Obtaining archived tumour material or unstained slides from an archived tumour block will suffice to meet this requirement. The availability of the tumour tissue block must be confirmed at screening for a patient to be considered eligible. If no tissue block and fewer than 20 unstained slides are available, eligibility must be confirmed with the Study Chair or delegate (see Section 6.7.3.3).
6. ECOG performance status 0 to 1 inclusive (see Appendix 1).
7. Participants must have adequate organ and marrow function as defined below:
    - Absolute neutrophil count ≥ 1.5 x $10^9$/L
    - Platelets ≥ 100 x $10^9$/L
    - ALT and AST ≤ 2.5 x upper limit of normal (ULN), or ≤ 5 x ULN if liver metastases are present
    - Total serum bilirubin ≤ 1.5 x ULN
    - Serum creatinine ≤ 1.5 x ULN, **or** creatinine clearance > 50mL/min
8. Participants must be suitable for oral drug administration.
9. Life expectancy > 3 months.
10. Female patients of childbearing potential (see below) must:

    d) Be on highly effective contraception. Highly effective contraception methods include:

    - total abstinence, or
    - sterilisation (see below), or
    - combination of any two of the following (a+b, or a+c, or b+c):
        - Use of oral, injected or implanted hormonal methods of contraception. Hormonal contraceptives include any marketed contraceptive agent that includes an oestrogen and/or a progestin.
        - Placement of an intrauterine device (IUD)
        - Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/cream/ vaginal suppository

    e) Have a negative serum or urine pregnancy test performed within the 7 days before start of treatment.

    f) Highly effective contraception for females of child bearing potential must be maintained throughout the study and for 6 months after study drug discontinuation.

11. Female patients **not** of child-bearing potential. Women are considered **not** of child bearing potential if they have had either:

    - 12 months of natural (spontaneous) amenorrhoea with an appropriate clinical profile (eg. age appropriate, history of vasomotor symptoms), or
    - A surgical bilateral oophorectomy (with or without hysterectomy), or
    - Tubal ligation at least 6 weeks ago.

    In the case of unilateral oophorectomy alone, a woman is considered not of child-bearing potential *only* once the reproductive status has been confirmed by follow up hormone level assessment.

12. Sexually active males must use a condom during intercourse while taking the drug and for 6 months after stopping treatment and should not father a child in this period. A condom is required to be used also by vasectomised men in order to prevent delivery of the drug via seminal fluid.

13. Absence of any psychological, familial or sociological condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before trial entry.

14. Ability to understand and the willingness to sign a written informed consent. Before study entry, written informed consent must be obtained from patient prior to performing any study-related procedures.

## *4.2 Exclusion criteria*

1. Active CNS lesions are excluded (i.e. those with radiographically unstable, symptomatic lesions). Patients treated with stereotactic therapy or surgery are eligible if patient remains without evidence of disease progression within the CNS ≥ 1 month. Previous whole brain radiotherapy is not allowed with the exception of patients who have had definitive resection or stereotactic therapy of all radiologically detectable parenchymal lesions.

2. History of or known spinal cord compression, or carcinomatous meningitis.

3. Patients who have had any systemic cytotoxic/biologic or investigational therapies within 4 weeks prior to study entry or who have not recovered from the side effects of such earlier therapy.

4. Previous malignancies within the past 5 years are excluded except for adequately treated carcinoma in-situ of the cervix. Isolated elevation in PSA in the absence of radiographic evidence of metastatic prostate cancer is allowed.

5. Participants who have had radiotherapy and/or major surgery within 2 weeks prior to study entry.

6. Anticipated or concurrent use of any other anti-cancer therapies or study agents.

7. Clinical significant cardiac disease including any of the following:

    a. unstable angina,
    b. symptomatic or otherwise uncontrolled arrhythmia requiring medication (does not include stable, lone atrial fibrillation),

c. QTcF > 480 msecs (See Appendix 2 for Fridericia's correction formula) or a history of congenital long QT syndrome,
d. uncontrolled hypertension,
e. symptomatic congestive heart failure (NYHA II, III, IV, See Appendix 3),
f. myocardial infarction ≤ 6 months prior to first study treatment,
g. serious uncontrolled cardiac arrhythmia

8. Patients with active uncontrolled infection.
9. Known history of human immunodeficiency virus (HIV) infection.
10. Known history of active hepatitis B or C.
11. Other severe, acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration, or may interfere with the interpretation of study results, which in the judgment of the investigator would make the patient inappropriate for entry into this study.
12. Patients who are receiving treatment with medications known to be strong CYP3A4 inhibitors within 7 days before starting treatment with erlotinib and vemurafenib or strong inducers of CYP3A4 within 14 days before starting treatment with erlotinib and vemurafenib.

    A comprehensive list of inhibitors, inducers and substrates may be found at http://medicine.iupui.edu/flockhart/table.htm.
13. Nursing (lactating) women.
14. Severe hypersensitivity to any of the study drugs, study drug classes, or excipients in the formulation of either erlotinib or vemurafenib (see section 5).
15. Patients with EGFR mutant lung adenocarcinoma.

# 5 INVESTIGATIONAL DRUG AND TREATMENT SCHEDULE

Confidential pharmaceutical information for erlotinib and vemurafenib is provided in the Investigator Brochures.

## *5.1 Formulation, Appearance, Storage and Handling*

- **Erlotinib:**

Ingredients: Tarceva® (erlotinib) tablets for oral administration are available in 3 dosage strengths containing erlotinib hydrochloride (27.3 mg, 109.3 mg and 163.9 mg) equivalent to 25 mg, 100 mg and 150 mg erlotinib and the following inactive ingredients: lactose monohydrate, hypromellose, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate and titanium dioxide. The tablets also contain trace amounts of color additives, including FD&C Yellow No. 6 (25 mg only) for product identification.

Appearance: Tablets are *bi*convex and will have "Tarceva [dose in mg]"and a logo in brownish yellow on one side.

Storage and Handling: Erlotinib tablets are supplied for clinical trials in blister packs and should be stored below 30°C.

- **Vemurafenib:**

Ingredients: Zelboraf® (vemurafenib) tablet for oral administration is available as 240 mg film-coated tablets for oral administration in adults containing vemurafenib and the following inactive ingredients: croscarmellose sodium, colloidal anhydrous silica, magnesium stearate, and hydroxypropylcellulose.

Appearance: Film coated 240 mg tablets are oval, biconvex, pinkish white to orange white tablets with 'VEM' engraved on one side.

Storage and Handling: Vemurafenib tablets are supplied in packages of 56 tablets (7 blisters of 8 tablets) and should be stored below 30°C.

## *5.2 Administration*

The investigator needs to instruct the patient to take the study drug as per protocol. Treatment duration is well described in Section 6.4. All doses prescribed and dispensed to the patient and all dose changes or interruptions must be recorded in the dosage administration record CRF, as appropriate.

Erlotinib and vemurafenib should be taken as follows:

Patients should be instructed to take their once-a day dose (erlotinib) and twice-a day dose (vemurafenib) at approximately the same time every day.

Each daily dose of erlotinib and vemurafenib should be taken with a glass of water and consumed over as short a time as possible (e.g. 1 tablet every 2 minutes)

Patients should be instructed to swallow tablets whole and to not chew or crush.

Both erlotinib and vemurafenib should be taken either 1 hour before or 2 hours after a meal. As vemurafenib will be given twice a day, the second dose of vemurafenib should be taken in the evening approximately 12 hours later.

Patients must avoid grapefruit, pomegranate, star fruit and Seville (sour) oranges during the study treatment. The juices and products containing these fruits must also be avoided.

If vomiting occurs during the course of the treatment, then no re-dosing of the patient is allowed before the next scheduled dose.

Patients should inform the investigational site staff of any missed or delayed doses.

Patients will be given a dosing diary to record the time and date of study medication administration for days study treatment is administered outside of clinic. Administration dates will be recorded in the CRF by the study coordinators.

All patients should be advised to minimize sun exposure and use sun block and lip balm with broad-spectrum, UVA and UBV protection (minimum of SPF 30, re-applied every 2 to 3 hours) during vemurafenib treatment and for at least 5 to 10 days after study drug discontinuation.

## *5.3 Drug supply and storage*

Erlotinib and vemurafenib will be supplied by Roche. Study drug must be received by a designated person at the study site, handled and stored according to the instructions specified on the drug labels, and kept in a secured location to which only the investigator and designated assistants have access.

Medication labels will conform to local legal requirements. They will supply no information about the patient; patient number will be added by the site pharmacist. The storage conditions for study drug will be described on the medication label.

The Pharmacy Department at participating institutions will maintain a record of drug dispensed for each patient, including the drug name, batch number, expiry date and amount dispensed. The Pharmacy will also maintain a record of drug destruction as appropriate. Erlotinib will be administered orally once a day while vemurafenib will be administered orally twice a day. The investigational site staff will inform each patient of their actual daily dose, and this will be recorded on the appropriate CRF.

Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study, or at the time of study treatment discontinuation.

At the end of the study, Roche will obtain confirmation from BaCT that all study drugs provided by Roche have been adequately accounted for and destroyed.

## *5.4 Missed Doses, Dose Modifications, Interruptions and Delays*

### 5.4.1 Erlotinib

#### 5.4.1.1 Missed Doses

If the patient forgets to take his/her dose, then that day's dose should be omitted and the patient should continue treatment with the next scheduled dose.

#### 5.4.1.2 Dose Modifications due to toxicities that are likely attributable to erlotinib

Reduction/interruption of dosing for adverse events may take place at any time during the study. In the event of any toxicity that is

- not controlled by optimal supportive care, or
- not tolerated due to symptomatology, disfigurement, or interference with normal daily activities, regardless of severity

When dose reduction is needed, dose reduction in 50 mg increments is recommended based on individual safety and tolerability. Table 2 and Table 3 outline erlotinib dosage modification criteria for erlotinib related toxicities as well as guidelines for their management.

Within 15 days following a dose reduction, erlotinib related toxicity must improve by at least one NCI-CTC grade and be NCI-CTC Grade ≤ 2, or further dose reduction by one level will be required. Dosing may be interrupted for a maximum of 3 weeks if clinically indicated and if the toxicity is not controlled by optimal supportive medication. Once a patient has had a dose reduction for toxicity, the dose will not be re-escalated except in the case of erlotinib related rash. In the event of a rash, dose can be re-escalated when rash is ≤ Grade 2 (Table 2).

**Table 2 Dosage modification criteria and guidelines for management of erlotinib related rash**

| Grade (CTC-AE)* | Study drug dosage modification | Guideline for management |
|---|---|---|
| Grade 1 | None | Any of the following: minocycline**, topical tetracycline, topical clindamycin, topical silver sulfadiazine, diphenhydramine, oral prednisone (short course) at discretion of the investigator. |
| Grade 2 | None | Manage as described above |
| Grade 3 (or intolerable Grade 2) | Dose reduction; dose can be re-escalated when rash is ≤ Grade 2 | Manage as described above |
| Grade 4 | Discontinue permanently | Manage as described above |

** The intensity of clinical adverse events graded by the Common Terminology Criteria for Adverse Events v4.0 (CTC-AE)*

*** Recommended dose: 200 mg po b.i.d (loading dose) followed by 100 mg po b.i.d × 7–10 days.*

**Table 3 Dosage modification criteria and guidelines for management of erlotinib related diarrhoea**

| Grade (CTC-AE)* | Study drug dosage modification | Guideline for management |
|---|---|---|
| Grade 1 | None | Consider Loperamide (4mg at first onset, followed by 2 mg every 2 – 4 hours until diarrhea free for 12 hours) |
| Grade 2 | None | Loperamide (4mg at first onset, followed by 2 mg every 2 – 4 hours until diarrhea free for 12 hours) |
| Grade 3 | Interrupt | Interrupt until resolution to Grade ≤ 1, and restart at reduced dose |
| Grade 4 | Discontinue permanently | |

#### 5.4.1.3 Dosage Interruption

Patients who require an interruption in dosing of > 21 consecutive days (counting from the first day when a dose was missed) will discontinue erlotinib treatment and be taken off study.

### 5.4.2 Vemurafenib

#### 5.4.2.1 Missed Doses

Missed or delayed doses (> 4 hours after normal administration time) should be skipped and not administered as a double dose at the next administration. Missed doses should be recorded in the patient diary.

#### 5.4.2.2 Dose Modifications due to toxicities that are likely attributable to vemurafenib

Management of symptomatic adverse events (e.g., arthralgia, fatigue, rash) or prolongation of QTc may require dose reduction, temporary interruption or treatment discontinuation of vemurafenib (see Table 4). Dose modifications or interruptions are not recommended for cutaneous squamous cell carcinoma (cuSCC). When dose reduction is needed, dose reduction in 240 mg B.I.D. increments is recommended based on individual safety and tolerability. Dose reductions resulting in a dose below 480 mg twice daily are not recommended. Dose escalation after dose reduction is generally not recommended unless under special circumstances i.e. increased likelihood of clinical benefit for the dose increase and no safety concerns. This should be done after discussion with the Study Chair. Dose increases above 960 mg B.I.D will NOT be allowed.

The daily dose of vemurafenib will be decreased according to the schedule displayed in Table 4.

Dose modifications should be made according to Table 4.

**Table 4 Dose modifications criteria for vemurafenib**

| Grade (CTC-AE)* | Recommended vemurafenib Dose Modification |
|---|---|
| **Grade 1 or Grade 2 (tolerable)** | 100% of starting dose |
| **Grade 2 (intolerable) or Grade 3** | |
| 1st Appearance | Interrupt treatment until grade 0 – 1<br>Reduce by 240 mg twice daily |
| 2nd Appearance | Interrupt treatment until grade 0 – 1<br>Reduce by 240 mg twice daily |
| 3rd Appearance | Discontinue permanently |
| **Grade 4** | |
| 1st Appearance | Discontinue permanently or interrupt treatment until grade 0 – 1<br>Reduce to 50% of starting dose |
| 2nd Appearance | Discontinue permanently |

#### 5.4.2.3 Dose Interruptions and Delays

If a patient's study dose has been interrupted for > 21 consecutive days (counting from the first day when a dose was missed) (adverse event, progressive disease) the patient will be considered to have discontinued from study. Exception will be granted for reversible laboratory abnormalities with no clinical sequelae and/or clinical significance in the opinion of the Site.

### 5.4.3 Rescue medication/procedures

The use of rescue medication/ procedures, such as any surgery or radiation therapy during the study is not permitted. Patients requiring rescue intervention should be withdrawn from the study.

## *5.5 Concomitant medications*

At study initiation, patients should continue with their concomitant medications, as directed by their physician. Patients should be advised to consult with their physician before taking any medications listed in Table 5. Please refer to http://medicine.iupui.edu/flockhart/table.htm for an updated list of drugs that are primarily eliminated by CYP1A1, CYP1A2, CYP2C9, CYP2D6 and CYP3A4.

Concomitant medications will be recorded at baseline and continually reported along with adverse events throughout study treatment. Concomitant medications will be followed for up to 28 days post last dose of erlotinib and vemurafenib. Additionally, any diagnostic, therapeutic, or surgical procedure performed during the study period should be recorded including the date, indication, description of the procedure(s) and any clinical findings.

Due to the underlying illness and the frequency of co-existent medical conditions in this patient population, all concomitant medication or treatment required by the patient will be at the discretion of the treating physician. The following medications and treatments are NOT allowed while the patient is on study:

- Other anti-cancer therapies
- Concomitant alternative therapies and herbal preparations
- Radiotherapy for the treatment of disease during study, the exception will be limited field radiotherapy for palliative bone pain due to pre-existing bone metastasis if not considered a target lesion for RECIST assessments.

Patients who require the use of any of these agents will be discontinued from study treatment and followed for safety outcomes for 28 days after the last dose of study treatment or until initiation of another anticancer therapy, whichever comes first. Follow-up for efficacy and exploratory outcomes will continue until disease progression, which will be followed by survival follow-up until death, loss to follow-up or withdrawal of consent.

The use of oral contraceptives and implantable hormonal contraception is allowed during the study (see Inclusion criterion #11 in Section 4.1).

**Table 5 Permitted and prohibited concomitant medications**

| Interacting Categories | Erlotinib | Vemurafenib |
|---|---|---|
| **Avoid Combination**<br>*The specified agents may interact with each other in a clinically significant manner. The risks associated with concomitant use of these agents usually outweigh the benefits. These agents are generally considered contraindicated.* | Conivaptan<br>Proton Pump Inhibitors | Axitinib<br>Bosutinib<br>Highest Risk QTc-Prolonging Agents<br>Mifepristone<br>Moderate Risk QTc-Prolonging Agents<br>Pirfenidone<br>Silodosin<br>Topotecan<br>Vincristine (Liposomal) |
| **Consider Therapy Modification**<br>*The two medications may interact with each other in a clinically significant manner. A patient-specific assessment must be conducted to determine whether the benefits of concomitant therapy outweigh the risks. Specific actions must be taken in order to realize the benefits and/or minimize the toxicity resulting from concomitant use of the agents. These actions may include aggressive monitoring, empiric dosage changes, choosing alternative agents.* | Antacids<br>CYP3A4 Inducers (Strong)<br>CYP3A4 Inhibitors (Strong)<br>Herbs (CYP3A4 Inducers)<br>H2-Antagonists<br>Mifepristone<br>Rifampin | ARIPiprazole<br>Colchicine<br>Dabigatran Etexilate<br>Everolimus<br>QTc-Prolonging Agents (Indeterminate Risk and Risk Modifying) |
| **Monitor Therapy**<br>*The specified agents may interact with each other in a clinically significant manner. The benefits of concomitant use of these two medications usually outweigh the risks. An appropriate monitoring plan should be implemented to identify potential negative effects. Dosage adjustments of one or both agents may be needed in a minority of patients.* | Amphotericin B<br>Antifungal Agents (Azole Derivatives, Systemic)<br>Cardiac Glycosides<br>Ciprofloxacin (Systemic)<br>CYP3A4 Inhibitors (Moderate)<br>Dasatinib<br>Deferasirox<br>Fenofibrate<br>FluvoxaMINE<br>Herbs (CYP3A4 Inducers)<br>Ivacaftor<br>Simvastatin<br>Tocilizumab<br>Vitamin K Antagonists | Agomelatine<br>Amphotericin B<br>ARIPiprazole<br>Cardiac Glycosides<br>CYP1A2 Substrates<br>CYP3A4 Inducers (Strong)<br>CYP3A4 Inhibitors (Strong)<br>P-glycoprotein/ABCB1 Inducers<br>P-glycoprotein/ABCB1 Inhibitors<br>P-glycoprotein/ABCB1 Substrates<br>Prucalopride<br>Rivaroxaban<br>Saxagliptin<br>Vitamin K Antagonists |

*From Lexi-Interact Online Drug Interactions Program (data dated 05 June 2013)*

**Medications affecting the QT interval**

Certain medications could affect the QT interval on ECG measurements required in this study. Specifically, anti-emetics other than those belonging to the 5-HT3 receptor antagonist class (i.e., granisetron, ondansetron, dolasetron, palonosetron) are preferred since the latter have the potential to prolong the QT interval. Investigators are advised to avoid or take precautions in closely monitoring patients who are on medications or herbal and vitamin supplements that may increase the QT interval. Alternative treatment options for medications known to affect the QT interval should be discussed with each patient prior to his or her inclusion into this study. A list of medications that may cause QT interval prolongation is provided in Appendix 6. Please refer to http://www.azcert.org/ for additional information and references.

## *5.6 Medication precautions in case of drug-drug interactions*

### 5.6.1 Vemurafenib and other medicinal products

Patients receiving concomitant medications that are deemed medically necessary but that are known to strongly inhibit and/or induce CYP3A4 should be excluded from the study. Patients should be instructed not to take grapefruit, St John's wort or Seville (sour) orange juice while receiving vemurafenib treatment throughout the study due to potential CYP3A4 inhibition.

Concomitant use of vemurafenib with agents with narrow therapeutic windows that are metabolized by CYP1A2 and CYP2D6 is not recommended as vemurafenib may alter their concentrations. If coadministration cannot be avoided, exercise caution and consider a dose reduction of the concomitant CYP1A2 and CYP2D6 substrate drug.

Exercise caution and consider additional INR monitoring when vemurafenib is used concomitantly with warfarin.

### 5.6.2 Erlotinib and other medicinal products

Coadministration of drugs reducing gastric acid production (i.e. omeprazole, a proton pump inhibitor; ranitidine, an H2-receptor antagonist) with Tarceva should be avoided where possible. Increasing the dose of Tarceva when coadministered with such agents is not likely to compensate for this loss of exposure. If patients need to be treated with such drugs, then an H2-receptor antagonist such as ranitidine should be considered and used in a staggered manner (Tarceva must be taken at least 2 hours before or 10 hours after the H2-receptor antagonist dosing).

Coumarins (coumadin. Warfarin) are strongly discouraged during Tarceva therapy. If the patient requires anti-coagulation therapy, then the use of low molecular weight heparin instead of coumarins is recommended where clinically possible. If inevitable, frequent monitoring of INR and prothrombin time must be performed.

The combination of Tarceva and a statin may increase the potential for statin-induced myopathy, including rhabdomyolysis, which was observed rarely.

Caution should be exercised when Tarceva is co-administered with CYP3A4 inhibitors and inducers. As grapefruit juice has the potential to inhibit CYP3A4 activity, it is recommended that patients do not drink grapefruit juice during the study.

Patients should be encouraged to stop smoking as smoking might negatively affect the exposure to Tarceva as well as the efficacy.

## *5.7 Study drug compliance and accountability*

### 5.7.1 Study drug compliance

Compliance will be assessed by the investigator and/or study personnel from the patient diary at each patient visit. Information provided by the patient and/or caregiver will be recorded in the Drug Accountability Form. This information must be captured in the case report form at each patient visit.

To assess compliance of erlotinib and vemurafenib, patients will be instructed to return all used and unused drug supply containers at each visit. Study personnel will assess compliance based on the number of tablets prescribed, dispensed, and returned.

### 5.7.2 Study drug accountability

The investigator, or a responsible party designated by the investigator such as the Pharmacy Department at participating institutions, must maintain a careful record of the inventory and disposition of the investigative agent. A pharmacy file will be provided for the purpose and will collect information such as drug name, batch number, expiry date, amount dispensed and disposal of supplies via approved procedures at the end of the study. Under no circumstances will the investigator supply study drug to a third party or allow the study drug to be used in any other ways than as directed by this protocol. Patients should return any unused supplies of study drug to their treating institution.

# 6 VISIT ASSESSMENTS AND PROCEDURES

## *6.1 Summary of visit schedule*

The Schedule of Assessments is presented in Table 6.

- Identification and consent of patient as potential participant.
- Screening investigations will occur up to 28 days prior to study treatment (Day 1) if found eligible (for details see Section 6.3).
- Safety assessments (Physical examination, haematology and biochemistry) and performance status will be conducted at screening, Day 1, end of Weeks 2, 4, 6, 8, 12, 16, 20, 24 and every 8 weeks thereafter until 28 days after end of treatment (see Section 6.7.1). ECG will be performed at: screening, Week 2, 4, 8, 12, 24 and every 8 weeks thereafter until 28 days after end of treatment. Skin examination should be performed ideally by a dermatologist with an attention of finding of any side effects associated with the use of vemurafenib such as cuSCC, rash, and photosensitivity at: screening, Week 4, 8, 16, 24 and every 8 weeks thereafter until 28 days after end of treatment.
- Assessment of tumour response (CR, PR, SD or PD) will occur at Week 8, 16, 24 and every 8 weeks thereafter until evidence of disease progression or until patient withdrawal for other reasons (see Section 6.7.2).
- FDG-PET (optional in patients with cancers other than CRC and lung adenocarcinoma) at screening, Week 4 and at progressive disease (see Section 6.7.3).
- Optional fresh tumour sample obtained from accessible metastatic site (e.g. liver biopsy, fine needle aspirates) for pharmacodynamics biomarker studies. Samples may be taken pre-treatment, at Day 14 (Week 2), and at disease progression.
- Optional paired eyebrow hair follicle plucks taken pre-treatment and at Day 14 for pharmacodynamics biomarker studies.
- Blood sample for exploratory biomarkers including circulating tumour DNA (ctDNA) will be collected baseline, Week 2, 4, 8 and then every 8 weeks thereafter and at disease progression.
- End of Treatment Visit is to be performed when disease progression, intolerable toxicity, withdrawal of consent for protocol specified procedures, or discontinuation from the study for any other reason (see Section 6.5).
- Follow-Up Visits for:
  - Toxicities (see Section 6.6.1).
  - Response (see Section 6.6.2).
  - Survival (see Section 6.6.3).

**Table 6 Schedule of Assessments**

| | **Screening** *[a]* | **Treatment** | | | | | | | | | | **At Progression** *[n]* | **EOT visit** *[p]* | **FU off treatment** *[q]* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit number | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | | **every 8 weeks thereafter (until Progression)** | | 28 days + 7 days after last dose | |
| Day of treatment | Day -28 to Day 1 | Day 1 | Day 14 | Day 28 | Day 42 | Day 56 | Day 84 | Day 112 | Day 140 | Day 175 | | | | |
| **Week of treatment** *[b]* | | **Week 1** | **End of Week 2** | **End of Week 4** | **End of Week 6** | **End of Week 8** | **End of Week 12** | **End of Week 16** | **End of Week 20** | **End of Week 24** | | | | |
| **Informed consent** | X | | | | | | | | | | | | | |
| **Disease status/Stage** | X | | | | | | | | | | | | | |
| **Medical history** *[c]* | X | | | | | | | | | | | | | |
| **Physical examination** *[d]* | X | X | X | X | X | X | X | X | X | X | X | | X | |
| **Skin toxicity assessment** *[e]* | X | | | X | | X | | X | | X | X | | X | |
| **ECOG performance status** | X | X | X | X | X | X | X | X | X | X | X | | X | |
| **ECG** | X | | X | X | | X | X | | | X | X | | X | |
| **Haematology** *[f]* | X | X | X | X | X | X | X | X | X | X | X | | X | |
| **Blood biochemistry** *[g]* | X | X | X | X | X | X | X | X | X | X | X | | X | |
| **Serum/ Urine pregnancy test** *[h]* | X | Additional tests may be performed, as determined necessary, at any time during participation in the study | | | | | | | | | | | | |
| **DLT observation** *[i]* | | x | x | x | | | | | | | | | | |
| **CT/MRI chest, abdomen and pelvis** *[j]* | X | | | | | X | | X | | X | X | | X *[p]* | X *[q]* |
| **Archival tumour (slides/blocks)** | X | | | | | | | | | | | | | |
| **FDG-PET** | X | | | X | | | | | | | | X | | |

| | **Screening** ***[a]*** | **Treatment** | | | | | | | | | | **At Progression** ***[n]*** | **EOT visit** ***[p]*** | **FU off treatment** ***[q]*** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit number | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | | **every 8 weeks thereafter (until Progression)** | | 28 days + 7 days after last dose | |
| Day of treatment | Day -28 to Day 1 | Day 1 | Day 14 | Day 28 | Day 42 | Day 56 | Day 84 | Day 112 | Day 140 | Day 175 | | | | |
| **Week of treatment** ***[b]*** | | **Week 1** | **End of Week 2** | **End of Week 4** | **End of Week 6** | **End of Week 8** | **End of Week 12** | **End of Week 16** | **End of Week 20** | **End of Week 24** | | | | |
| **Blood sample for exploratory Circulating Blood biomarkers** ***[k]*** | X | | X | X | | X | | X | | X | X | X | | |
| **Optional fresh tumour biopsy for exploratory biomarkers** | X | | X | | | | | | | | | X | | |
| **Optional eyebrow hair follicle plucks for pharmacodynamic biomarkers** | X | | X | | | | | | | | | | | |
| **Concomitant medications** ***[l]*** | X | X | X | X | X | X | X | X | X | X | X | | X | |
| **Adverse events/SAE** ***[l]*** | X | X | X | X | X | X | X | X | X | X | X | | X | |
| **Erlotinib & vemurafenib dosing** | | DAILY until PD, Death, Unacceptable Toxicity or Patient withdrawal | | | | | | | | | | | | |
| **Review of medication diary** | | At each visit until end of protocol treatment | | | | | | | | | | | | |
| **Survival follow-up** ***[o]*** | | | | | | | | | | | | | | X |

***[a]*** All study specific assessments must be conducted only after the patient has consented to participate. The screening visit must be done within Day -28 to –Day 1, except pregnancy test (see footnote *[h]*).

***[b]*** Visits that occur ± 4 days from the scheduled date (Day 1, end of Weeks 2, 4, 6, 8, 12, 16, 20 and 24) will not constitute protocol deviations. Beyond visit Week 24 (i.e. Week 32 and Follow-up for response), window allowance is ± 7 days.

***[c]*** Medical history, including BRAF V600E mutation status (performed any time prior to screening), HIV and hepatitis history, smoking history, a complete dermatological history of prior medications and cuSCC risk factors, concomitant medications and prior therapies

***[d]*** A complete physical examination, which will include height (only at screening), weight, vital signs (temperature, respiratory rate, pulse rate, blood pressure), the examination of general appearance, skin, head and neck, eyes, lungs, heart, abdomen, back and extremities, will be performed at screening and EOT visits. For other visits during the study treatment period, an abbreviated physical examination, which will only include the examination of vital signs (temperature, respiratory rate, pulse rate, blood pressure), general appearance, eyes, head and neck, lungs, heart and abdomen, will be performed.

***[e]*** Skin examination should be performed ideally by a dermatologist with an intention of finding of any side effects associated with the use of vemurafenib such as cuSCC, rash, and photosensitivity.

***[f]*** Haemoglobin, white blood cell count with differential, and platelet count.

***[g]*** Serum electrolytes (including sodium, potassium, total calcium and magnesium) and serum chemistries (urea, creatinine, glucose, LDH, total protein, albumin, total bilirubin, AST and ALT)

***[h]*** Women of childbearing potential must have a negative pregnancy test performed within the 7 days before start of treatment. Additional tests may be performed, as determined necessary, at any time during participation in the study (See Section 4.1 Inclusion Criteria for contraceptive measures required for both female and male participants).

***[i]*** Dose-Limiting Toxicity observation period is from Day 1 to Day 28 in Lead-In Phase.

***[]*** Partial response (PR) and Complete response (CR) must be confirmed by repeat assessments at the next scheduled visit (not less than 4 weeks).

***[k]*** Blood sample for exploratory circulating blood biomarkers will be collected at repeated timepoints, before dosing with study drugs.

***[l]*** Concomitant medications and AE/SAE are to be recorded at each visit from informed consent to 28 days after last dose of study drugs.

***[n]*** FDG-PET, blood sample and optional fresh tumour biopsy for exploratory biomarkers is to be performed as soon as feasible after confirmation of progressive disease.

***[o]*** Survival status collected from all subjects with disease progression and who have not withdrawn informed consent. Subjects will be contacted approximately every 12 weeks until death, withdrawal of consent, lost to follow-up or study end.

***[p]*** End of Treatment (EOT) Visit is to be performed when disease progression (determined according to RECIST 1.1), intolerable toxicity, death, withdrawal of consent for protocol specified procedures, or discontinuation from the study for any other reason. This visit should occur from 28 to 35 days (28 + 7 days) after last dose. If protocol treatment ceased due to reasons other than disease progression and response has not been evaluated within at least 4 weeks, a tumour evaluation should be performed at EOT visit.

***[q]*** Follow-up **off** treatment:

- For participants whose treatment is interrupted or discontinued due to toxicity: weekly for 4 weeks then 4-weekly until resolution or stabilisation of AE.
- For participants who withdraw before disease progression: if consent, response assessment 8-weekly (± 7 days) for 1st year then once every 12 weeks (± 7 days) until disease progression, death, lost to follow-up or the study is closed out.
- For participants who have progressive disease according to RECIST 1.1 – survival status every 12 weeks (± 7 days) until death, withdrawal of consent or study closure.

## *6.2 Screening evaluation*

The ICF must be signed by the patient prior to any study-specific screening assessments. Routine procedures that may have been previously performed as part of the patient's routine care may be used to satisfy inclusion criteria.

Patients who are found not to be eligible for the study may be allowed to be re-screened, after discussion with the Study Chair.

Screening assessments will include:

- Demographics including date of birth, initials (where permitted), sex and childbearing potential.
- Relevant medical history including BRAF V600E mutation status (performed any time prior to screening, HIV and hepatitis history, smoking history, a complete dermatological history of prior medications and cuSCC risk factors (i.e., radiation therapy, sun exposure, immunosuppression, prior SCC, using of tanning beds, precursor lesions and photochemotherapy for psoriasis) and current medical conditions.
- Medical history on specific cancer including:
  - Date of diagnosis
  - Stage of disease at the time of diagnosis and at the time of screening.
  - Prior anti-neoplastic therapy therapies and/or any other therapies administered for the treatment of metastatic colorectal cancer (Lead-In Phase and mCRC Expansion Cohort), lung adenocarcinoma or other tumours for which there is a strong rationale for treatment with this combination (Exploratory Expansion Cohort).
- A complete physical examination, including skin examination (see Section 6.7.1.1).
- Performance status per ECOG criteria (see Appendix 1).
- 12 lead electrocardiogram (ECG) (see Section 6.7.1.3).
- Blood collection for the following laboratory tests (see Section 6.7.1.4):
  - Haematology
  - Blood biochemistry
  - Circulating Blood Biomarkers studies
- Urine or serum pregnancy test (women of childbearing potential) performed within 7 days before start of treatment.
- CT and/or MRI of chest, abdomen and pelvis (see Section 6.7.2) and evaluation of lesions via RECIST 1.1 criteria (see Appendix 5).
- FDG-PET (optional in patients with cancers other than CRC and lung adenocarcinoma).
- All medications and significant nondrug therapies taken within 14 days before the first dose is administered.
- Archived tissue from a previous biopsy (see Section 6.7.3.3) will be sent to the Centre for Translational Pathology at the University of Melbourne
- Paired pre-treatment fresh tumour sample from metastases collected (optional in all patients), where feasible, will be sent to the Centre for Translational Pathology at the University of Melbourne for pharmacodynamics biomarker studies (see Section 6.7.3.4).
- Paired pre-treatment eyebrow hair follicle plucks (optional in all patients), where feasible, will be sent to the Centre for Translational Pathology at the University of Melbourne for pharmacodynamics biomarker studies (see Section 6.7.3.4).

### 6.2.1 Information to be collected on screening failures

Patients, who sign informed consent but fail to be started on treatment for any reason, will be considered a screen failure. The reason for not being started on treatment will be entered in the Screening Log and his/her demographic information will be recorded in the site document. No other data will be entered into the clinical data base for screen failure patients.

## *6.3 Registration*

The Investigator should ensure that all of the following requirements are met prior to patient enrolment:

- The patient meets all inclusion criteria and none of the exclusion criteria apply.
- The patient has signed and dated consent forms.
- All baseline assessments and investigations have been performed and recorded in the patients' medical records (i.e. source documents).
- The registration Case Report Form(s) (CRF) have been completed, signed and dated by the Investigator.

