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Clinical Trial Results

A Phase Ib Dose-Escalation Study of the Safety, Tolerability, and Pharmacokinetics of Cobimetinib and Duligotuzumab in Patients with Previously Treated Locally Advanced or Metastatic Cancers with Mutant KRAS

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Trial Information

- **ClinicalTrials.gov Identifier**: NCT01986166
- **Sponsor(s)**: Genentech, Inc.
- **Principal Investigator**: Christopher Lieu
- **IRB Approved**: Yes

Lessons Learned

- Cobimetinib and duligotuzumab were well tolerated as single agents and in combination with other agents.
- The cobimetinib and duligotuzumab combination was associated with increased toxicity, most notably gastrointestinal, and limited efficacy in the patient population tested.

Abstract

Background. *KRAS*-mutant tumors possess abnormal mitogen-activated protein kinases (MAPK) pathway signaling, leading to dysregulated cell proliferation. Cobimetinib blocks MAPK signaling. The dual-action antibody duligotuzumab (MEHD7945A) inhibits ligand binding to both epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 3 (HER3). Blockade of EGFR/HER3 and inhibition of mitogen-activated protein kinase (MEK) in *KRAS*-mutant tumors may provide additive benefit.

Methods. Patients with *KRAS*-mutant solid tumors were eligible for this phase Ib dose-escalation study with a planned expansion phase. Duligotuzumab was given intravenously (IV) at 1,100 mg every 2 weeks (q2w), while cobimetinib was given orally in a standard 3 + 3 design to identify the recommended phase II dose (RP2D). The primary objective was to evaluate the safety and tolerability of this combination.

Results. Twenty-three patients were enrolled. Dose-limiting toxicities (DLTs) included grade 4 hypokalemia and grade 3 mucosal inflammation, asthenia, and dermatitis acneiform. Seventy percent of patients experienced grade 3 or worse adverse events (AEs). Five (22%) and 12 (52%) patients missed at least 1 dose of duligotuzumab and cobimetinib, respectively, and 9 (39%) patients required a cobimetinib dose reduction. Three (13%) patients discontinued due to an AE. Best response was limited to 9 patients with stable disease and 13 patients with progressive disease.

Conclusion. Given the limited tolerability and efficacy of this combination, the study did not proceed to expansion stage and closed for enrollment. ***The Oncologist*** 2017;22:1024–e89

Discussion

Dysregulated human epidermal growth receptor (HER)-family signaling plays an important role in tumorigenesis [1, 2]. The mitogen-activated protein kinases (MAPK) pathway is activated by mutations in KRAS, NRAS, and BRAF oncogenes, which have been identified in multiple cancers. MAPK pathway inhibition promotes EGFR activation by releasing EGFR from extracellular signal regulated kinases (ERK)-dependent negative feedback [3–6] and/or inducing EGFR-ligand expression [7]. Furthermore,

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Table 2. Efficacy summary

	1,100 mg duligotuzumab q2w + cobimetinib dose					
Response	**Cohort 1 (*n* = 3) 40 mg QD 21/7 *n* (%)**	**Cohort 2 (*n* = 10) 80 mg 2x wkly *n* (%)**	**Cohort 3 (*n* = 7) 100 mg 2x wkly *n* (%)**	**Cohort 4 (*n* = 3) 120 mg 2x wkly *n* (%)**	**Total *N* = 23 *n* (%)**	**CRC patients, (*n* = 15) *n* (%)**
PFS						
Estimated median in days	50.5	54.0	NE	54.0	53.0	51.0
95% CI	(50, 51)	(51, 277)	(43, NE)	(51, 57)	(51, 236)	(50, 57)
Range	28[a]–51	1[a]–277	10–113[a]	51–57	1[a]–277	10–113[a]
Best overall response						
Stable disease	1 (33%)	4 (40%)	4 (57%)	—	9 (39%)	5 (33%)
Disease progression	2 (67%)	5 (50%)	3 (43%)	3 (100%)	13 (57%)	10 (67%)
Missing or unevaluable	—	1 (10%)	—	—	1 (4%)	—

[a]Censored.
Abbreviations: —, no data; CI, confidence interval; CRC, colorectal; NE, not evaluable; PFS, progression-free survival; q2w, every 2 weeks; QD, once daily; wkly, weekly.

MEK inhibition results in MYC-dependent transcriptional upregulation of HER3 [8]. Thus, combining duligotuzumab with cobimetinib in RAS-mutant tumors may overcome resistance observed with either approach alone.

