Supplementary Appendix

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

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Vemurafenib in Multiple Nonmelanoma *BRAF*^{V600}-Mutated Cancers

Hyman DH, Puzanov I, Vivek Subbiah V et al.

Supplemental Materials

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Figure S1. Study design. CT, indicates computed tomography; MRI, magnetic resonance imaging; RR, response rate.

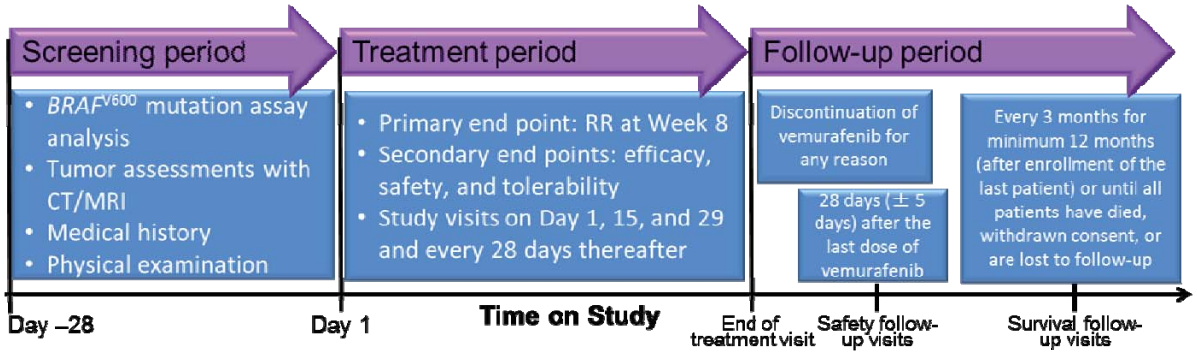


Figure S2. Pretreatment and on-treatment response assessments. (A) Non-small cell lung cancer. (B) Cholangiocarcinoma. (C) Anaplastic thyroid cancer. (D) Ovarian Cancer. (E) Pancreatic cancer. (F) Erdheim-Chester disease. (G) Langerhans cell histiocytosis. (H) Glioblastoma. (I) Salivary Gland Cancer.

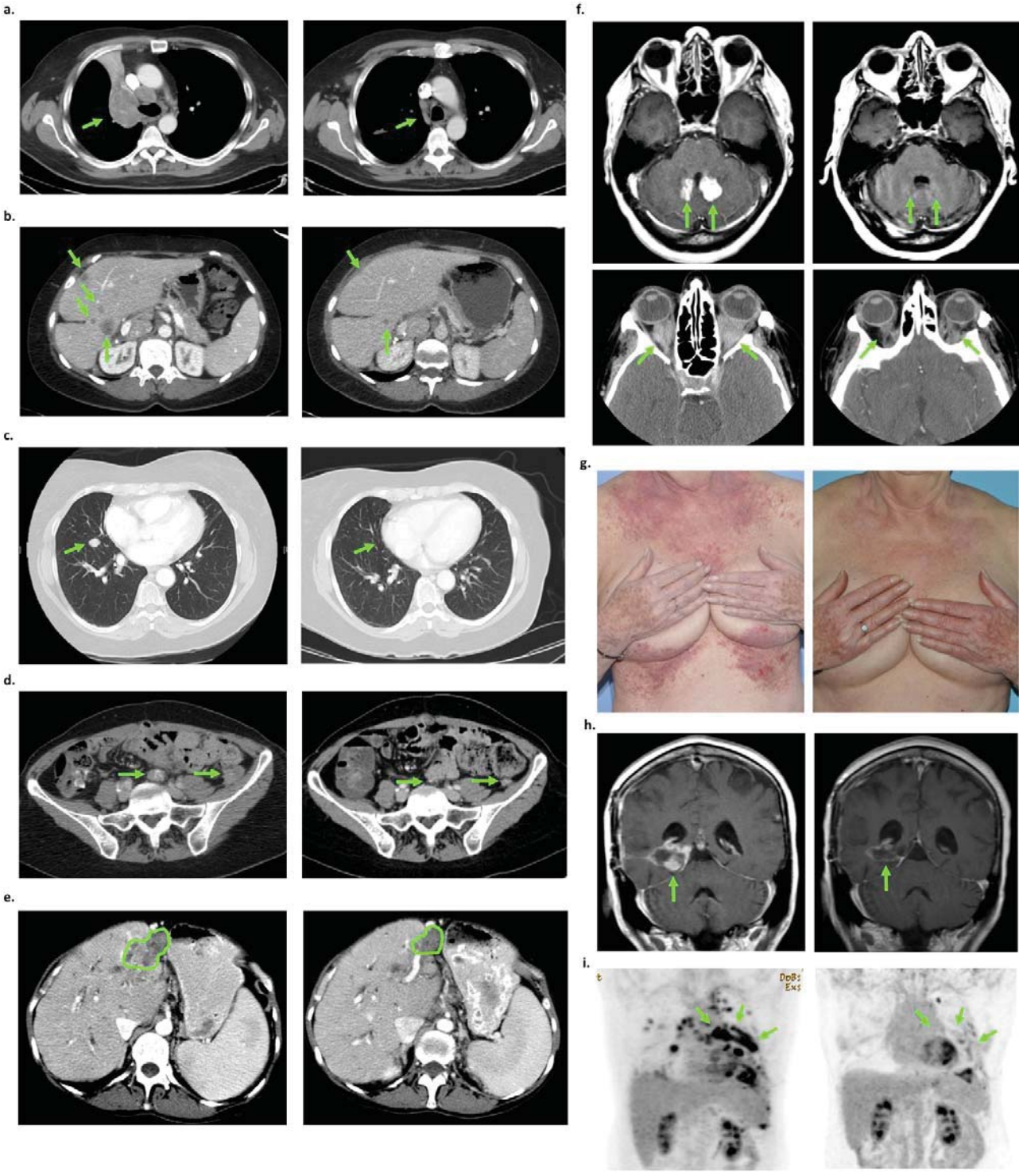
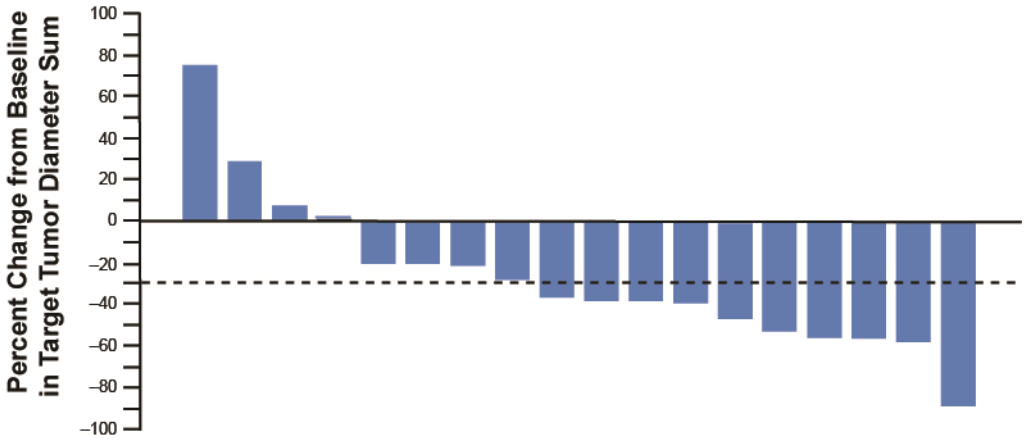
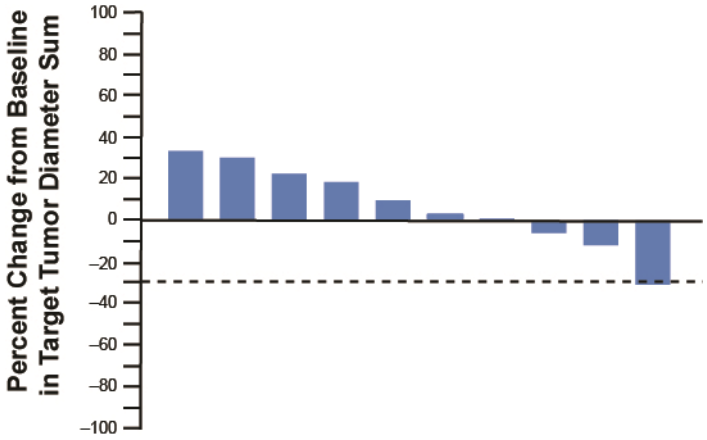


Figure S3. Maximum percentage change from baseline in target lesion diameter sum. (A) NSCLC cohort.a,b (B) Colorectal cancer cohort (vemurafenib monotherapy).b (C) Colorectal cancer cohort (vemurafenib + cetuximab combination therapy). *Indicates patients in the dose escalation stage (dose levels 1 and 2).b (D) Cholangiocarcinoma cohort.b (E) ECD/LCH cohort. †Indicates patient has LCH.b (F) Anaplastic thyroid cancer cohort.b (G) Other tumor cohort.a,b,c aOne patient died before evaluation. bIncludes only patients who had measurable disease at baseline based on RECIST and at least one posttreatment tumor evaluation. cIncludes brain tumor, head and neck cancer, pancreatic cancer, esophageal and gastric cancer, sarcoma, low-grade serous ovarian cancer, multiple myeloma, and carcinoma of unknown primary. ECD/LCH indicates Erdheim-Chester disease/Langerhans cell histiocytosis; NSCLC, non-small cell lung cancer; PXA, pleomorphic xanthoastrocytoma; RECIST, Response Evaluation Criteria In Solid Tumors, version 1.1.

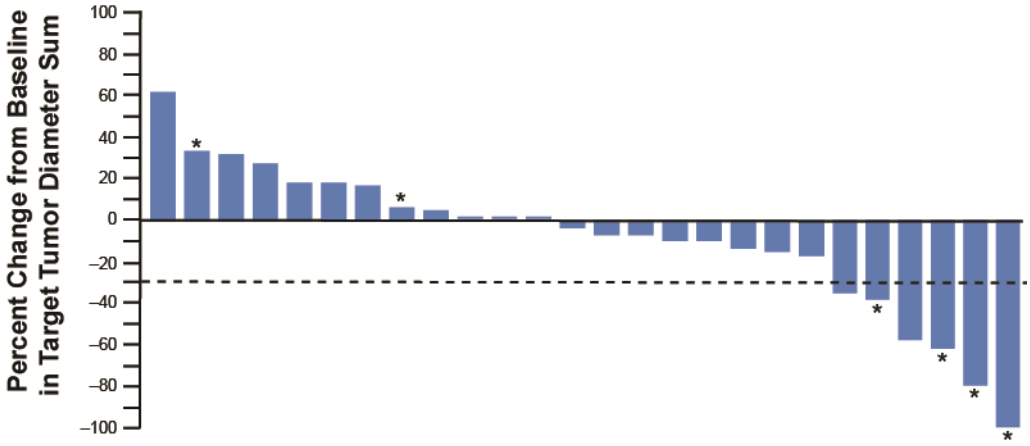
A. NSCLC



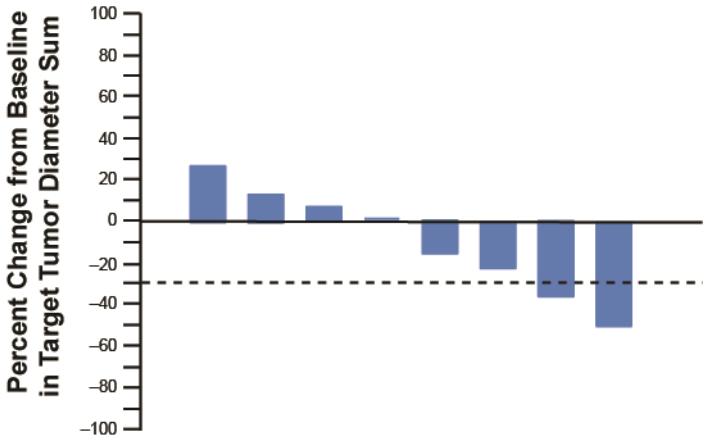
B. Colorectal cancer (vemurafenib monotherapy)



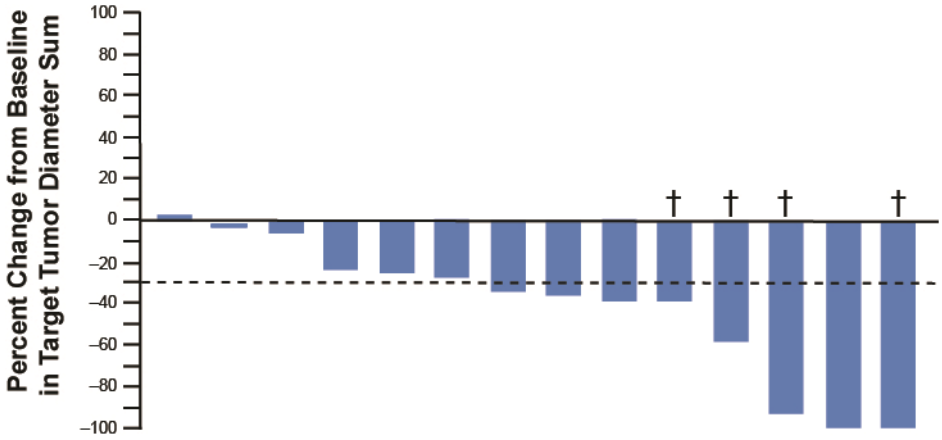
C. Colorectal cancer (vemurafenib + cetuximab)



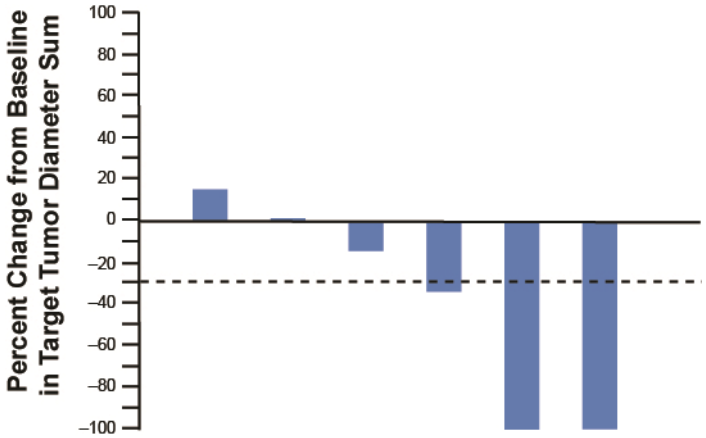
D. Cholangiocarcinoma



E. ECD/LCH



F. Anaplastic thyroid



G. Other

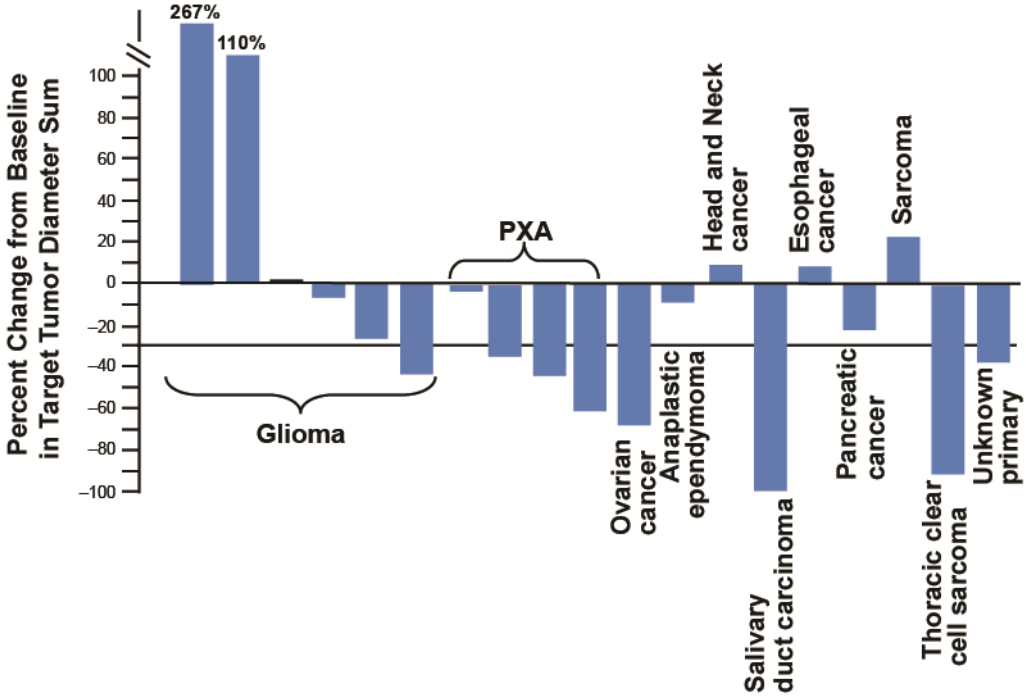
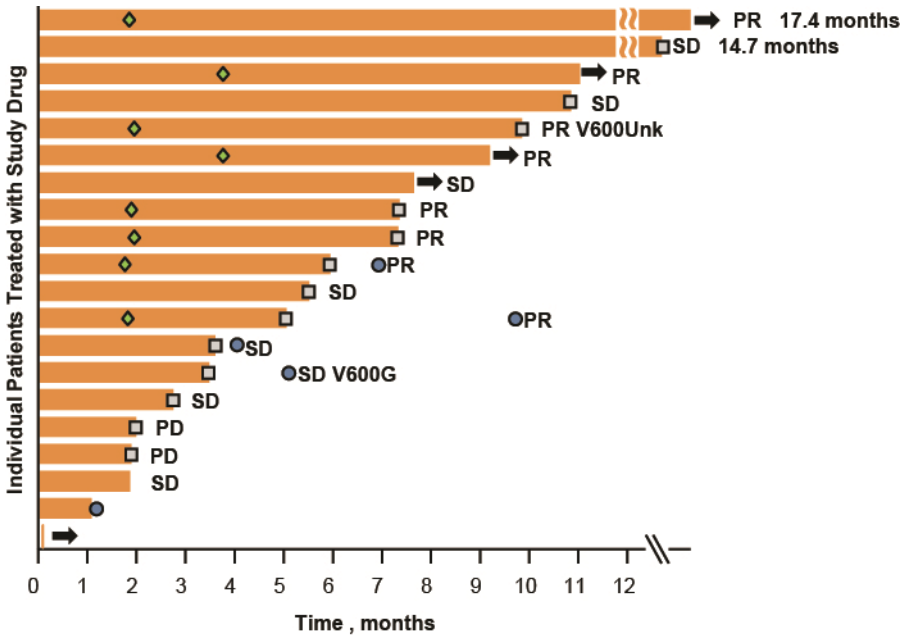
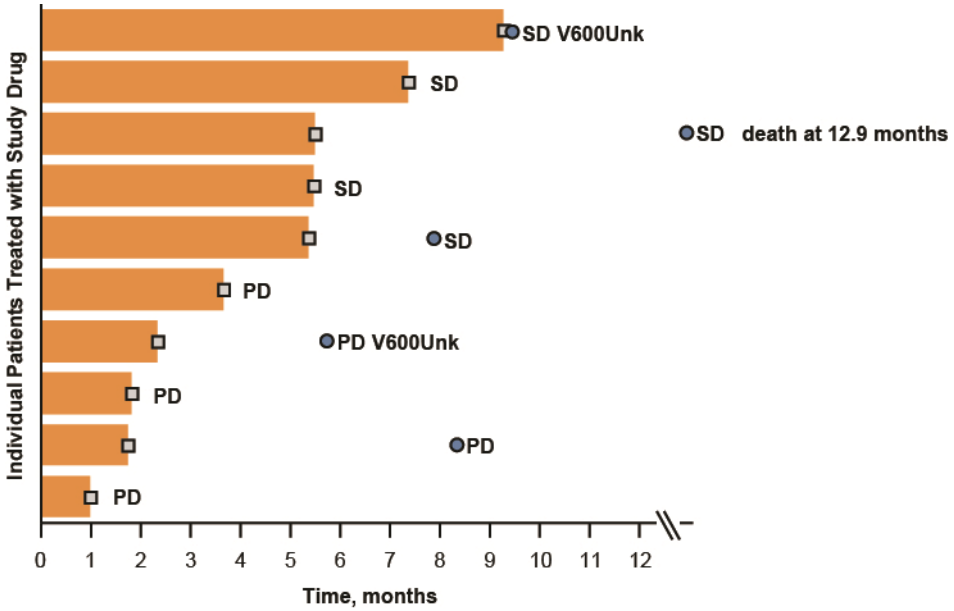