To register a patient to EVICT the following documents must be faxed to Centre for Biostatistics and Clinical Trials (BaCT) on 03 9656 1420:

- Completed EVICT Registration Form
- De-identified supporting documents for the eligibility check (see Checklist in the Registration Coversheet).

Once the Trial Manager has verified the entries on the Registration Form and checked patient's eligibility, an email will be sent to the Research Nurse/Study Coordinator and Investigator to confirm the patient is registered.

## *6.4 Treatment phase*

The investigator should instruct the patient to take the study drug as described in detail in Section 5.2. The first dose of study treatment is administered on Day 1 (of study treatment) at the study centre. All dosages prescribed and dispensed to the patient and all dose changes must be recorded in the CRF. Patients should continue to receive daily erlotinib and vemurafenib until disease progression (determined according to RECIST 1.1), intolerable toxicity, death, withdrawal of consent for protocol specified procedures, or discontinuation from the study for any other reason.

Following study registration and initiation of study treatment (Day 1) the patient should visit the study site at the end of Weeks 2, 4, 6, 8, 12, 16, 20, then at Week 24 for primary endpoint and every 8 weeks thereafter during the treatment phase until End of Treatment (which may be due to disease progression, intolerable toxicity, withdrawal of consent for protocol specified procedures, or discontinuation from the study for any other reason) or death (prior to disease progression).

For details of assessments and windows, refer to Table 6 and Section 6.7. In brief, it will include safety and response assessments as described as below:

- An abbreviated physical examination, performance status, blood collection for haematology and biochemistry will be conducted at: Day 1, end of Week 2, 4, 6, 8, 12, 16, 20, 24 and every 8 weeks thereafter until end of treatment.
- Skin examination should be performed ideally by a dermatologist with an attention of finding of any side effects associated with the use of vemurafenib such as cuSCC, rash, and photosensitivity at: end of Week 4, 8, 16, 24 and every 8 weeks thereafter until end of treatment.

- ECG will be performed at: end of Week 2, 4, 8, 12, 24 and every 8 weeks thereafter until end of treatment.
- Urine or serum pregnancy test (women of childbearing potential) as determined necessary.
- CT and/or MRI of chest, abdomen and pelvis- Response to treatment will be determined at end of Weeks 8, 16, 24, and every 8 weeks thereafter according to the RECIST 1.1 until disease progression, death, lost to follow-up or the study is closed out. The same method of assessment and the same technique should be used to characterise each individual and reported lesion at baseline and during study treatment. Partial Response (PR) and Complete Response (CR) must be confirmed by repeat assessments at the next scheduled visit (not less than 4 weeks). Clinical suspicion of disease progression at any time requires a physical examination and radiological confirmation to be performed promptly rather than waiting for the next scheduled radiological assessment.
- FDG-PET (optional in patients with cancers other than CRC and lung adenocarcinoma) will be performed at Week 4 and at progressive disease.
- Blood sample for circulating blood-biomarkers will be collected at Weeks 2, 4, 8 and then every 8 weeks thereafter and at disease progression.
- Paired fresh tumour samples from metastases (optional in all patients) will be collected at Day 14 and at disease progression.
- Paired eyebrow hair follicle plucks (optional in all patients) will be collected at Day 14.
- Review of patient diaries to ascertain drug compliance.
- Review of concomitant conditions.
- Assessment of AEs and serious adverse events (SAEs).

Patients, who receive the dose which are confirmed not to be MTD, will not be included in response-evaluable patient group. However, safety and response assessments are required to perform until disease progression or study drugs discontinuation and survival follow-up is obliged like in the evaluable patients.

## *6.5 End of Treatment*

Patients who discontinue study treatment for any reasons except death, lost to follow-up, total withdrawal and discovery of patient ineligibility, should be seen within 28 - 35 days of the previous visit, at which time all of the assessments listed for the End of Treatment (EOT) visit will be performed and the patient will enter the follow up period of the study.

If premature withdrawal occurs (see Section 7.1), or if the patient fails to return for visits, the investigator must determine the primary reason for a patient's premature withdrawal from the study and record this information on the CRF and notify BaCT.

The following assessments will be performed during the End of Treatment Visit:

- Current/new therapies and/or any other therapies administered for the treatment of the current cancer since the last dose of study treatment.
- A complete physical examination, which will include weight, vital signs (temperature, respiratory rate, pulse rate, blood pressure), the examination of general appearance, skin, neck, eyes, ears, nose, throat, lungs, heart, abdomen, back and extremities.
- Performance status per ECOG criteria.
- ECG
- Blood collection for haematology and biochemistry tests.

- Radiographic tumour assessment and evaluation of lesions via RECIST criteria version 1.1. Radiographic tumour assessments and evaluation of lesions will not need to be repeated if they have been performed within 4 weeks of the EOT visit.
- Review of patient diaries to ascertain drug compliance.
- Review of concomitant conditions.
- Assessment of AEs and serious adverse events (SAEs).

## *6.6 Follow-up visit*

### 6.6.1 Follow-up for toxicities

All patients will be followed for adverse events and serious adverse events for 28 days following the last dose of erlotinib and vemurafenib. Patients whose treatment is interrupted or permanently discontinued due to an adverse event must be followed at least once a week (if not stated otherwise) for 4 weeks, and subsequently at 4-week intervals, until resolution or stabilisation of the event, whichever comes first. If a patient requires a study treatment interruption of > 21 consecutive days (counting from the first day when a dose was missed), then the patient must be discontinued from study treatment. However, the patient will continue to be followed for toxicity as previously described.

### 6.6.2 Follow up for response

Patients who discontinue erlotinib and vemurafenib treatment prior to documented progression of disease, for any other reason other than withdrawal of consent to further study participation, lost to follow-up, death or discovery of patient ineligibility, will continue to have tumour evaluations once every 8 weeks (± 7 days) for the first year, then once every 12 weeks (± 7 days) until disease progression, death, lost to follow-up or the study is closed.

### 6.6.3 Survival follow up phase

Study treatment and tumour evaluations will be discontinued for patients who have documented disease progression according to RECIST 1.1. They will be followed for survival status by the investigator every 12 weeks until death, withdrawal of consent to further study participation, lost to follow-up or the study is closed. In rare cases, patients may be considered lost to follow-up and hence not followed for their survival status.

Patients lost to follow-up should be recorded as such on the CRF and the investigator should show "due diligence" by documenting steps taken to contact the patient, *e.g.*, dates of telephone calls, registered letters, etc., in the source documents.

## *6.7 Assessment types*

### 6.7.1 Safety assessments

Safety will be monitored by assessing for the occurrence of adverse events (AEs), serious adverse events (SAEs) and dose limiting toxicities (DLTs, in Lead-In Phase) at every visit. For details on AE documentation and reporting, refer to Section 9.

#### 6.7.1.1 Physical examination

A complete physical examination, which will include height (only at screening), weight, vital signs (temperature, respiratory rate, pulse rate, blood pressure), the examination of general appearance,

skin, head and neck, eyes, lungs, heart, abdomen, back and extremities, *will be performed at screening and EOT visits.*

An abbreviated physical examination, which will include the examination of vital signs (temperature, respiratory rate, pulse rate, blood pressure), general appearance, head and neck, eyes, lungs, heart and abdomen, *will be performed during the treatment period of the study*.

Additional examinations may be performed at the investigator's discretion.

Blood pressure will be measured according to standardised techniques with documented repeat readings if ≥ 160 mmHg systolic and/or ≥ 95 mmHg diastolic.

Body weight will be measured in indoor clothing, but without shoes.

Skin examination should be performed ideally by a dermatologist with an attention of finding of any side effects associated with the use of vemurafenib such as cuSCC, rash, photosensitivity.

Significant findings that were present prior to the signing of informed consent must be included in the Relevant Medical History/Current Medical Conditions page on the patient's CRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's CRF.

#### 6.7.1.2 Performance status

Performance status will be recorded on the CRF as defined by the ECOG Performance Status scale (see Appendix 1).

#### 6.7.1.3 Electrocardiogram (ECG)

QTc will be calculated and reported using the Fridericia correction formula (see Appendix 2).

If an increase of ≥ 60 ms in QTcF from screening and/or QTcF ≥ 501 ms is noted (and confirmed with duplicate ECG) at any time point, both vemurafenib and erlotinib must be stopped. For consideration of retreatment, QTcF must return to < 500 ms. Determination of eligibility to restart study medication may include clinical evaluations that could be appropriate (monitoring serum electrolytes, concomitant medications, cardiology consult). If this patient is deemed eligible to continue study treatment after consultation with the Study Chair, 12-lead ECGs will be performed on a schedule agreed to by the Study Chair and Investigator.

#### 6.7.1.4 Laboratory evaluations

The laboratory investigations should include the following and should be done at screening, every on-treatment visit at any other time during treatment if clinically indicated, and at EOT visit.

**Haematology** - haemoglobin, white blood cell count with differential, and platelet count.

**Blood biochemistry** - Serum electrolytes (including sodium, potassium, total calcium and magnesium) and serum chemistries (urea, creatinine, glucose, LDH, total protein, albumin, total bilirubin, AST and ALT).

**Pregnancy testing** - should be done within 7 days prior to the first dose on women of childbearing potential (see inclusion criterion 12 which provides definition of female patients not of childbearing potential). Additional tests may be performed, as determined necessary, at any time during participation in the study.

### 6.7.2 Efficacy assessments

Tumor response assessment (using RECIST 1.1 criteria, see Appendix 5) will be performed at screening, end of Weeks 8, 16, 24 and every 8 weeks from Week 24 while still on study treatment until disease progression, death, total withdrawal, lost to follow-up or the study is closed. The 8 weeks interval should be respected regardless of whether treatment with either vemurafenib or erlotinib or both is temporarily withheld. In case of an unscheduled or delayed tumour assessment for any reason, subsequent tumour assessments should be performed according to the originally planned schedule (treatment start date) unless tumor assessment has been performed within the last 2 weeks.

- All patients must undergo chest, abdomen and pelvis CT and/or MRI scan consistently throughout the study.
- CT with intravenous (i.v.) contrast is the preferred modality for disease assessment. If a patient is known to have a medical contraindication to i.v. contrast for CT scans or develops one during the study, a chest, abdomen and pelvis CT scan without i.v. contrast and an MRI scan of the relevant local disease if applicable may be performed instead. Contrast-enhanced CT of chest, abdomen and pelvis should preferably be performed using a contiguous reconstruction algorithm of 5 mm or less. CT/MRI scan slice thickness/reconstruction algorithm should not exceed 8 mm. Ultrasound scans cannot be used for tumour assessment.
- All known lesions (measurable, non measurable) should be accounted for at baseline when assessing objective tumour status. For subsequent scans on the same patient all lesions that were present at baseline should be accounted for and evaluated using the same technique as used at baseline.
- Criteria required for determining partial or complete response should be confirmed by a subsequent imaging assessment at least 4 weeks later. If an off-schedule imaging assessment is performed to confirm response or if progression is suspected, subsequent imaging assessments should be performed in accordance with the original imaging schedule unless the next scheduled imaging timepoint is within 2 weeks, in which case the scheduled imaging timepoint can be omitted.
- Any lesions that have been previously treated with radiotherapy should not be used as target lesions, unless they have shown definite progression since their last radiation treatment.
- The CT component of a PET/CT scan may not be used for assessment of tumour response per RECIST 1.1.
- Imaging evaluations will be performed at the End of Treatment (EOT) visit. If a patient is known to have PD at a scheduled study visit, EOT imaging evaluations do not need to be repeated for the EOT visit.

### 6.7.3 Exploratory assessments

Exploratory assessments in this study include functional imaging by FDG-PET, biomarker studies by using blood samples, archival tumour samples and fresh tumour samples and eyebrow hair follicle plucks as described in detail below.

#### 6.7.3.1 Functional Imaging

Target inhibition will be evaluated with FDG-PET. Scans performed pre-treatment, 4 weeks and at disease progression in all patient groups (compulsory for CRC and lung adenocarcinoma patients; optional for other cancer patients).

#### 6.7.3.2 Circulating biomarkers

Forty millilitres (40 mL) of venous blood will be collected at repeated timepoints, before dosing with study drugs (see Table 6) in order to evaluate changes in circulating biomarkers. Where necessary, matched tumour tissue (archival or fresh frozen) will be used for correlative analysis.

Sampling procedures, storage conditions, and shipment instructions for all blood samples will be detailed in the EVICT Laboratory Manual.

#### 6.7.3.3 Biomarker assessments performed in archival tumour samples

Patients must have available archival tumour tissue sample required by the inclusion criteria. The samples will be sent to the Centre for Translational Pathology at the University of Melbourne. These samples will be tested to confirm the BRAF V600E mutation. Confirmed cases will also be tested for

a. Mutations in related pathways including PIK3CA, PTEN, KRAS and NRAS and EGFR (only for lung adenocarcinomas) using the TruSeq cancer amplicon panel.
b. Microsatellite instability or mismatch repair proficiency by IHC
c. Expression determined by IHC including EGFR, epiregulin, amphiregulin
d. EGFR copy number by ISH

The archival tumour material submitted may have been obtained at any time during the course of the patient's disease prior to the start of this trial (e.g. obtained as a part of a diagnostic biopsy or surgical procedure). If the patient has multiple archival tumour samples available from different times in their course of disease (e.g., from original diagnosis or treatment, and from any follow-up surgery or biopsies), it is preferable to receive a sample from each archival specimen if possible. If only 1 sample is available, then this should be from their most recent biopsy/surgery.

It is preferable to receive formalin fixed paraffin embedded blocks instead of slides. If slides are to be sent, approximately 20-30 slides, or as many as possible, containing 5 µm tissue sections on Superfrost Plus slides are requested.

It is acknowledged that it may not be possible to obtain all samples before commencement of study-related treatment. Any unused slides/blocks can be sent back to the original pathology laboratory at the end of the trial upon request.

#### 6.7.3.4 Pharmacodynamic assessments performed in fresh tumour biopsy samples and hair follicles

Fresh biopsies of metastatic tumours will be collected at baseline (prior to study drug dosing), on Day 14 and at the time of developing progressive disease. Hair follicles will be collected at baseline (prior to study drug dosing) and on Day 14. This collection applies to patients in both Lead-In Phase and Dose Expansion phase if the patient has consented for optional pharmacodynamic studies.

The fresh tumour sample and hair follicles will be used for pharmacodynamics biomarker studies. Collection of fresh tissue samples will require the on-site attendance of a laboratory technician to ensure the tissues are optimally collected and preserved. Arrangements can be made with 24 hrs notice by calling Dr Irma Gresshoff, Centre for Translational Pathology at the University of Melbourne on 03- 90358778.

For detailed procedures for collection, processing, storage and transport of samples see the Study Coordinator Manual.

Please notify the laboratory in advance of collections, as well as by phone on the day of collection.

The original tumour sample collection date should be entered on the appropriate CRF (i.e. the date of the initial biopsy or surgery when the archival tumour sample was taken from the patient, not the date that the sample was supplied to the investigational site).

Biomarkers to be analysed from all tumour samples may include (but are not limited to):

- Assays for pathway activation/inhibition including pEGFR, pAKT, pS6, PRAS40, pERK by IHC and where possible by other methods (eg. Western, reverse phase protein arrays, Multiple Reaction Monitoring).

Additional relevant biomarkers may be analysed during the study if indicated by new findings from literature.

# 7 SUBJECT WITHDRAWAL, REPLACEMENT AND TRANSFER

## *7.1 Subject withdrawal*

Patients may voluntarily withdraw from the study or withdrawn from it at the discretion of the investigator at any time. Patients may be withdrawn from the study if any of the following occur:

- Pregnancy discovery
- Discovery of patient ineligibility
- Treatment noncompliance
- Use of another antineoplastic therapy
- Use of radiotherapy or surgical therapy other than that specified in the protocol
- Toxicity requiring treatment discontinuation
- Investigator decision
- Patient refused/withdrew consent.

In addition to the general withdrawal criteria, the following *study specific criteria* will also require study treatment discontinuation:

- Dose delay of > 21 days due to study treatment-related toxicities, unless the patient has experienced evidence of clinical benefit.
- Drug interruption due to drug related adverse events as noted in Section 5.4.1.3 and Section 5.4.2.3.

The End of Treatment visit and the required assessments should occur within 28 days after the decision to withdraw a patient from the study.

## *7.2 Patient replacement*

### 7.2.1 Phase I Lead-In Phase

Patients enrolled in the Lead-In Phase who do not receive at least 21 days of treatment during the observation period (28 days) for reasons other than treatment related toxicity, cease treatment or withdraw from the study for any reason unrelated to study treatment prior to completion of the 4 week DLT observation period will not be evaluable and will therefore be replaced in that cohort.

### 7.2.2 Phase II Dose Expansion Phase

During Dose Expansion Phase no replacement will occur.

## *7.3 Patient transfers*

Every effort should be made for a trial participant moving from the area to continue their treatment and/or follow-up at another participating trial site and for this trial site to take over responsibility for the participant.

Until the new trial site formally agrees (in writing) to take over responsibility, the patient remains the responsibility of the original trial site.

Source documentation will remain at the original Trial Site. One copy of the participant's CRFs must be sent to the new Trial Site and one copy will remain at the original trial site.

# 8 END OF STUDY, EARLY TERMINATION AND SAFETY MONITORING COMMITTEE

## *8.1 End of Study*

Study closure will occur when all patients have been followed for a minimum of 18 months after treatment commencement or when all patients have progressed, died, or withdrawn consent, whichever occurs first.

If, for any patient, study treatment is permanently discontinued, the (primary) reason for study completion will be recorded on the CRF. All cancer medications/therapies given to a patient ≤ 28 days after the last dose of study treatment must be recorded in the CRF.

At the end of the study, if the subject would benefit from continued treatment, the investigator should consult with the Study Chair to obtain approval for continuing treatment.

Investigational sites will be notified of the clinical cut-off date. Subjects who continue to receive study drug after the clinical cut-off date will continue to be monitored and at a minimum, the following data will be collected: study agent administration; serious adverse events, concomitant medications, and laboratory abnormalities associated with a serious adverse event; any related adverse events and associated, abnormal laboratory values, disease progression, and overall survival.

## *8.2 Premature termination of the study*

Consideration will be given to stopping or modification of the trial if:

- A patient death is reported in the first 28 days of commencing protocol treatment which is possibly, probably, or definitely drug related.
- Suspected Unexpected Serious Adverse Drug Reaction (SUSAR) which is likely related to vemurafenib and/or erlotinib.
  (*SUSAR is a serious adverse event for which there is some degree of probability that the event is an adverse reaction to the administered drug and the adverse reaction is unexpected*).
- It is confirmed that the combination dose level D-1 is not safe (see Section 3.1.1.1 and Schema 2).
- 0 responses (CR or PR prior to disease progression and within the first 24 weeks of treatment commencement) are observed in the first 9 evaluable mCRC patients (see Section 10.1.2).
- It is recommended by the Safety Monitoring Committee (SMC).
- Evidence becomes available during the accrual phase of the trial, which clearly demonstrates that it is unethical to register patients to the trial.

## *8.3 Safety Monitoring Committee*

A Safety Monitoring Committee (SMC) will be established for the purposes of advising on serious safety considerations and ensuring the scientific and ethical integrity of the trial.

This group will consist of at least:

- Study Chair

- At least one Investigator who is in the same clinical discipline as the Study Chair and associated with the project (if there are DLTs, the investigator of the site which the patient(s) experienced DLT(s) is strongly required)
- At least one Investigator who is in the same clinical discipline as the Study Chair, but is not associated with the project
- Study statistician

Meetings may be by telephone or with email consensus as required – at least 4 members are required for decisions relating to dose escalation/des-escalation or trial modification.

The SMC will be responsible for safeguarding the interests of study participants, assessing the safety and efficacy of the interventions during the study, and for monitoring the overall conduct of the clinical study. The SMC will provide recommendations about stopping or continuing the study.

To contribute to enhancing the integrity of the study, the SMC may also formulate recommendations relating to: (1) patient selection, recruitment, and retention, and (2) patient management and adherence to protocol procedures and treatment. In addition, the SMC may make recommendations for data management and quality control procedures.

The SMC will meet to review the progress of the trial and may request additional meetings or safety reports as deemed necessary (see Section 8.2).

- During Lead-In Phase: 1 meeting for every 3 patients to determine the MTD.
- During Dose Expansion Phase: a review will occur after 9 evaluable patients (see Section 10.1.2) have received 24 weeks of treatment and undergone a response assessment in order to decide whether the study may continue with the second stage.
- Two other meetings in Dose Expansion Phase (or more often if needed, see Section 8.2).

# 9 SAFETY INSTRUCTIONS AND GUIDANCE

The safety reference document for erlotinib and vemurafenib is the Investigators Brochure.

The investigator at each trial site is responsible for assessing and reporting AEs as part of patient safety, routine clinical care and data collection. A subset of AEs will be classified as 'serious' and will require expedited reporting.

## *9.1 Adverse Events*

### 9.1.1 Definition

According to the International Conference of Harmonisation [ICH], an AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign [including an abnormal laboratory finding], symptom, or disease temporally associated with the use of a medicinal [investigational] product, whether or not considered related to the medicinal [investigational] product. Pre-existing conditions which worsen during a study are to be reported as AEs.

Any treatment-emergent abnormal laboratory result which is clinically significant, i.e., meeting one or more of the following conditions, should be recorded as a single diagnosis on the AE page in the CRF.

- Accompanied by clinical symptoms
- Leading to a change in study drug (e.g. dose modification, interruption or permanent discontinuation)
- Requiring a change in concomitant therapy (e.g. addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment)

**This applies to** any protocol and non-protocol specified safety and efficacy laboratory result from tests performed after the first dose of study drug, which falls outside the laboratory reference range and meets the clinical significance criteria.

**This does not apply to** any abnormal laboratory result which falls outside the laboratory reference range but which does not meet the clinical significance criteria (which will be analysed and reported as laboratory abnormalities) or those which are the result of an AE which has already been reported.

### 9.1.2 AE severity

Intensity of all adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events v 4.0 (CTCAE) on a five-point scale (Grade 1 to 5) (see Appendix 4) and reported in detail on the CRF.

Adverse events not listed on the CTCAE should be graded as shown in Table 7

**Table 7 Common Toxicity Criteria for Grading Adverse Events**

| CTC Grade[1, 2] | Equivalent To: | Definition |
|---|---|---|
| Grade 1 | Mild | Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. |
| Grade 2 | Moderate | Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[4]. |
| Grade 3 | Severe | Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL[5]. |
| Grade 4 | Life threatening | Life-threatening consequences; urgent intervention indicated. |
| Grade 5[3] | Death | Death related to AE. |

[1] A Semi-colon indicates 'or' within the description of the grade; A single dash (-) indicates a grade is not available.

[2] Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

[3] Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

[4] Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[5] Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

### 9.1.3 Adverse event reporting period

Investigators will seek information on adverse events at each patient contact.

All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event CRF.

**After informed consent** has been obtained **but prior to initiation of study drug**, only serious adverse events caused by a protocol-mandated intervention should be reported (e.g., serious adverse events related to invasive procedures such as biopsies).

**After initiation of study drug**, all adverse events, regardless of relationship to study drug, will be reported until 28 days after the last dose of study drug. After this period, investigators should report any deaths, serious adverse events (including new primary cancers), or other adverse events of concern that are believed to be related to prior treatment with study drug.

### 9.1.4 Drug – AE relationship

The causality relationship of study drug to the adverse event will be assessed by the investigator as either: **Yes or No**

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug.

- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (where applicable).
- Known association of the event with the study drug or with similar treatments.
- Known association of the event with the disease under study.
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event.
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event.

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

### 9.1.5 Follow-up of AEs

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, the patient withdraws consent or death. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event Log CRF and in the patient's medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event Log CRF.

#### 9.1.5.1 Trial Sites/Investigators responsibilities

All adverse events (including those that are non-serious or expected), which occur whilst the participant is enrolled on the trial (from the time a participant signs the consent form to within 28 days of the final protocol-specified treatment), must be reported in the patients' medical records and recorded on the relevant CRF.

As far as possible, each adverse event should be evaluated to determine:

- The severity (see Section 9.1.2)
- Its duration (Start and end dates) (see Section 9.1.3)
- Its relationship to the study treatment (see Section 9.1.4)
- Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued)
- Outcome (resolved without sequelae, resolved with sequelae, ongoing, fatal, unknown)

#### 9.1.5.2 BaCT responsibilities

Data from the CRF will be entered into the trial database at BaCT and accessed when required by BaCT. Regular analyses of cumulative AE data should occur at the SMC (see Section 8.3). If significant safety issues are identified from analyses the TMC must inform the Therapeutic Goods Administration (TGA), other investigators and responsible HRECs as well as Roche.

## *9.2 Serious adverse events*

### 9.2.1 Definition

A serious adverse event is any experience that suggests a significant hazard, contraindication, side effect or precaution. It is any Adverse Event that at any dose fulfils at least one of the following criteria:

- is fatal; (results in **death**; NOTE: death is an outcome, not an event)*
- is Life-Threatening (NOTE: the term "Life-Threatening" refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe).
- required in-patient hospitalization or prolongation of existing hospitalisation**;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect;
- is medically significant or requires intervention to prevent one or other of the outcomes listed above.

**The term sudden death should be used only when the cause is of a cardiac origin as per standard definition. The terms death and sudden death are clearly distinct and must not be used interchangeably.*

*** unless hospitalisation is for:*

- *Routine treatment or monitoring of the studied indication*
- *Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent*
- *Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission*
- *Social reasons and respite care in the absence of any deterioration in the patient's general condition*
- *Hospice placement for terminal care*

Due to the significant information they provide, every SAE**, regardless of suspected causality**, **requires expedited reporting** (see Section 9.2.2).

### 9.2.2 Reporting of SAEs

#### 9.2.2.1 Trial Sites/Investigators responsibilities

All serious adverse events (SAEs) that occur from the time a participant signs the consent form to within 28 days of the final protocol-specified treatment (see Section 9.1.3), intervention or procedure are required to be reported to BaCT whether or not it is considered related to the treatment under investigation. Any SAEs experienced after this 28 day period should also be reported to BaCT ifthe investigator suspects a causal relationship to the study treatment.

The Principal Investigator (PI) at each site must:

- Determine whether an AE is 'Serious' (see Section 9.2.1)
- For SAEs, the PI must then ascertain the suspected cause*.
- The attribution to the SAE must be recorded in the patients' medical records and reported on the SAE form.
- The PI in discussion with the Study Chair must then determine whether the SAE (or Serious Adverse Drug Reaction) is expected or unexpected. *An unexpected AE is one, the nature or severity of which is not consistent with the applicable product information.*

- Both expected and unexpected Serious Adverse Events must be recorded in the patients' medical records and reported to BaCT, and the approving Health Research Ethics Committee, in accordance with their requirements.

** Causality is initially assessed by the investigator. For SAEs, possible causes of the event are indicated by selecting one or more options.*

- *Pre-existing/Underlying disease - specify*
- *Study treatment – specify the drug(s) related to the event*
- *Other treatment (concomitant or previous) – specify*
- *Protocol-related procedure*
- *Other (e.g. accident, new or intercurrent illness) – specify*

The term severe is a measure of intensity, thus a severe AE is not necessarily serious. For example, nausea of several hours' duration may be rated as severe, but may not be clinically serious.

Suspected unexpected serious adverse drug reactions (SUSARs) that are fatal or life threatening need to be reported to the TGA within 7 days. Other SUSAR, must also be reported to the TGA within 15 days.

SAEs must be reported by completing the Trial SAE form and FAXING it to the following:

| Fax To: | Fax Number: |
|---|---|
| BaCT | +61 3 9656 1420 |

SAE forms are required at the following points:

| | |
|---|---|
| Initial Report | **Within *one* working day/24 hours** of discovery or notification of the event. If the reporting of an SAE is delayed by more than 24 hours, an explanation must be provided in the comments section of the SAE form. |
| Incomplete Reports* | If all details are not available at the time of the initial report a completed report must be sent within the next 10 days. |
| Updated Report | If the event is not resolved (or is 'on-going') at the time of the initial report, the 'UPDATE: Outcome of Event' section' of the SAE Form must be completed and the form submitted to BaCT and the SAE reviewer as soon as the event is resolved (with or without sequelae) or if death has occurred. |
| *The Investigator is ultimately responsible for reporting the SAE and must sign the SAE report(s). Should this Investigator not be available to sign the initial SAE form within the 24-hour period, a comment to this effect must be written on the form and the form faxed without signature to BaCT. The investigator must sign the SAE form as soon as possible and re-fax to BaCT.<br><br>The Investigator at the Trial Site is responsible for determining the local SAE reporting requirements of the responsible HREC and subsequently notifying the HREC of SAEs as required. | |

#### 9.2.2.2 BaCT responsibilities

BaCT is responsible for:

- Implementing and maintaining a suitable recording system to record information from all SAEs received from Trial Sites.

- Ensuring that each SAE to be assessed by the appropriate reviewers for nature (expected/unexpected), causality (related/unrelated) and whether the TGA needs to be notified of the SAE.Transmitting SAE and pregnancy reports (initial and follow-up) by either electronically or fax within the specified timelines to Roche and complying with safety reporting obligations and BaCT related activities as defined in the Safety Data Exchange Procedure (see Attachment 5 in Roche Supported Clinical Trial Agreement Institution).
- Under the direction of the SAE Reviewer or Safety Monitoring Committee, notifying the TGA (Australia) in accordance with the regulatory authority's detailed guidance of any SUSARs that are fatal or life threatening as soon as possible but no later than 7 days after the site gained first knowledge of the event. Incomplete reports must be completed and forwarded as soon as soon as possible within 8 additional calendar days. All other SUSAR should be reported to the TGA within 15 days after the site gained first knowledge of the event.
- Considering information provided by (non-serious) adverse event data.
- Informing each trial site of new information arising from serious and non-serious adverse events and adverse drug reactions that may affect the conduct of the Trial, or the rights, interests, safety or wellbeing of Trial Participants, as identified and directed by the Study Chair and/or the Safety Monitoring Committee.
- Under the direction of the Study Chair, notifying the TGA of any significant issue that has arisen from analysis of overseas reports or action that has been taken by another country's regulatory authority within 72 hours of first knowledge.

## *9.3 Reporting requirements for pregnancies*

### 9.3.1 Pregnancies in female patients

A female clinical trial patient must be instructed to stop taking the study drug and immediately inform the investigator if she becomes pregnant during the study. Pregnancies occurring up 6 months after the completion of the study drug must also be reported to the investigator. The patient should be counselled by the investigator, or by a specialist, to discuss the risks of continuing with the pregnancy and the possible effects on the foetus. Monitoring of the patient should continue until conclusion of the pregnancy.

The investigator should report all pregnancies of female clinical trial patients to the Study Chair, BaCT **within one working day** of becoming aware of them using the Pregnancy Reporting Form. Pregnancy should not be recorded on the Adverse Event CRF.

If the investigator becomes aware of a pregnancy occurring in the partner of a patient participating in the study, the pregnancy should be reported to the Study Chair, BaCT **within one working day** of obtaining written consent from the pregnant partner.

The investigator will make arrangements for the partner to be counselled to discuss the risks of continuing with the pregnancy and the possible effects on the foetus. Monitoring of the partner should continue until conclusion of the pregnancy.

NOTE: The Pregnancy Reporting Form should only be completed by the investigator, if the pregnant partner has signed a Pregnant Partner Data Release Form.

### 9.3.2 Pregnancies in female partners of male patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during study treatment or within 6 months after the last dose of study drug. A Pregnancy Report Form should be completed by the investigator within 24 hours after learning of the pregnancy. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign a Pregnant Partner Information and Data Release Form to allow for follow-up on her pregnancy. Once the authorization has been signed, the investigator will update the Pregnancy Report Form with additional information on the course and outcome of the pregnancy. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the foetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

## *9.4 Overdoses*

Any overdose of the trial drug must be reported to BaCT if the event(s) associated with the overdose meet the SAE definitions in Section 9.2.1. If no serious adverse events are experienced the overdose must be reported in the patient's medical record and transcribed onto the relevant trial CRF.

## *9.5 Progression of underlying malignancy*

**Progression of underlying malignancy is not reported as an adverse event** if it is clearly consistent with the suspected progression of the underlying cancer as defined by RECIST criteria, or other criteria as determined by protocol. Hospitalization due solely to the progression of underlying malignancy should NOT be reported as a serious adverse event. Clinical symptoms of progression may be reported as adverse events if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy, or does not fit the expected pattern of progression for the disease under study.

Symptomatic deterioration may occur in some patients. In this situation, progression is evident in the patient's clinical symptoms, but is not supported by the tumour measurements. When the disease progression is so evident, the investigator may elect not to perform further disease assessments, the determination of clinical progression is based on symptomatic deterioration. These determinations should be a rare exception as every effort should be made to document the objective progression of underlying malignancy.

If there is any uncertainty about an adverse event being due only to the disease under study, it should be reported as an AE or SAE.

# 10 STATISTICAL CONSIDERATIONS

## *10.1 Trial Design and Sample Size Determination*

### 10.1.1 Lead-In Phase

The Lead-In Phase will involve a standard 3+3 design with the aim of identifying the MTD for use in the Phase II Dose Expansion Phase. Only three dose levels will be considered if required. A maximum of 6 patients will be enrolled at each dose level therefore the sample size in the Lead-In Phase will be between 6 and 18 patients.

### 10.1.2 Expansion Phase

Simon's optimal two-stage design will be implemented for the mCRC patient cohort in the Expansion Phase. Non-CRC patients will be enrolled in an exploratory cohort of the Expansion Phase which will run in parallel. It is expected that approximately 10 patients will be enrolled into this exploratory cohort.

For the mCRC patient cohort which is of primary interest, the study is designed to distinguish a favourable true response rate (CR or PR) within the first 24 weeks of treatment of ≥20% from a null (uninteresting) rate of ≤5% and will allow early stopping if there is no strong evidence suggesting that the treatment combination of vemurafenib and erlotinib is active.

The required sample size for the mCRC expansion cohort is a maximum of 24 patients, of whom the first 6 patients will be those treated with the MTD in the Lead-In Phase. In the first stage of the Expansion Phase, if 0 of the first 9 evaluable patients (including the 6 patients treated with the MTD in the Lead-In Phase) achieve a CR or PR within the first 24 weeks of treatment, the mCRC expansion cohort may not proceed to the second stage. Otherwise, the mCRC expansion cohort will proceed to the second stage and accrue an additional 15 evaluable patients for a total of 24 evaluable patients. The treatment combination of vemurafenib and erlotinib will be considered active at the end of the second stage if 3 or more patients achieve a CR or PR within the first 24 weeks of treatment. These calculations are based on a significance level of 0.10 and power of 0.80.