This phase Ib dose escalation trial enrolled 23 patients with *KRAS* mutant cancers, 65% with metastatic colorectal cancer. DLTs are summarized below. The study was revised to twice weekly (2x wkly) dosing of cobimetinib with the same fixed dose of duligotuzumab, and it was determined that cohort 4 dosing exceeded the maximum tolerated dose (MTD), and cohort 3 dosing was the RP2D.

Overall, while most AEs were manageable, combination therapy required frequent dose holds and/or reductions (Table 1). A comparison of the AE profile of the combination of cobimetinib and duligotuzumab versus the previously characterized AE profiles of the respective single agents showed that AEs occurred at a higher frequency (≥10%) versus either single agents [9].

Duligotuzumab and cobimetinib pharmacokinetic (PK) findings were consistent with the PK observed in the respective single-agent studies, suggesting that there was no interaction.

In 23 evaluable patients, the best Response Evaluation Criteria In Solid Tumors (RECIST v1.1) response was stable disease in 9 patients (39%), with 4/9 experiencing stable disease beyond 4 cycles (Table 2). Among 15 patients with colorectal cancer (CRC), 5 had stable disease, with 2/5 experiencing stable disease beyond 4 cycles. Upon evaluation of past treatment history for the 4 patients experiencing stable disease beyond 4 cycles, all patients had atypical extended times on prior systemic therapy when compared with historical average time on those standard therapies, indicating that these may be atypical patients who had more indolent disease.

Due to limited efficacy, safety and tolerability of the combination, dose expansion was not pursued, and the combination of duligotuzumab and cobimetinib is no longer being developed in solid tumors.

Trial Information	
Disease	Advanced cancer/solid tumor only
Stage of Disease/Treatment	Metastatic/advanced
Prior Therapy	More than 2 prior regimens
Type of Study - 1	Phase I
Type of Study - 2	Prospective, open-label, dose finding
Primary Endpoint	Safety
Secondary Endpoint	Pharmacodynamic
Additional Details of Endpoints or Study Design	
Primary Endpoint: Safety and tolerability of duligotuzumab plus cobimetinib	
Primary Endpoint: Identify DLTs, MTD, and RP2D dose and schedule	
Secondary Endpoint: Pharmacokinetics, tumor assessment	
Investigator's Analysis	Level of activity did not meet planned endpoint

Drug Information for Phase I Single Arm	
Drug 1	
Generic/Working name	Cobimetinib
Trade name	Cotellic

Company name	Genentech, Inc.
Drug type	Small molecule
Drug class	MEK
Dose	milligrams (mg) per flat dose
Route	oral (po)
Drug 2	
Generic/Working name	MEHD7945A/duligotuzumab
Trade name	n/a
Company name	Genentech, Inc.
Drug type	Biological
Drug class	EGFR
Dose	milligrams (mg) per flat dose
Route	IV

Dose-Escalation Table

Dose level	Dose of drug: cobimetinib	Dose of drug: MEHD7945A/duligotuzumab	Number enrolled
Cohort 1	40 mg daily on 21/7	1,100 mg q2w	3
Cohort 2	80 mg twice weekly	1,100 mg q2w	10
Cohort 3	100 mg twice weekly	1,100 mg q2w	7
Cohort 4	120 mg twice weekly	1,100 mg q2w	3

Abbreviation: q2w, every 2 weeks.

Patient Characteristics for Phase I Single Arm

Number of patients, male	15
Number of patients, female	8
Stage	n/a
Age	Median (range): 58 (38–77)
Number of prior systemic therapies	Median (range): 4 (1–7)
Performance Status: ECOG	0 — 11
	1 — 11
	2 — 1
	3 — 0
	unknown — 0
Cancer Types or Histologic Subtypes	Colon 10
	Rectum 5
	Lung 3
	Pancreas 2
	Salivary gland 1
	Anus 1
	Cervix 1

Primary Assessment Method for Phase I Single Arm

Assessment	
Number of patients enrolled	23
Number of patients evaluable for toxicity	23

Number of patients evaluated for efficacy	23
Response assessment CR	$n = 0$ (0%)
Response assessment PR	$n = 0$ (0%)
Response assessment SD	$n = 9$ (39%)
Response assessment PD	$n = 13$ (57%)
Response assessment OTHER	$n = 1$ (4%)
(Median) duration assessments PFS	53 days, confidence interval (CI): 51–236