Figure S4. Time to events by patient and best overall response (confirmed). (A) NSCLC cohort.a,b (B) Colorectal cancer cohort (vemurafenib monotherapy).b (C) Colorectal cancer cohort (vemurafenib + cetuximab). *Indicates patients in the dose escalation stage (dose levels 1 and 2).b (D) Cholangiocarcinoma cohort.b (E) ECD/LCH cohort. †Indicates patient has LCH.b (F) Anaplastic thyroid cancer cohort.b (G) Other tumors cohort.b,c Bar length for those patients who do not have disease progression (box) or death (circle) represents progression-free survival duration. BRAFV600G and unknown BRAFV600 mutations are indicated by V600G and V600Unk, respectively. aOne patient died before evaluation. bIncludes only patients who had measurable disease at baseline based on RECIST and at least one posttreatment tumor evaluation. cIncludes breast cancer (BC), cervical cancer (CC), brain tumors, head and neck cancer, esophageal and gastric cancer (ECG), pancreatic cancer, sarcoma, low-grade serous ovarian cancer, multiple myeloma, and carcinoma of unknown primary. AE indicates anaplastic ependymoma; CLC, cholangiocarcinoma; ECD/LCH, Erdheim-Chester disease/Langerhans cell histiocytosis; HNC, head and neck cancer; NSCLC, non-small cell lung cancer; OC, low-grade serous ovarian cancer; PXA, anaplastic pleomorphic xanthoastrocytoma; SGC, salivary gland carcinoma; TCC, thoracic clear cell.

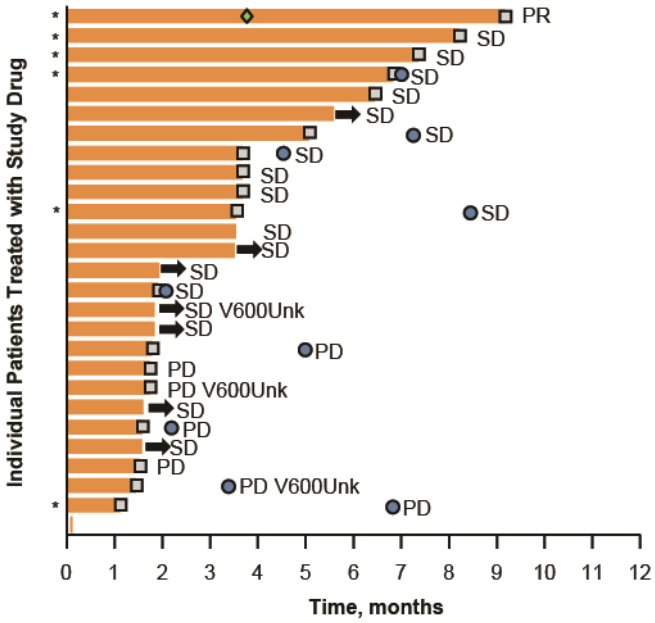
A. NSCLC



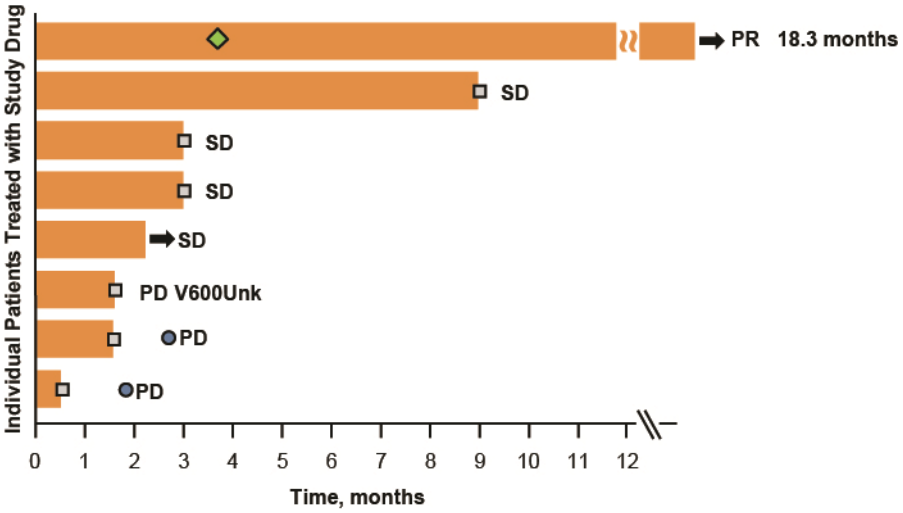
B. Colorectal cancer (vemurafenib monotherapy)



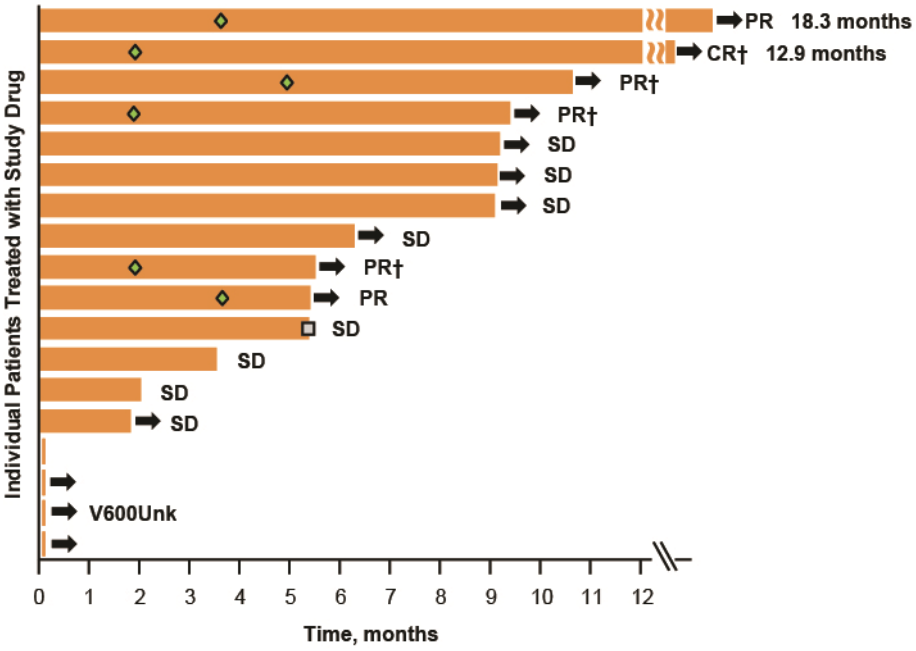
C. Colorectal cancer (vemurafenib + cetuximab)



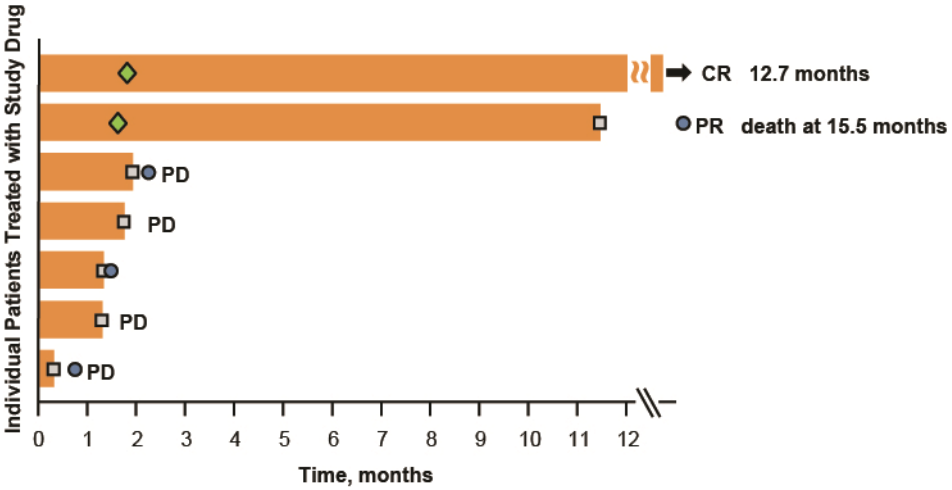
D. Cholangiocarcinoma



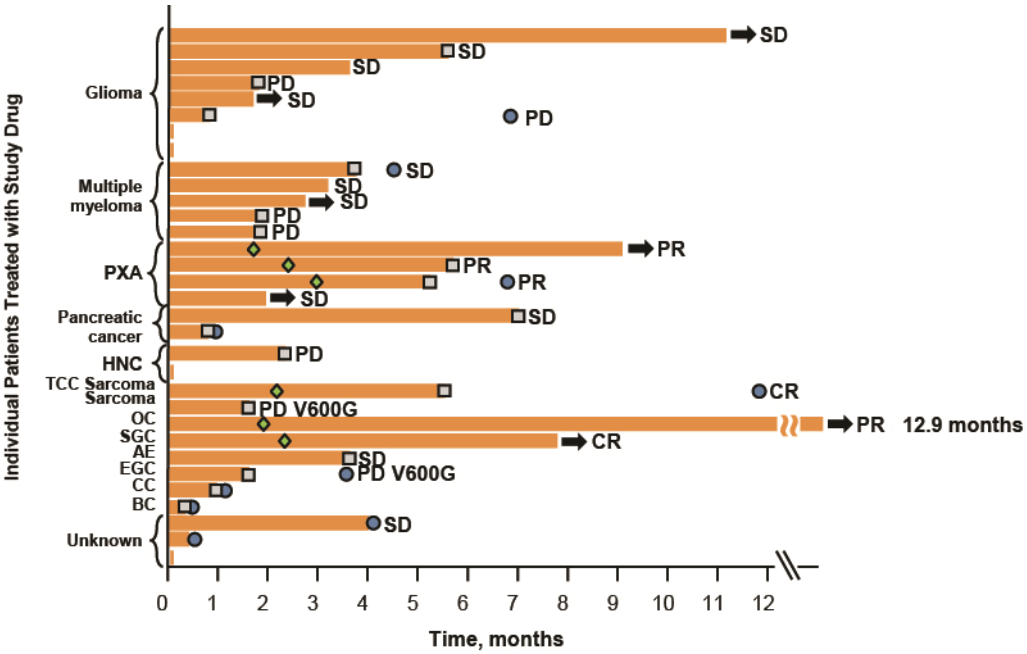
E. ECD/LCH



F. Anaplastic thyroid



G. Other



Legend

- VEM ongoing
- Time to Progression
- Time to Response
- Died

Table S1. International Melanoma Working Group Uniform Response Criteria (*adapted with permission from Macmillan Publishers Ltd, copyright 2006*)[1]

Response subcategory	**Response criteria (each of the following criteria must be met)[a]**
Complete response	• Negative immunofixation on the serum and urine • Disappearance of any soft tissue plasmacytomas • ≤5% plasma cells in bone marrow
Stringent complete response	All of the criteria of a complete response plus • Normal free light chain ratio • Absence of clonal cells in bone marrow (repeat biopsy not needed) by immunohistochemistry or immunofluorescence[b]
Very good partial response	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥90% or greater reduction in serum M-protein plus urine M-protein level <100mg per 24 h
Partial response	• ≥50% reduction of serum M-protein and reduction in 24-h urinary M-protein by≥90% or to <200mg per 24 h[c] • In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required
Stable disease (not recommended for use as indicator of response)	• Not meeting criteria for complete response, very good partial response, partial response, or progressive disease
Response subcategory	**Response criteria (one or more of the following criteria must be met)**
Progressive disease	Increase of ≥25% from baseline in • Serum M-component (the absolute increase must be ≥0.5 g/dl)[d] • Urine M-component (the absolute increase must be ≥200 mg/24 h) o Only in patients without measurable serum and urine M-protein levels: The absolute increase must be >10 mg/dl for the difference between involved and uninvolved free light chain levels • Bone marrow plasma cell percentage: the absolute % must be ≥10%[e] • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas • Development of hypercalcemia (corrected serum calcium >11.5 mg/dl or 2.65 mmol/l) that can be attributed solely to the plasma cell proliferative disorder
Clinical relapse	• Direct indicators of increasing disease and/or end organ dysfunction (CRAB features)[d] 1. Development of new soft tissue plasmacytomas or bone lesions 2. Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion 3. Hypercalcemia (>11.5 mg/dl) [2.65 mmol/l] 4. Decrease in hemoglobin of ≥2 g/dl [1.25 mmol/l] 5. Rise in serum creatinine by ≥2 mg/dl [≥177 μmol/l]
Relapse from complete response (to be used only if endpoint is disease-free survival)	• Reappearance of serum or urine M-protein by immunofixation or electrophoresis • Development of ≥5% plasma cells in the bone marrow[e] • Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcemia see below)

[a]All response categories require two consecutive assessments made at anytime before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements.

[b]Presence/absence of clonal cells is based upon the k/λ ratio.

