The Oncologist®

Clinical Trial Results

# Multicenter Phase II Study of Panitumumab in Platinum Pretreated, Advanced Head and Neck Squamous Cell Cancer

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## Trial Information

- **ClinicalTrials.gov Identifier**: NCT02643056
- **Sponsor(s)**: SENDO Foundation
- **Principal Investigators**: Nicolas Mach, Michele Ghielmini, Vittoria Espeli, Marco Siano
- **IRB Approved**: Yes

## Lessons Learned

- Panitumumab shows activity in terms of disease control rate and preventing disease progression but not for tumor shrinkage in head and neck squamous cell cancer for second-line treatment. Epidermal growth factor receptor (EGFR) copy number gain, a property of tumor cells that theoretically could identify patients more likely to experience disease response, was common among patients having disease control.
- Our trial, given the lower toxicity with an every-2-week schedule, provides guidance for future trials, for example, in combinations of immune therapies and anti-EGFR-antibodies.

## Abstract

***Background***. The objective of this study was to investigate the efficacy and safety of panitumumab (anti-epidermal growth factor receptor [EGFR] antibody) given as a single agent in platinum-pretreated head and neck squamous cell cancer (HNSCC).

***Methods***. Patients with advanced HNSCC previously treated with platinum-containing therapy were included. