Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Study Inclusion and Exclusion Criteria

Eligibility criteria (Prodige 18 - Accord 22)
Inclusion criteria: 1. Histologically or cytologically proven colorectal adenocarcinoma expressing wild-type RAS (KRAS and NRAS). 2. Progressive metastatic disease after first-line treatment with only one previous chemotherapy based on 5-FU (IV or per os) with irinotecan or oxaliplatin associated with bevacizumab. 3. Prior fluoropyrimidine-based adjuvant chemotherapy (for the primary tumor) with oxaliplatin is allowed if the time interval between the end of this chemotherapy and the beginning of the first-line metastatic treatment is ≥6 months. 4. Measurable disease (at least one measurable metastatic lesion by RECIST V1.1 criteria, with lesion not located in a previous field of radiation). 5. Previous radiotherapy is authorized if discontinued ≥15 days prior to randomization and if the measurable metastatic lesions are outside the radiation area. 6. Sites of disease evaluated within 28 days prior to randomization with thoracic-abdominal-pelvic CT scan (or abdominal-pelvic MRI and chest X-ray) 7. Age ≥18 years 8. Patient with ECOG 0 or 1 9. Life expectancy ≥12 weeks 10. Hematologic function: polynuclear neutrophils ≥ $1.5.10^9$/L; platelets ≥100.10^9/L; hemoglobin ≥9 g/dL 11. Hepatic function: transaminases ≤2.5 times upper limit of normal (ULN) (≤5 ULN in case of hepatic metastases), alkaline phosphatases ≤2.5 x ULN (≤5 ULN in case of hepatic metastases), total bilirubin ≤1.5 x ULN 12. Renal function: creatinemia ≤1.5 x ULN; creatinine clearance ≥50 mL/min (Cockcroft and Gault); urine test strip <+2. If proteinuria is ≥+2 at inclusion, the serum urea test must be redone and show proteinuria ≤1 g/L within 24 h) 13. Patients having completed the EORTC QLQ-C30 quality of life form 14. Negative pregnancy test for women of child-bearing age 15. Information given to the patient and signed informed consent 16. Public Health insurance coverage
Exclusion criteria: 1. Known meningeal or brain metastases 2. Patient previously treated with an anti-EGFR 3. Specific contraindication or known hypersensitivity to one of the study treatments 4. Patients who received a dose de-escalation scheme e.g.LV5FU bevacizumab followed by FOLFOX or FOLFIRI with bevacizumab. 5. Patient with known allergy or hypersensitivity to monoclonal antibodies (bevacizumab, cetuximab), or to Chinese hamster ovarian cell products or any other humanized or recombined antibodies or any other chemotherapies under study, and their excipients. 6. Clinically significant coronaries affection or myocardial infarction within 6 months prior to inclusion. 7. Peripheral neuropathy of grade >1 (CTCAE V4.0). 8. Known dihydropyrimidine dehydrogenase (DPD) deficiency.

9. Acute intestinal obstruction or sub-obstruction, history of inflammatory intestinal disease or extended resection of the small intestine. Presence of a colic prosthesis.
10. Unhealed wound, active gastric or duodenal ulcer, or bone fracture
11. History of abdominal fistulas, trachea-esophageal fistulas or any other grade 4, gastro-intestinal perforations or non-gastrointestinal fistulas or intra-abdominal abscesses during the 6 months before inclusion.
12. Uncontrolled arterial hypertension (systolic pressure >150 mmHg and/or diastolic pressure >100 mmHg with and without antihypertensive medication. Patients with high hypertension are eligible if antihypertensive medication lowers their arterial pressure to the level specified by the inclusion criterion.
13. History of hypertensive crisis or hypertensive encephalopathy
14. Thromboembolic event in the 6 months before inclusion (e.g. transitory ischemic stroke, stroke, subarachnoid hemorrhage) except peripheral deep vein thrombosis treated with anticoagulants
15. Other concomitant malignancy or history of cancer (except in situ carcinoma of the cervix, or non-melanoma skin cancer, treated with curative intent treatment) except if considered in complete remission for at least 5 years before randomization.
16. Existence of any other pathology, metabolic problem, anomaly during the clinical examination or biological anomaly which may reasonable suspect an underlying pathology which would contra-indicate the use of the study medication or any other risk of complication related to the treatment.
17. Any treatment including an experimental drug, or participation in another clinical trial within 28 days before randomization.
18. Pregnant women, or women who could possibly be pregnant (or who expect to fall pregnant within 6 months of the end of treatment), or who are breast feeding are not eligible.
19. Men and women of child-bearing age who do not accept to use a highly effective contraceptive (as per currently acceptable institutional standards) or abstinence during the study and for the 6 months after the last administration of the study treatments.
20. Persons deprived of liberty or under guardianship.
21. Psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule.

eTable 2. Overall Tumor Response and Efficacy According to *RAS* and *BRAF* Status

Overall tumor response	**Bevacizumab + Chemotherapy**	**Cetuximab + Chemotherapy**
wt*KRAS* *(exon 2)*	(n=65)	(n=67)
Best overall response (%)		
Complete response	3 (4.6)	0 (0)
Partial response	13 (20.0)	20 (29.9)
Stable disease	45 (69.2)	34 (50.7)
Progressive disease	4 (6.1)	8 (11.9)
Not evaluable	0 (0)	1 (1.5)
Objective response rate, n (%) [95% CI]	16 (24.6) [14.1–35.1]	20 (31.8) [20.3–43.2]
wt*KRAS*, and wt*NRAS*	(n=41)	(n=40)
Best overall response (%)		
Complete response	1 (2.4)	0 (0)
Partial response	11 (26.8)	13 (32.5)
Stable disease	28 (68.3)	19 (47.5)
Progressive disease	2 (4.9)	6 (15.0)
Not evaluable	0 (0)	2 (5.0)
Objective response, n (%) [95% CI]	12 (29.3) [15.3–43.2]	13 (34.2) [19.1–49.3]
wt*KRAS*, wt*NRAS*, and wt*BRAF*	(n=36)	(n=37)
Best overall response (%)		
Complete response	0 (0)	0 (0)
Partial response	11 (30.6)	13 (35.1)
Stable disease	24 (66.7)	17 (45.9)
Progressive disease	1 (2.8)	5 (13.5)
Not evaluable	0 (0)	2 (5.4)
Objective response, n (%) [95% CI]	30.5 [15.1–45.6]	13 (37.1) [21.1–53.2]

Efficacy according to *RAS* and *BRAF* status	**Bevacizumab + Chemotherapy**	**Cetuximab + Chemotherapy**	**Hazard Ratio (95 % CI)**	***P* value**
wt*KRAS* (exon 2)				
No. of patients	65	67		
4-month PFS rate, % (95% CI)	80.3 (68.0–88.3)	66.7 (53.6–76.8)		
Median PFS (months) (95% CI)	7.1 (5.7–8.2)	5.6 (4.2–6.5)	0.710 (0.495–1.018)	.0622
Median OS (months) (95% CI)	15.8 (9.5–22.3)	10.4 (7.0–16.2)	0.688 (0.456–1.038)	.0750

wt*KRAS* and wt*NRAS*				
No. of patients	41	40		
4-month PFS rate, % (95% CI)	88.8 (71.2–94.3)	65.7 (48.5–78.5)		
Median PFS (months) (95% CI)	7.8 (5.8–8.5)	5.6 (3.5–7.1)	0.661 (0.416–1.049)	.0792
Median OS (months) (95% CI)	21.0 (10.0–28.2)	10.7 (6.8–22.4)	0.759 (0.438–1.316)	.3257
wt*KRAS*, wt*NRAS*, and wt*BRAF*				
No. of patients	36	37		
4-month PFS rate, % (95% CI)	90.9 (74.4–97.0)	68.6 (50.5–81.2)		
Median PFS (months) (95% CI)	8.2 (6.6–8.6)	5.7 (4.1–7.1)	0.665 (0.407–1.087)	.1035
Median OS (months) (95% CI)	21.1 (12.3–35.1)	12.6 (6.8–22.5)	0.758 (0.416–1.383)	.3669

Abbreviations: CI, confidence interval; OS, overall survival; PFS, progression-free survival; wt, wild-type.

eTable 3. Overview of Main Adverse Events

Adverse Events, n (%)	Bevacizumab + Chemotherapy (n=65)		Cetuximab + Chemotherapy (n=67)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Anemia	43 (66.1)	3 (4.6)	46 (68.6)	9 (13.4)
Neutropenia	40 (61.5)	12 (18.5)	35 (52.2)	10 (14.9)
Thrombocytopenia	40 (61.5)	0 (0)	30 (44.8)	2 (3.0)
Febrile neutropenia	0 (0)	3 (4.6)	0 (0)	0 (0)
Skin disorders	25 (38.5)	0 (0)	57 (85.1)	13 (19.4)
Nausea	38 (58.5)	3 (4.6)	25 (37.3)	1 (1.5)
Vomiting	15 (23.1)	1 (1.5)	14 (20.9)	2 (3.0)
Anorexia	21 (32.3)	3 (4.6)	22 (32.8)	1 (1.5)
Fatigue	54 (83.1)	7 (10.8)	50 (74.6)	7 (10.4)
Stomatitis	19 (29.2)	1 (1.5)	24 (35.8)	5 (7.5)
Paronychia	- (-)	- (-)	13 (19.4)	3 (4.5)
Diarrhea	42 (64.6)	5 (7.7)	25 (37.3)	6 (8.9)
Peripheral neuropathy	26 (40.0)	2 (3.1)	27 (40.3)	3 (4.5)
Epistaxis	12 (18.5)	0 (0)	5 (7.5)	0 (0)
Thromboembolic event	1 (1.5-)	1 (1.5)	1 (1.5)	1 (1.5)