[c]If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved free light chain levels is required in place of the M-protein criteria If serum and urine M-protein are unmeasurable, and serum free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥30%.
[d]For progressive disease, serum M-component increases of ≥1 gm/dl are sufficient to define relapse if starting M-component is ≥5 g/dl.
[e]Relapse from CR has the 5% cutoff versus 10% for other categories of relapse

Table S2. Disease-Specific Patient Characteristics.

Characteristic — no. (%)	All Enrolled Patients
NSCLC cohort	(n = 20)
Race	
White	12 (60)
Black	1 (5)
Asian	0
Other	0
Not collected (per local regulations)	7 (35)
Smoking history	
Current smoker/former smoker	13 (65)
Never smoker	7 (35)
BRAF^{V600} detection method*, n (%)	
Sanger	6 (30)
PCR	4 (20)
Sequenom	3 (15)
SNaPshot	4 (20)
NGS	3 (15)
Sites of metastasis	
Liver	8 (40)
Lymph nodes	18 (90)
Pleura	11 (55)
Peritoneum	1 (5)
Skin	0
Soft tissues	2 (10)
Bone	8 (40)
Brain	3 (15)
Other	7 (35)
Any systemic therapy	19 (95)
Platinum-containing therapy*	18 (90)
Docetaxel/paclitaxel*	10 (50)
Colorectal cancer cohort (vemurafenib monotherapy)	(n = 10)
Primary tumor location	
Colon	6 (60)
Rectum	2 (20)
Colon and rectum	2 (20)
BRAF^{V600} detection method*, n (%)	
cobas 4800	2 (20)
Sanger	2 (20)
PCR	2 (20)
Sequenom	4 (40)
Sites of metastasis	
Liver	3 (30)
Lung	7 (70)
Lymph nodes	5 (50)
Pleura	1 (10)
Peritoneum	6 (60)
Soft tissues	1 (10)
Bone	2 (20)
Brain	1 (10)
Other	3 (30)
Any systemic therapy	10 (100)
FOLFOX*†	10 (100)

Characteristic — no. (%)	All Enrolled Patients
FOLFIRI*‡	8 (80)
Cetuximab or panitumumab (EGFR antibody)*	7 (70)
Bevacizumab*	5 (50)
Colorectal cancer cohort (vemurafenib/cetuximab)	(n = 27)
Primary tumor location	
Colon	22 (81)
Rectum	4 (15)
Colon and rectum	1 (4)
BRAF^{V600} detection method*, n (%)	
cobas 4800	2 (7)
Sanger	3 (11)
PCR	9 (33)
Sequenom	5 (19)
SNaPshot	5 (19)
NGS	2 (7)
Other**	1 (4)
Sites of metastasis	
Liver	18 (67)
Lung	11 (41)
Lymph nodes	12 (44)
Pleura	2 (7)
Peritoneum	9 (33)
Skin	2 (7)
Soft tissues	1 (4)
Bone	1 (4)
Brain	0
Other	2 (7)
Any systemic therapy	27 (100)
FOLFOX*†	21 (78)
FOLFIRI*‡	21 (78)
Cetuximab or panitumumab (EGFR antibody)*	12 (44)
Bevacizumab*	20 (74)
Multiple myeloma cohort (included in “other” cohort for efficacy analysis)	(n = 5)
M protein	
Immunoglobulin M	5 (100)
International staging system at diagnosis	
I	2 (40)
II	2 (40)
III	1 (20)
IV	0
BRAF^{V600} detection method*, n (%)	
Sequenom	1 (20)
Other**	4 (80)
Any systemic therapy	5 (100)
Thalidomide/lenalidomide*	5 (100)
Bortezomib/carfilzomib*	3 (60)
Etoposide*	3 (60)
Platinum-containing therapy*	3 (60)
Cholangiocarcinoma/biliary tract cancer cohort	(n = 8)
Origin of primary tumor	
Intrahepatic	6 (75)

Characteristic — no. (%)	All Enrolled Patients
Perihilar	0
Distal	1 (13)
Other	1 (13)
Histology	
Adenocarcinoma	8 (100)
Other	0
BRAF^{V600} detection method*, n (%)	
Sanger	2 (25)
PCR	2 (25)
Sequenom	1 (13)
NGS	3 (38)
Any systemic therapy	8 (100)
Platinum-containing therapy*	8 (100)
ECD/LCH cohort	(n = 18)
Histology	
ECD	14 (78)
LCH	3 (17)
Langerhans cell sarcoma	1 (6)
BRAF^{V600} detection method*, n (%)	
cobas 4800	1 (6)
PCR	7 (39)
Sequenom	5 (28)
NGS	2 (11)
Other**	3 (17)
Sites of disease	
Bone	14 (78)
Brain	7 (39)
Orbit	6 (33)
Soft tissues	6 (33)
Heart	5 (28)
Skin	5 (28)
Lung	4 (22)
Peritoneum	3 (17)
Retroperitoneal	3 (17)
Lymph nodes	2 (11)
Vessels	2 (11)
Pleura	1 (6)
Other	2 (11)
Any systemic therapy	11 (61)
Interferon*	4 (22)
Anakinra*	1 (6)
Anaplastic thyroid cancer cohort	(n = 7)
BRAF^{V600} detection method*, n (%)	
Sanger	1 (14)
PCR	1 (14)
Sequenom	4 (57)
NGS	1 (14)
Sites of metastasis	
Liver	0
Lung	5 (71)
Lymph nodes	6 (86)
Pleura	1 (14)

Characteristic — no. (%)	All Enrolled Patients
Peritoneum	0
Skin	1 (14)
Soft tissues	0
Bone	2 (29)
Brain	0
Other	0
Any systemic therapy	7 (100)
Tyrosine kinase inhibitor therapy§*	4 (57)
Anthracycline-containing therapy*	3 (43)
Other tumors cohort*	(n = 27)
Brain	13 (50)
Glioma/glioblastoma/astrocytoma — no.	8
Pleomorphic xanthoastrocytoma — no.	4
Anaplastic ependymoma — no.	1
Head and neck	3 (12)
Carcinoma of unknown primary	3 (12)
Pancreas	2 (8)
Sarcoma	2 (8)
Ovary (low-grade serous)	1 (4)
Esophagus	1 (4)
Cervix	1 (4)
Breast	1 (4)
BRAF^{V600} detection method*, n (%)	
Sanger	7 (26)
PCR	5 (19)
Sequenom	5 (19)
SNaPshot	4 (15)
NGS	3 (11)
Other**	3 (11)

ATC indicates anaplastic thyroid cancer; CRC, colorectal cancer; ECD/LCH, Erdheim-Chester disease/Langerhans cell histiocytosis; NSCLC, non-small cell lung cancer.
*Based on manual review of cohort listings.
**Includes capillary electrophoresis single-strand conformation analysis, single-strand conformation analysis, melting, locked nucleic acid, and pyrosequencing.
NGS denotes next-generation sequencing (includes FoundationOne, TAQMAN, and other non–Sanger-based high-throughput sequencing methods); PCR, polymerase chain reaction.
†Includes leucovorin, 5-flourouracil, and oxaliplatin.
‡Includes leucovorin, 5-flourouracil, and irinotecan.
§Includes pazopanib.

Table S3. Preliminary Efficacy by Cohort.

	NSCLC (n = 20)	CRC (n = 10)	CRC (n = 27)	CLC (n = 8)	ECD/LCH (n = 18)	ATC (n = 7)
Drug administered	Vemurafenib	Vemurafenib	Vemurafenib + cetuximab	Vemurafenib	Vemurafenib	Vemurafenib
Stage 1 — no.	7	7	7*	7	7	7
Stage 1 week 8 overall response rate — % (95% CI)	14 (0.4-58)	0	0*	0	14 (0.4-58)	29 (4-71)
CR — no. (%)	0	0	0*	0	1 (14)	0
PR — no. (%)	1 (14)	0	0*	0	0	2 (29)
SD — no. (%)	5 (71)	5 (71)	2 (29)*	4 (57)	6 (86)	0
PD — no. (%)	1 (14)	2 (29)	4 (57)*	3 (43)	0	4 (57)
Nonevaluable/missing — no. (%)	0	0	1 (14)*	0	0	1 (14)
Patients with at least one postbaseline assessment — no.	19‡	10	26	8	14	7
Best overall response						
CR — no. (%)†	0	0	0	0	1 (7)	1 (14)
PR — no. (%)†	8 (42)	0	1 (4)	1 (13)	5 (36)	1 (14)
SD — no. (%)†	8 (42)	5 (50)	18 (69)	4 (50)	8 (57)	0
PD — no. (%)†	2 (11)	5 (50)	7 (27)	3 (38)	0	4 (57)
Missing — no. (%)†‡	1 (5)	0	0	0	0	1 (14)
Response (CR+PR) — no. % [95% CI]	8 (42) [20 to 67]	0	1 (4)	1 (13) [0.3 to 53]	6 (43) [18 to 71]	2 (29) [4 to 71]
Clinical benefit rate — no. (%)†§ [95% CI]	16 (84) [60 to 97]	5 (50) [19 to 81]	19 (73) [52 to 88]	5 (63) [25 to 92]	14 (100) [77 to 100]	2 (29) [4 to 71]
Median PFS — days (95% CI)	223.0 (106.0, 330.0)	138.0 (31.0, 168.0)	113.0 (54.0, 155.0)**	Not determined	Not determined	Not determined
Events— no.	14	10	13	5	1	5
Median OS —days (95% CI)	NE	283.0 (172.0, NE)	218.0 (135.0, NE)**	Not determined	Not determined	Not determined
Events— no.	5	5	6	2	0	4

ATC, anaplastic thyroid cancer; CLC, cholangiocarcinoma; CRC, colorectal cancer; CR, complete response; ECD/LCH, Erdheim-Chester disease/Langerhans cell histiocytosis; NE, nonestimable; NSCLC, non-small cell lung cancer; PD, progressive disease; PR, partial response, SD, stable disease.
*Stage 1 was based on patients receiving dose level 3 in accordance with protocol.
†Denominator is number of patients with postbaseline assessment or early withdrawal.
‡All patients with missing data were early withdrawals.
§Clinical benefit rate is the sum of partial response, complete response, and stable disease.
**Median progression-free survival and median overall survival were calculated using the patients enrolled in dose level 3 (n = 21).

Table S4. Common Adverse Events in All Patients Who Received Vemurafenib, Pooled Across Cohorts.*

Adverse Event — no. (%)	**Vemurafenib Monotherapy (n = 95)**	
	All grades	***Grade 3 or 4***
Any adverse event	93 (98)	69 (73)
Most common adverse events†	*All grades*	*Grade 3 or 4*
Arthralgia	38 (40)	4 (4)
Decreased appetite	28 (30)	2 (2)
Nausea	27 (28)	1 (1)
Hyperkeratosis	25 (26)	2 (2)
Diarrhea	23 (24)	0
Pruritus	23 (24)	0
Skin papilloma	23 (24)	1 (1)
Vomiting	23 (24)	1 (1)
Alopecia	21 (22)	0
Asthenia	19 (20)	4 (4)
Palmar-plantar erythrodysesthesia syndrome	19 (20)	1 (1)
Select adverse events‡	All grades	Grade 3‡
Rash§	65 (68)	15 (16)
Fatigue¶	53 (56)	11 (12)
Photosensitivity reaction**	25 (26)	0
Cutaneous squamous cell carcinoma††	22 (23)	22 (23)
Noncutaneous squamous cell carcinoma‡‡	2 (2)	2 (2)
Adverse event — no. (%)	**Vemurafenib + cetuximab, All dose levels (n = 27)**	
	All grades	***Grade 3 or 4***
Any adverse event	27 (100)	20 (74)
Most common adverse events†	*All grades*	*Grade 3 or 4*
Diarrhea	12 (44)	1 (4)
Arthralgia	12 (44)	1 (4)
Abdominal pain	11 (41)	2 (7)
Asthenia	8 (30)	0
Decreased appetite	8 (30)	0
Vomiting	7 (26)	0
Nausea	7 (26)	0
Erythema	7 (26)	0
Lipase increased	6 (22)	6 (22)
Select adverse events	*All grades*	*Grade 3‡*
Rash§	20 (74)	1 (4)
Fatigue¶	14 (52)	0
Photosensitivity reaction**	9 (33)	0
Cutaneous squamous cell carcinoma††	3 (11)	3 (11)
Noncutaneous squamous cell carcinoma‡‡	1 (4)	1 (4)

*Cohort-specific adverse events are reported in Table S3.
†The most common adverse events were those that occurred in at least 20% of the patients.
‡No grade 4 or 5 selected adverse events were reported.
§Includes rash, rash maculopapular, erythema, folliculitis, rash papular, rash macular, rash pruritic, rash erythematous, and rash follicular.
¶Includes fatigue, asthenia, and cachexia.
**Includes photosensitivity reaction and sunburn.
††Includes squamous cell carcinoma of the skin and keratoacanthoma.
‡‡Includes squamous cell carcinoma and squamous cell carcinoma of the tongue.

Table S5. Most Common Adverse Events* by Cohort.