Phase I Single Arm Adverse Events

All Dose Levels, All Cycles							
Name	**NC/NA**	**1**	**2**	**3**	**4**	**5**	**All grades**
Diarrhea	13%	30%	30%	26%	0%	0%	87%
Nausea	48%	35%	13%	4%	0%	0%	52%
General disorders and administration site conditions—dermatitis acneiform, rash, rash erythematous, rash maculo−papular	22%	9%	52%	17%	0%	0%	78%
Headache	57%	30%	13%	0%	0%	0%	43%
Vomiting	57%	17%	22%	4%	0%	0%	43%
Fatigue	65%	9%	26%	0%	0%	0%	35%
General disorders and administration site conditions—asthenia	70%	13%	13%	4%	0%	0%	30%
General disorders and administration site conditions—decreased appetite	74%	17%	9%	0%	0%	0%	26%
Hypokalemia	74%	9%	0%	13%	4%	0%	26%
Hypomagnesemia	74%	22%	0%	4%	0%	0%	26%
General disorders and administration site conditions—pyrexia	74%	26%	0%	0%	0%	0%	26%
General disorders and administration site conditions—stomatitis	75%	17%	4%	4%	0%	0%	25%

Abbreviation: NC/NA, No Change from Baseline/No Adverse Event.

Serious Treatment-Emergent Adverse Events Regardless of Relationship to Study Treatments by Frequency of Preferred Term, Safety-Evaluable Patients

1,100 mg duligotuzumab q2w+cobimetinib dose					
	Cohort 1 $n = 3$ 40 mg QD 21/7 *n* (%)	**Cohort 2 $n = 10$ 80 mg 2x wkly *n* (%)**	**Cohort 3 $n = 7$ 100 mg 2x wkly *n* (%)**	**Cohort 4 $n = 3$ 120 mg 2x wkly *n* (%)**	**All patients ($N = 23$)**
Total number of patients with at least one adverse event	1 (33.3%)	2 (20.0%)	2 (28.6%)	2 (66.7%)	7 (30.4%)
Total number of events	2	5	4	3	14
Malignant neoplasm progression	0	1 (10%)	1 (14.3%)	0	2 (8.7%)
Abdominal pain	0	1 (10.0%)	0	0	1 (4.3%)
Abdominal pain upper	0	0	0	1 (33.3%)	1 (4.3%)
Asthenia	0	1 (10%)	0	0	1 (4.3%)
Ataxia	0	0	1 (14.3%)	0	1 (4.3%)

Dehydration	0	0	1 (14.3%)	0	1 (4.3%)
Diarrhea	0	0	0	1 (33.3%)	1 (4.3%)
Hypokalemia	1 (33.3%)	0	0	0	1 (4.3%)
Mucosal inflammation	1 (33.3%)	0	0	0	1 (4.3%)
Neck pain	0	1 (10.0%)	0	0	1 (4.3%)
Subileus	0	1 (10.0%)	0	0	1 (4.3%)
Tumor pain	0	0	1 (14.3%)	0	1 (4.3%)

Abbreviations: q2w, every 2 weeks; QD, once daily; wkly, weekly

Dose-Limiting Toxicities						
Dose level	**Dose of drug: cobimetinib**	**Dose of drug: MEHD7945A/ duligotuzumab**	**Number enrolled**	**Number evaluable for toxicity**	**Number with a dose-limiting toxicity**	**Dose-limiting toxicity information**
Cohort 1	40 mg daily on 21/7	1,100 mg q2w	3	3	2	Hypokalemia ($n = 1$); mucosal inflammation with hypokalemia ($n = 1$)
Cohort 2	80 mg twice weekly	1,100 mg q2w	10	7	1	Asthenia
Cohort 3	100 mg twice weekly	1,100 mg q2w	7	6	0	
Cohort 4	120 mg twice weekly	1,100 mg q 2w	3	3	1	Dermatitis acneiform

Abbreviation: q2w, twice weekly.

Pharmacokinetics/Pharmacodynamics

Duligotuzumab and cobimetinib PK consistent with single agent studies suggesting no interaction.

Assessment, Analysis, and Discussion

Completion	Study terminated before completion
Terminated Reason	Toxicity
Investigator's Assessment	Level of activity did not meet planned endpoint

The mitogen-activated protein kinases (MAPK) signaling pathway is a key intracellular signaling network that regulates cellular proliferation and differentiation. Abnormal activation leads to tumorigenesis by contributing to uncontrolled proliferation, invasion, metastasis and diminished apoptosis. The mitogen-activated protein kinases, MEK1 and MEK2, are key signaling hubs for inhibition of the MAPK signaling pathway because they directly phosphorylate the extracellular signal regulated kinases, ERK1 and ERK2, which directly translocate into the nucleus to activate multiple transcription factors. The MAPK pathway is activated by mutations in the KRAS, NRAS, and BRAF oncogenes, which have been identified in multiple cancers such as pancreatic adenocarcinomas (90%), colorectal adenocarcinomas (30%–50%), and non-small cell lung cancers (30%) [10].