**Table 8 Summary of two-stage study design for the mCRC cohort in the Expansion Phase**

| | | | | Stage 2 (n=24) |
|---|---|---|---|---|
| Outcome | Definition of outcome | Criterion | Stage 1 (n=9) Proceed to stage 2 if: | The treatment combination of vemurafenib and erlotinib declared active if |
| Response rate | Proportion of all eligible mCRC patients who commence treatment with vemurafenib and erlotinib at the MTD and who satisfy RECIST criteria 1.1 for a complete or partial response within the first 24 weeks of treatment | >5% | 1 or more responders | 3 or more responders |

The probability of the cohort stopping early at the end of the first stage is 63% if the true response rate is 5%. At the end of the study, the probability of declaring the treatment combination active in the cohort given a true response rate of 5% (null hypothesis) is 10%. The probability of declaring the treatment combination active in the cohort given a true response rate of 20% (alternate hypothesis) is 80%.

## *10.2 Expected Duration*

It is expected that the total accrual time to both the Lead-In and Expansion Phases is 2 years. All patients will be followed for a minimum of 18 months from treatment commencement therefore the total study duration is expected to be 3.5 years (42 months).

## *10.3 Statistical Methods*

All patients registered on the trial will be accounted for in reports of trial outcomes. Baseline patient characteristics will be summarised by cohort (dose level cohorts in the Lead-In Phase and cancer type cohorts in the Expansion Phase) using descriptive statistics and will be reported for continuous variables as number of patients, mean, median, minimum and maximum; and for categorical variables as counts and percentages.

For the Lead-In Phase, analysis will be focused primarily on adverse events, particularly DLTs reported in the DLT observation period. These will be tabulated descriptively for each dose level cohort separately.

The majority of the statistical analysis to be performed for this study will take place at the completion of the Expansion Phase. Details of the planned analyses are summarised below.

### 10.3.1 Analysis of primary endpoint for the Expansion Phase

The proportion of patients achieving a CR or PR within the first 24 weeks of treatment will be estimated separately for each cancer type cohort (mCRC and non-CRC) together with 95% confidence intervals (95% CIs) calculated based on exact values of the binomial distribution. The estimates will be calculated for each cohort using the evaluable patient population as defined previously.

If the observed response rate is high enough to warrant an investigation of associations between patient characteristics and response, exploratory binary logistic regression analyses will be performed. Patient prognostic factors considered will include age, sex, disease characteristics, performance status and previous treatment history.

### 10.3.2 Analysis of secondary endpoints for the Expansion Phase

The proportion of patients experiencing clinical benefit lasting until 16 weeks after commencement of treatment and corresponding 95% CI will be calculated separately for each cancer type cohort using the evaluable patient populations. Exploratory binary logistic regression analyses investigating associations between patient characteristics and clinical benefit will also be performed if the observed clinical benefit rate is high enough to warrant further investigation.

The incidence, worst grade and relatedness to study treatment of toxicities/adverse events, clinically important new or changed laboratory results and other safety data will be summarised in detail using descriptive statistics for each cancer type cohort. All patients who commenced treatment with vemurafenib and erlotinib will be included in this analysis.

Time-to-event secondary endpoints of time to progression, progression-free survival and overall survival will be estimated for each cohort separately using the Kaplan-Meier product limit method; annual rates will be calculated along with 95% CIs. The association of patient prognostic factors and time-to-event endpoints will be assessed using the log-rank test and Cox proportional hazards regression models where appropriate.

## *10.4 Analysis Plan*

Table 9 below provides a summary of the timing of analyses of all endpoints within each study phase:

**Table 9 Summary of timing of analyses of all endpoints within each cohort**

| Analysis | Evaluable patients | Timing |
|---|---|---|
| **PHASE I: LEAD-IN PHASE** | | |
| DLT assessment for each cohort of 3 patients to determine MTD | All registered, eligible mCRC patients who commenced vemurafenib and erlotinib treatment at the dose level to which they were accrued and who either: (i) experiences a DLT during the observation period; or (ii) receives at least 21 days of treatment during the observation period (28 days) without experiencing a DLT. Patients who do not receive at least 21 days of treatment during the observation period (28 days) for reasons other than treatment related toxicity, cease treatment or withdraw from the study for reasons unrelated to study treatment prior to completion of the DLT observation period will not be evaluable and will therefore be replaced in that cohort. | Approximately 4 weeks after the 3rd evaluable patient in each cohort commenced treatment |
| **PHASE II: EXPANSION PHASE** | | |
| **Interim analysis of primary response endpoint for early stopping** | | |
| Interim analysis of response rate (primary endpoint) | All registered, eligible mCRC patients who commenced vemurafenib and erlotinib treatment at the MTD | Approximately 24 weeks after the 9th evaluable patient commenced treatment |
| **Final analysis of primary and secondary response endpoints (for mCRC and non CRC cohorts)** | | |
| Final analysis of response rate (primary endpoint) | All registered, eligible patients who commenced vemurafenib and erlotinib treatment at the MTD | Approximately 24 weeks after the 24th evaluable patient commenced treatment |
| Final analysis of clinical benefit rate (secondary endpoint) | All registered, eligible patients who commenced vemurafenib and erlotinib treatment at the MTD | |
| Final analysis of safety and tolerability | All registered, eligible patients who commenced vemurafenib and erlotinib treatment at the MTD | |
| **Final analysis of time-to-event secondary endpoints (for mCRC and non CRC cohorts)** | | |
| Time to progression | All registered, eligible patients who commenced vemurafenib and erlotinib treatment at the MTD | Approximately 18 months after the last patient accrued commenced treatment |
| Progression-free survival | All registered, eligible patients who commenced vemurafenib and erlotinib treatment at the MTD | |
| Overall survival | All registered, eligible patients who commenced vemurafenib and erlotinib treatment at the MTD | |

# 11 DATA MANAGEMENT AND QUALITY ASSURANCE

## *11.1 Trial Site Data Management*

BaCT Study coordinators will supply CRFs. Principal Investigators (and/or Sub-investigators) at participating Trial Sites must transcribe source data from the source documents onto the CRFs as soon as they are collected.

Completed original CRFs should be returned to BaCT at times requested (refer to CRFs) and a copy of each CRF should be kept at the Trial Site.

Trial Participants are to be identified by initials, trial registration/randomisation number and Trial Site. All CRFs should be completed in black ink and never in pencil. All requested information must be entered on the CRFs. If an item is not available or is not applicable, this fact should be indicated; do not leave a space blank. A correction should be made by striking through the incorrect entry with a single line and by entering the correct information adjacent to it. The correction must be initialled and dated by an adequately qualified and authorised member of the research support team at the Trial Site.

## *11.2 Source Documents*

Source data, including medical histories, pathology/histology reports, ECG reports, radiological imaging, laboratory tests, chemotherapy and radiotherapy treatment records must be retained for 15 years after completion of the trial and be available for checking or clarification of queries by BaCT if required, in accordance with ICH GCP Guidelines.

## *11.3 Quality Assurance Reviews*

Quality assurance reviews will be undertaken by BaCT who will require a copy of the ethics approval letter for each site participating in this trial. Copies of the Clinical Trial Notification (CTN) letter will also be requested from each site (if applicable). Copies of contracts, agreements and other regulatory documents required for the trial will also be collected by BaCT.

Throughout the trial, copies of relevant documents (such as participant diaries, clinical history notes, pathology/histology reports, CT reports, ECG reports and blood test results) may be requested for CRF edit checks and source data verification.

## *11.4 Site Visits and Monitoring*

The arrangements for remote monitoring, or site visits if required, are outlined in detail in the Study Coordinator's manual.

# 12 ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

## *12.1 Ethical Principles and Regulatory Compliance*

The trial will be conducted according to the following regulations and guidelines:

- Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) annotated with TGA comments (Australia, July 2000)
- The Australian Code for Responsible Conduct of Research (August 2007)
- Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects (last amended by the World Medical Association, 2008)
- Guideline on the Regulation of Therapeutic Products in New Zealand. Part 11: Clinical Trials – Regulatory Approval and Good Clinical Practice Requirements (New Zealand, Edition 1.1, May 2011),
- National Statement on Ethical Conduct in Human Research, (Australia, 2007)
- Ethical Guidelines for Intervention Studies (NZ, November 2009), and
- Guidelines for Researchers on Health Research Involving Maori (NZ, version 2, 2010)

This Protocol, including the Participant information Sheet and Consent Form (PIC) must be approved by the responsible HREC before enrolment of trial participants.

If applicable, a CTN form must be submitted to the responsible HREC and returned to BaCT. It is the responsibility of the investigator not to enter participants onto the trial before CTN acknowledgment is received from the TGA.

## *12.2 Adherence to Protocol*

Investigators ascertain they will apply due diligence to avoid protocol deviations. Except for an emergency situation in which proper care for the protection, safety and well being of the trial participant requires that an alternative treatment be used, the trial shall be conducted exactly as described in the approved protocol. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by the sponsor and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

## *12.3 Protocol amendments*

Any change or addition to this protocol requires a written protocol amendment that must be approved by the sponsor before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study, require approval by the HREC of all trial sites. A copy of the written approval by the HREC must be sent to the Trial Centre.

These requirements for approval should in no way prevent any immediate action from being taken by the investigator or by the sponsor in the interests of preserving the safety of subjects included in the trial. However, the investigator may only implement a deviation from or change in the protocol to eliminate an immediate hazard(s) to trial subjects without prior HREC approval/favourable opinion, but the implemented deviation or change must be submitted as soon as possible to the

sponsor for agreement. After consultation with the Study Chair and the Safety Monitoring Committee, the amendment will be sent to the HREC for approval then communicated to all sites.

The HREC of each centre must be kept informed of administrative changes to the protocol, such as:

- changes in the staff used to monitor trials.
- minor administrative changes such as contact details
- corrections of minor errors in the protocol such as formatting errors.

## *12.4 Informed Consent procedures*

A template PIC for this trial is provided in a separate document. The Principal Investigator must insert site-specific information into the template and have this approved by BaCT prior to submitting the PIC to the responsible HREC for final approval.

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol).

Women of child bearing potential should be informed that taking the study medication may involve unknown risks to the foetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

Informed consent for tumour biopsies and hair follicles plucks for exploratory biomarkers is optional but encouraged in this trial.

## *12.5 Confidentiality, audits and inspections*

The trial will be conducted in accordance with applicable Privacy Acts and Regulations. All information regarding trial participants must be treated in strict confidence. Data, which identify any trial participant, must not be revealed to anyone not directly involved in the trial or the clinical care of that participant. An exception is where the trial participant has provided written consent for his/her records to be included in source document verification. In this instance, the records may be inspected by (a) a representative of BaCT for the purposes of source document verification or quality audit as stipulated in the ICH GCP Guidelines, or (b) a representative of a government regulatory authority for the purposes of official inspection. Records must be made available for inspection on the understanding that all information relating to trial participants will be treated in strict professional confidence.

## *12.6 Tissue storage*

Consent to store tissue samples obtained in this study will be part of the patient informed consent form. The samples will be de-identified and, at any stage, a trial participant may withdraw consent for their tissue samples to be retained in the Centre for Translational Pathology at the University of

Melbourne (tumour and hair follicle samples) and Gibbs Lab at the Walter and Eliza Hall Institute (blood biomarker samples) for up to 15 years.

As the knowledge of potential biomarkers is continually evolving, the definitive list of analyses markers may be modified based on new information. Results from the biomarker analyses may therefore be published separately from the results of the clinical trial, and will not identify individual patients. Results of this research will not be communicated to individual patients, but will facilitate the development of better treatments for BRAF V600E mutant cancer patients in the future.

# 13 PUBLICATION AND PRESENTATION POLICY

## *13.1 Reporting of Results*

The Safety Monitoring Committee (SMC) will be responsible for decisions regarding presentations and publications arising from this trial.

Access to data during the trial will be limited to BaCT, the SMC and appropriate regulatory bodies. The trial statistician will perform the primary analysis of trial results, for publication. The principal investigators will publish the primary trial results.

Acknowledgement of BaCT is required in all publications, abstracts and presentations. Publications and abstracts must be presented to the TMC for review and approved prior to submission. In addition, BaCT must review publications prior to submission and BaCT staff directly involved in the project such as the protocol development coordinator, statistician and the clinical trial manager should be authors on any publications coming out of the study.