Adverse Event — no. (%)	All	Grade 3 or 4
NSCLC cohort (n = 20)		
Any adverse event	19 (95)	16 (80)
Most common adverse events*		
Decreased appetite	7 (35)	2 (10)
Nausea	7 (35)	0
Dyspnea	6 (30)	3 (15)
Hyperkeratosis	6 (30)	0
Vomiting	6 (30)	1 (5)
Hypertension	5 (25)	3 (15)
Pruritus	5 (25)	0
Pyrexia	5 (25)	0
Arthralgia	4 (20)	0
Alopecia	4 (20)	0
Constipation	4 (20)	0
Cough	4 (20)	0
Diarrhea	4 (20)	0
Dysgeusia	4 (20)	0
Neuropathy peripheral	4 (20)	0
Weight decreased	4 (20)	0
Selected adverse events	*All grades*	*Grade 3*†
Rash‡	13 (65)	1 (5)
Fatigue§	12 (60)	4 (20)
Photosensitivity reaction¶	5 (25)	0
Cutaneous squamous cell carcinoma**	7 (35)	7 (35)
Noncutaneous squamous cell carcinoma††	0	0
CRC vemurafenib monotherapy cohort (n = 10)		
Any adverse event	10 (100)	5 (50)
Most common adverse events*		
Decreased appetite	6 (60)	0
Arthralgia	6 (60)	1 (10)
Hyperkeratosis	4 (40)	0
Pruritus	4 (40)	0
Dysgeusia	3 (30)	0
Milia	3 (30)	0
Mucosal inflammation	3 (30)	1 (10)
Skin papilloma	3 (30)	0
Alopecia	2 (20)	0
Dermal cyst	2 (20)	0
Erythema	2 (20)	0
Myalgia	2 (20)	0
Nausea	2 (20)	0
Papilloma viral infection	2 (20)	0
Peripheral sensory neuropathy	2 (20)	0
Weight decreased	2 (20)	0
Select adverse events	*All grades*	*Grade 3*†
Rash‡	7 (70)	3 (30)
Fatigue§	8 (80)	0
Photosensitivity reaction¶	1 (10)	0
Cutaneous squamous cell carcinoma**	1 (10)	1 (10)
Noncutaneous squamous cell carcinoma‡‡	0	0
Multiple myeloma cohort (n = 5)		
Any adverse event	5 (100)	5 (100)

Adverse Event — no. (%)	**All**	**Grade 3 or 4**
Most common adverse events in ≥2 patients		
Keratosis pilaris	2 (40)	1 (20)
Lower respiratory tract infection	2 (40)	1 (20)
Blood creatinine increased	2 (40)	0
Diarrhea	2 (40)	0
Hypokalemia	2 (40)	0
Seborrheic keratosis	2 (40)	0
Anemia	2 (40)	2 (40)
Select adverse events	*All grades*	*Grade 3*[†]
Rash‡	3 (60)	0
Fatigue§	0	0
Photosensitivity reaction¶	2 (40)	0
Cutaneous squamous cell carcinoma**	0	0
Noncutaneous squamous cell carcinoma††	0	0
Cholangiocarcinoma cohort (n = 8)		
Any adverse event	8 (100)	7 (88)
Most common adverse events*		
Diarrhea	4 (50)	0
Nausea	4 (50)	0
Arthralgia	3 (38)	0
Decreased appetite	3 (38)	0
Vomiting	3 (38)	0
Alopecia	2 (25)	0
Back pain	2 (25)	1 (13)
Blood creatinine increased	2 (25)	0
Cholestasis	2 (25)	2 (25)
Cough	2 (25)	0
Dry skin	2 (25)	0
Dyspepsia	2 (25)	0
Dyspnea	2 (25)	1 (13)
Headache	2 (25)	0
Hyperbilirubinemia	2 (25)	0
Hyperglycemia	2 (25)	0
Hypokalemia	2 (25)	0
Hyponatremia	2 (25)	1 (13)
Lymphocyte count decreased	2 (25)	2 (25)
Select adverse events	*All grades*	*Grade 3*[†]
Rash‡	7 (88)	1 (13)
Fatigue§	5 (63)	2 (25)
Photosensitivity reaction¶	1 (13)	0
Cutaneous squamous cell carcinoma**	1 (13)	1 (13)
Noncutaneous squamous cell carcinoma††	0	0
ECD/LCH cohort (n = 18)		
Any adverse event	18 (100)	17 (94)
Most common adverse events*		
Arthralgia	11 (61)	3 (17)
Skin papilloma	9 (50)	1 (6)
Hypertension	8 (44)	3 (17)
Pruritus	8 (44)	0
Alopecia	7 (39)	0
Palmar-plantar erythrodysesthesia syndrome	7 (39)	0
Diarrhea	6 (33)	0

Adverse Event — no. (%)	All	Grade 3 or 4
Dry skin	6 (33)	0
Hyperkeratosis	6 (33)	1 (6)
Nausea	6 (33)	0
Vomiting	6 (33)	0
Cough	5 (28)	0
Actinic keratosis	4 (22)	2 (11)
Blood creatinine increased	4 (22)	0
Lipase increased	4 (22)	1 (6)
Selected adverse events	*All grades*	*Grade 3*†
Rash‡	14 (78)	5 (28)
Fatigue§	11 (61)	1 (6)
Photosensitivity reaction¶	5 (28)	0
Cutaneous squamous cell carcinoma**	8 (44)	8 (44)
Noncutaneous squamous cell carcinoma††	0	0
ATC cohort (n = 7)		
Any adverse event	6 (86)	3 (43)
Most common adverse events*		
Decreased appetite	3 (43)	0
Dysphagia	3 (43)	0
Pyrexia	3 (43)	1 (14)
Arthralgia	2 (29)	0
Candida infection	2 (29)	0
Chills	2 (29)	0
Cognitive disorder	2 (29)	0
Cough	2 (29)	0
Dehydration	2 (29)	1 (14)
Palmar-plantar erythrodysesthesia syndrome	2 (29)	0
Pruritus	2 (29)	0
Vomiting	2 (29)	0
Select adverse events	*All grades*	*Grade 3*†
Rash‡	4 (57)	1 (14)
Fatigue§	3 (43)	2 (29)
Photosensitivity reaction¶	2 (29)	0
Cutaneous squamous cell carcinoma**	1 (14)	1 (14)
Noncutaneous squamous cell carcinoma††	0	0

*The most common adverse events were those of any grade that occurred in at least 20% of the patients enrolled in the specific cohort.
†No grade 4 or 5 selected adverse events were reported.
‡Includes rash, rash maculopapular, erythema, folliculitis, rash papular, rash macular, rash pruritic, rash erythematous, and rash follicular.
§Includes fatigue, asthenia, and cachexia.
¶Includes photosensitivity reaction and sunburn.
**Includes squamous cell carcinoma of the skin and keratoacanthoma.
††Includes noncutaneous squamous cell carcinoma and squamous cell carcinoma of the tongue.

Reference

1. Durie BG, Harousseau JL, Miguel JS, et al. International uniform response criteria for multiple myeloma. Leukemia 2006;20:1467-73.