The epidermal growth factor receptor (EGFR) family consists of four members: EGFR, human epidermal growth receptor 2 (HER2), HER3, and HER4. Ligand binding induces the formation of homodimers and heterodimers and the activation of the intrinsic kinase activities of these receptors. The two major signaling pathways activated by the human epidermal growth receptor (HER)-family dimers are the MAPK pathway and the phosphatidylinositol-4,5-bisphosphate 3-kinase/protein kinase B (PI3K/AKT) pathway, which control a variety of cellular processes including cell proliferation, differentiation, and cell survival. Dysregulation of the HER-family signaling pathways plays an important role in tumorigenesis [1, 11], and two members of the HER family, EGFR (HER1) and HER2, have been successfully targeted for the treatment of cancer of epithelial origin [12–14]. HER3 is implicated in uncontrolled cell growth and requires heterodimerization with a fully functional kinase in order to signal [12, 15–18].

The extensive crosstalk among the HER-family receptors likely contributes to emerging reports that blockade of a particular signaling pathway can lead to activation of compensatory mechanisms such as negative feedback loops and, consequently, upregulates parallel pathways [2, 19]. These findings led to the hypothesis that inhibiting the signaling potential of more than one of the HER-family receptors may offer an opportunity for superior efficacy as well as potentially overcoming resistance to currently available EGFR and other directed therapies.

Activation of alternative pathways has been observed following MEK inhibition, suggesting that blocking upstream receptor tyrosine kinases when inhibiting downstream effectors of oncogenic RAS may be more effective as treatment for RAS mutant tumors. Inhibition of the MAPK pathway can promote EGFR activation and resultant signaling via the PI3K pathway by releasing EGFR from ERK-dependent negative feedback [3–6], and/or inducing EGFR-ligand expression [7]. Given these observations, blockade of EGFR/HER3 during inhibition of downstream signaling modulators of the MAPK pathway in RAS-mutant tumors may increase the responsiveness of such tumors and overcome or prevent the resistance observed with either approach alone.

Cobimetinib is a reversible selective inhibitor of MEK1 and MEK2 that is approved in combination with vemurafenib for the treatment of advanced BRAF mutated melanoma. Cobimetinib has been studied in over 1,000 cancer patients and generally is well tolerated. The main adverse events (AEs) were diarrhea, fatigue, rash, nausea, vomiting, and peripheral edema.

Duligotuzumab is a humanized monoclonal dual specific antibody that targets both HER3 and EGFR and inhibiting ligand binding to either receptor. Preclinical studies show that duligotuzumab prevents HER3 and EGFR receptor activation leading to inhibition of downstream signaling of AKT and ERK. Duligotuzumab has been studied in four other clinical trials in phase I and II, either as a single agent or in combination with chemotherapy. Common adverse events ($>$20%) associated with duligotuzumab monotherapy were rash, headache, diarrhea, pyrexia, nausea and vomiting, decreased appetite, paronychia, chills, dry skin, and fatigue.

In preclinical studies, the combination of duligotuzumab and cobimetinib enhanced inhibition of activation of ERK1 and ERK2 and AKT in various cancer cell lines and inhibited tumor growth in two CRC xenograft models.

This phase Ib study aimed to study the combination of cobimetinib and duligotuzumab in a variety of KRAS mutant tumors and had two components: a dose escalation and dose expansion stage. In the dose escalation stage, 23 patients were enrolled (table of patient characteristics). The dose escalation stage initially consisted of a fixed dose of duligotuzumab with three cohorts of cobimetinib at 40 mg daily on a 21-day out of a 28-day cycle (21/7), 60 mg daily on 21/7, and 80 mg daily on 21/7. At the first dose level (Cohort 1), all 3 patients experienced gastrointestinal toxicity, with 2/3 patients experiencing dose-limiting toxicities (DLTs) of hypokalemia associated with diarrhea, and thus the maximum tolerated dose (MTD) on the 21/7 schedule was exceeded at the lowest dose level. The protocol was modified where duligotuzumab was given at the optimal fixed dose of 1,100 mg in conjunction with 3 subsequent dosing schedules of cobimetinib 80–120 mg twice weekly.