## *13.2 Trial Registry*

The Principal Investigator is responsible for registering all trials with an appropriate clinical trials registry prior to the accrual of the first participant. All trials are registered at Australian and New Zealand Clinical Trials Registry (ANZCTR) www.anzctr.org.au.

# 14 FINANCIAL ASPECTS

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# 15 APPENDICES

## *15.1 Appendix 1: ECOG Performance status criteria*

As published in American Journal of Clinical Oncology (1982)

| Grade | ECOG |
|---|---|
| 0 | Fully active, able to carry on all pre-disease performance without restriction |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work |
| 2 | Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours |
| 3 | Capable of only limited self care, confined to bed or chair more than 50% of waking hours |
| 4 | Completely disabled. Cannot carry on any self care. Totally confined to bed or chair |
| 5 | Dead |

## *15.2 Appendix 2: Fridericia's Formula for Corrected QT interval*

$$QTcF = QT/RR^{0.33}$$

## *15.3 Appendix 3: New York Heart Association Functional Classification*

| NYHA Class | Symptoms |
|---|---|
| I | No symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc |
| II | Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity |
| III | Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest |
| IV | Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients |

## *15.4 Appendix 4: Toxicity Scoring*

Toxicity will be assessed according to NCI Common Terminology Criteria for Adverse Events version 4.03 (NCI CTC). The toxicity grades for laboratory parameters most relevant to this study are summarised in the table below.

**Table 10 Grades of toxicity relevant to EVICT study**

| **Adverse event** | | | **Grade** | | |
|---|---|---|---|---|---|
| | **1** | **2** | **3** | **4** | **5** |
| **Blood and lymphatic system disorders** | | | | | |
| Anemia | Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN -100 g/L | Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L | Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated | Life-threatening consequences; urgent intervention indicated | Death |
| Febrile neutropenia | | | ANC <1000/mm3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour | Life-threatening consequences; urgent intervention indicated | Death |
| Neutrophil count decreased | <LLN - 1.5 x $10^9$/L | <1.5 - 1.0 x $10^9$/L | <1.0 - 0.5 x $10^9$/L | <0.5 x $10^9$/L | - |
| Platelet count decreased | <LLN - 75.0 x $10^9$/L | <75.0 - 50.0 x $10^9$/L | <50.0 - 25.0 x $10^9$/L | <25.0 x $10^9$/L | - |
| **Cardiac disorders** | | | | | |
| Electrocardiogram QT corrected interval prolonged | QTc 450 - 480 ms | QTc 481 - 500 ms | QTc >= 501 ms on at least two separate ECGs | QTc >= 501 or >60 ms change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious | - |

| | | | | | |
|---|---|---|---|---|---|
| | | | | arrhythmia | |
| **Gastrointestinal disorders** | | | | | |
| Diarrhea | Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline | Increase of 4 - 6 tools per day over baseline; moderate increase in ostomy output compared to baseline | Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL | Life-threatening consequences; urgent intervention indicated | Death |
| Gastrointestinal perforation | - | Symptomatic; medical intervention indicated | Severe symptoms; elective operative intervention indicated | Life-threatening consequences; urgent intervention indicated | Death |
| Nausea | Loss of appetite without alteration in eating habits | Oral intake decreased without significant weight loss, dehydration or malnutrition | Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated | - | - |
| Vomiting | 1 - 2 episodes (separated by 5 minutes) in 24 hrs | 3 - 5 episodes (separated by 5 minutes) in 24 hrs | >=6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalization indicated | Life-threatening consequences; urgent intervention indicated | Death |
| **General disorders and administration site conditions** | | | | | |
| Fatigue | Fatigue relieved by rest | Fatigue not relieved by rest; limiting instrumental ADL | Fatigue not relieved by rest, limiting self care ADL | - | - |
| **Hepatobiliary disorders** | | | | | |
| Alanine aminotransferase (ALT) increased | >ULN - 3.0 x ULN | >3.0 - 5.0 x ULN | >5.0 - 20.0 x ULN | >20.0 x ULN | - |
| Aspartate | >ULN - 3.0 x ULN | >3.0 - 5.0 x ULN | >5.0 - 20.0 x ULN | >20.0 x ULN | - |

| | | | | | |
|---|---|---|---|---|---|
| aminotransferase (AST) increased | | | | | |
| Blood bilirubin increased | >ULN - 1.5 x ULN | >1.5 - 3.0 x ULN | >3.0 - 10.0 x ULN | >10.0 x ULN | - |
| **Metabolism and nutrition disorders** | | | | | |
| Hyperuricemia | >ULN - 10 mg/dL (0.59 mmol/L) without physiologic consequences | - | >ULN - 10 mg/dL (0.59 mmol/L) with physiologic consequences | >10 mg/dL; >0.59 mmol/L; life threatening consequences | Death |
| **Musculoskeletal and connective tissue disorders** | | | | | |
| Arthralgia | Mild pain | Moderate pain; limiting instrumental ADL | Severe pain; limiting self care ADL | - | - |
| **Skin and subcutaneous tissue disorders** | | | | | |
| Photosensitivity | Painless erythema and erythema covering <10% BSA | Tender erythema covering 10 - 30% BSA | Erythema covering >30% BSA and erythema with blistering; photosensitivity; oral corticosteroid therapy indicated; pain control indicated (e.g., narcotics or NSAIDs) | Life-threatening consequences; urgent intervention indicated | Death |
| Rash acneiform | Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness | Papules and/or pustules covering 10 - 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL | Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self care ADL; associated with local superinfection with oral | Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life | Death |

| | | | | | |
|---|---|---|---|---|---|
| | | | antibiotics indicated | threatening consequences | |
| Rash maculo-papular | Macules/papules covering <10% BSA with or without symptoms (e.g., pruritus, burning, tightness) | Macules/papules covering 10 - 30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL | Macules/papules covering >30% BSA with or without associated symptoms; limiting self care ADL | - | - |
| Papulopustular rash | Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness | Papules and/or pustules covering 10-30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL | Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated | Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life threatening consequences | Death |
| Rash pustular | - | Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral) | IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated | - | - |
| Stevens-Johnson syndrome | - | - | Skin sloughing covering <10% BSA with associated signs (e.g., erythema, purpura, epidermal detachment and mucous membrane detachment) | Skin sloughing covering 10 - 30% BSA with associated signs (e.g., erythema, purpura, epidermal detachment and mucous membrane detachment) | Death |
| Toxic epidermal necrolysis | - | - | - | Skin sloughing covering >=30% BSA with associated symptoms (e.g., erythema, purpura, or epidermal detachment) | Death |

## *15.5 Appendix 5: RECIST 1.1 criteria- Response Evaluation Criteria in Solid Tumours*

Only patients with measurable disease at baseline should be included in protocols where objective tumour response is the primary endpoint.

**Measurable disease** - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

**Measurable lesions** - lesions that can be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)

For malignant lymph nodes to be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and follow-up, only the short axis will be measured and followed.

**Non-measurable lesions** - all other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

All measurements should be taken and recorded in metric notation, using callipers if clinically assessed. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by colour photography, including a ruler to estimate the size of the lesion, is recommended.

**Methods of Measurement**

- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumours of the chest, abdomen and pelvis. Head and neck tumours and those of extremities usually require specific protocols.
- Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

**Baseline documentation of "Target" and "Non-Target" lesions**

- All measurable lesions up to a maximum of two lesions per organ and 5 lesions in total, representative of all involved organs should be identified as **target lesions** and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs and should be those that lend themselves to reproducible repeated measurements. On occasion, the largest lesion may not lend itself to reproducible measurement, in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.
- Only the short axis of lymph nodes identified as target lesions contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumour.
- A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference by which to characterise the objective tumour.
- All other lesions (or sites of disease) including pathological lymph nodes should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases 'unequivocal progression' of each should be noted throughout follow-up. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case report form (e.g. multiple enlarged pelvic lymph nodes or multiple liver metastases'.

**Table 11 RECIST 1.1 Response Criteria**

| | **Target lesions** | **Non-target lesions** |
|---|---|---|
| **Complete Response (CR)** | Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm | Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (<10 mm short axis) |
| **Partial Response (PR)** | At least a 30% decrease in the sum of diameters of target lesions, taking as *reference the baseline sum diameters* | Persistence of one or more non-target lesion(s) or/and maintenance of tumour marker level above the normal limits |
| **Progressive Disease (PD)** | At least a 20% increase in the sum of diameters of target lesions, taking as *reference the smallest sum on study* (this includes the baseline sum if that is the smallest on study). In addition, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression. | Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions (1) |
| **Stable Disease (SD)** | Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as *reference the smallest sum diameters while on study.* | |
| *(1) Although a clear progression of "non target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should ideally be confirmed later on by the review panel (or Study Chair).* | | |

**Confirmation**

- The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.
- To be assigned a status of PR or CR, changes in tumour measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.

- In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol.

**Evaluation of overall response**

| Target lesions | Non-target lesions | New lesions | Overall response |
|---|---|---|---|
| CR | CR | No | CR |
| CR | Non-CR/non-PD | No | PR |
| CR | Not evaluated | No | PR |
| PR | Non-PD or not all evaluated | No | PR |
| SD | Non-PD or not all evaluated | No | SD |
| Not all evaluated | Non-PD | No | Invaluable |
| PD | Any | Yes or No | PD |
| Any | PD | Yes or No | PD |
| Any | Any | Yes | PD |

## *15.6 Appendix 6: Medication Affecting QT Interval*

| | | | |
|---|---|---|---|
| Albuterol | Doxepin | Lithium | Quinidine |
| Alfuzosin | Droperidol | Mesoridazine | Ranolazine |
| Amantadine | Ephedrine | Metaproterenol | Risperidone |
| Amiodarone | Epinephrine | Methadone | Ritodrine |
| Amitriptyline | Erythromycin | Methylphenidate | Roxithromycin |
| Amphetamine | Felbamate | Mexiletine | Salmeterol |
| Arsenic trioxide | Fenfluramine | Midodrine | Sertindole |
| Astemizole | Flecainide | Moexipril | Sertraline |
| Atazanavir | Fluconazole | Moxifloxacin | Sibutramine |
| Atomoxetine | Fluoxetine | Nicardipine | Sibutramine |
| Azithromycin | Foscarnet | Nilotinib | Solifenacin |
| Bepridil | Fosphenytoin | Norepinephrine | Sotalol |
| Chloral hydrate | Galantamine | Nortriptyline | Sparfloxacin |
| Chloroquine | Gatifloxacin | Octreotide | Sunitinib |
| Chlorpromazine | Gemifloxacin | Ofloxacin | Tacrolimus |
| Ciprofloxacin | Granisetron | Ondansetron | Tamoxifen |
| Cisapride | Halofantrine | Oxytocin | Telithromycin |
| Citalopram | Haloperidol | Paliperidone | Terbutaline |
| Clarithromycin | Ibutilide | Paroxetine | Terfenadine |
| Clomipramine | Imipramine | Pentamidine | Thioridazine |
| Clozapine | Indapamide | Perflutren lipid microspheres | Tizanidine |
| Cocaine | Isoproterenol | Phentermine | Tolterodine |
| Desipramine | Isradipine | Phenylephrine | Trimethoprim-Sulfa |
| Dexmethylphenidate | Itraconazole | Phenylpropanolamine | Trimipramine |
| Disopyramide | Ketoconazole | Pimozide | Vardenafil |
| Dobutamine | Lapatinib | Probucol | Venlafaxine |
| Dofetilide | Levafloxacin | Procainamide | Voriconazole |
| Dolasetron | Levalbuterol | Protriptyline | Ziprasidone |
| Domperidone | Levomethadyl | Pseudoephedrine | |
| Dopamine | Lisdexamfetamine | Quetiapine | |

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