Ten patients were enrolled in Cohort 2 (80 mg twice weekly) with 1/7 DLT of asthenia. All 10 patients experienced an AE, and 70% experienced diarrhea. Seven patients were enrolled in Cohort 3 (100 mg twice weekly) with no DLTs, but all patients experienced diarrhea, with 1 patient experiencing grade $\geq$3 diarrhea. Three patients were enrolled in Cohort 4 (120 mg twice weekly), with 1 DLT of dermatitis acneiform and all patients experiencing grade $\geq$3 diarrhea. It was determined that Cohort 4 exceeded the MTD and the recommended phase II dose (RP2D) was determined to be 1,100 mg intravenous (IV) duligotuzumab every 2 weeks in combination with 100 mg cobimetinib orally twice weekly.

Five (22%) and 12 (52%) patients missed at least 1 dose of duligotuzumab and cobimetinib, respectively, and 9 (39%) patients required a cobimetinib dose reduction. Three (13%) patients discontinued due to an AE.

Among the 23 patients treated in the dose escalation stage, the best overall response was stable disease in 9 (39%) patients, disease progression in 13 (57%) patients, and unevaluable in 1 (4%) patients. Fifteen of the 23 patients had metastatic colorectal cancer. Among those patients, 5 (33%) had best response of stable disease and 10 (67%) had disease progression. None of the patients experienced a partial response. Time on study treatment was median 6.4 weeks (range 0–36.4). Evaluation of past cancer treatment history for the 4 patients experiencing stable disease beyond 4 cycles suggested these may be atypical patients who had more indolent disease.

Pharmacokinetic studies showed no interaction between cobimetinib and duligotuzumab. Cobimetinib pharmacokinetics were highly variable; the average exposure (area under the curve) was similar in Cohorts 1–3 but was higher than expected in Cohort 4 at Cycle 1, Day 15, though driven by high concentrations in 1 patient.

Because of the generally poor tolerability of the combination and limited efficacy seen in this limited patient population, the dose expansion was not pursued and the study was halted.

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Disclosures

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References

1. Sergina NV, Moasser MM. The HER family and cancer: Emerging molecular mechanisms and therapeutic targets. Trends Mol Med 2007;13:527–534.

2. Carracedo A, Ma L, Teruya-Feldstein J et al. Inhibition of mTORC1 leads to MAPK pathway activation through a PI3K-dependent feedback loop in human cancer. J Clin Invest 2008;118:3065–3074.

3. Turke AB, Song Y, Costa C et al. MEK inhibition leads to PI3K/AKT activation by relieving a negative feedback on ERBB receptors. Cancer Res 2012;72:3228–3237.

4. Mirzoeva OK, Das D, Heiser LM et al. Basal subtype and MAPK/ERK kinase (MEK)-phosphoinositide 3-kinase feedback signaling determine susceptibility of breast cancer cells to MEK inhibition. Cancer Res 2009;69:565–572.

5. Diep CH, Munoz RM, Choudhary A et al. Synergistic effect between erlotinib and MEK inhibitors in KRAS wild-type human pancreatic cancer cells. Clin Cancer Res 2011;17:2744–2756.

6. Young A, Lou D, McCormick F. Oncogenic and wild-type Ras play divergent roles in the regulation of mitogen-activated protein kinase signaling. Cancer Discov 2013;3:112–123.

7. Sunaga N, Kaira K, Imai H et al. Oncogenic KRAS-induced epiregulin overexpression contributes to aggressive phenotype and is a promising therapeutic target in non-small-cell lung cancer. Oncogene 2013; 32:4034–4042.

8. Sun C, Hobor S, Bertotti A et al. Intrinsic resistance to MEK inhibition in KRAS mutant lung and colon cancer through transciptional induction of ERBB3. Cell Rep 2014;7:86–93.

9. Fayette J, Wirth L, Oprean C et al. Randomized phase II study of duligotuzumab (MEHD7945A) vs. cetuximab in squamous cell carcinoma of the head and neck (MEHGAN Study). Front Oncol 2016;6: 232.

10. Johnson L, Mercer K, Greenbaum D et al. Somatic activation of the K-ras oncogene causes early onset lung cancer in mice. Nature 2001;410: 1111–1116.

11. Hynes NE, MacDonald G. ErbB receptors and signaling pathways in cancer. Curr Opin Cell Biol 2009;21:177–184.

12. Holbro T, Civenni, G, Hynes NE. The ErbB receptors and their role in cancer progression. Exp Cell Res 2003;284:99–110.

13. Moasser MM. Targeting the function of the HER2 oncogene in human cancer therapeutics. Oncogene 2007;26:6577–6592.

14. Ciardiello F, Tortora G. EGFR antagonists in cancer treatment. N Engl J Med 2008;358:1160–1174.

15. Riese DJ 2nd, van Raaij TM, Plowman GD et al. The cellular response to neuregulins is governed by complex interactions of the erbB receptor family. Mol Cell Biol 1995;15:5770–5776.

16. Pinkas-Kramarski R, Soussan L, Waterman H et al. Diversification of Neu differentiation factor and epidermal growth factor signaling by combinatorial receptor interactions. EMBO J 1996;15:2452–2467.

17. Jura N, Shan Y, Cao X et al. Structural analysis of the catalytically inactive kinase domain of the human EGF receptor 3. Proc Natl Acad Sci USA 2009; 106:21608–21613.

18. Shi F, Telesco SE, Liu Y et al. ErbB3/HER3 intracellular domain is competent to bind ATP and catalyze autophosphorylation. Proc Natl Acad Sci USA 2010;107:7692–7697.

19. Sergina NV, Rausch M, Wang D et al. Escape from HER-family tyrosine kinase inhibitor therapy by the kinase-inactive HER3. Nature 2007;445:437–441.

Table 1. All AEs in >25% patients regardless of causality, and all grade 3–4 AEs in ≥ 2 patients.

	1,100 mg duligotuzumab q2w + cobimetinib dose				
AE preferred term	**Cohort 1 (*n* = 3) 40 mg QD 21/7 *n* (%)**	**Cohort 2 (*n* = 10) 80 mg 2x wkly *n* (%)**	**Cohort 3 (*n* = 7) 100 mg 2x wkly *n* (%)**	**Cohort 4 (*n* = 3) 120 mg 2x wkly *n* (%)**	**Total *N* = 23 *n* (%)**
Any grade	3 (100%)	10 (100%)	7 (100%)	3 (100%)	23 (100%)
Diarrhea	3 (100%)	7 (70%)	7 (100%)	3 (100%)	20 (87%)
Nausea	2 (67%)	4 (40%)	5 (71%)	1 (33%)	12 (52%)
Rash[a]	2 (67%)	9 (90%)	4 (57%)	3 (100%)	18 (78%)
Headache	2 (67%)	5 (50%)	3 (43%)	0	10 (44%)
Vomiting	2 (67%)	3 (30%)	4 (57%)	1 (33%)	10 (44%)
Fatigue	3 (100%)	2 (20%)	2 (29%)	1 (33%)	8 (35%)
Asthenia	0	4 (40%)	3 (43%)	0	7 (30%)
Decreased appetite	1 (33%)	2 (20%)	3 (43%)	0	6 (26%)
Hypokalemia	2 (67%)	2 (20%)	2 (29%)	0	6 (26%)
Hypomagnesemia	1 (33%)	2 (20%)	2 (29%)	1 (33%)	6 (26%)
Pyrexia	1 (33%)	2 (20%)	2 (29%)	1 (33%)	6 (26%)
Stomatitis	0	3 (30%)	2 (29%)	1 (33%)	6 (26%)
Grade 3–5	3 (100%)	6 (60%)	4 (57%)	3 (100%)	16 (70%)
Diarrhea	2 (67%)	0	1 (14%)	3 (100%)	6 (26%)
Hypokalemia	2 (67%)	1 (10%)	1 (14%)	0	4 (17%)
Malignant neoplasm progression[b]	0	1 (10%)	2 (29%)	0	3 (13%)
Rash[a]	0	1 (10%)	0	2 (67%)	3 (13%)
Abdominal pain	0	1 (10%)	0	1 (33%)	2 (9%)
Hypophosphatemia	0	1 (10%)	1 (14%)	0	2 (9%)

Cut-off date: April, 28 2016. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0.

[a]Rash and related MedDRA Terms included: dermatitis acneiform, rash, rash erythematous, rash maculopapular.

[b]One grade 5 malignant neoplasm progression was included here, but not reported in clinical database in error (the patient was discontinued from study due to death attributed to disease progression).

Abbreviations: AE, adverse event; MedDRA, medical dictionary for regulatory activities; q2w, every 2 weeks; QD, once daily; wkly, weekly.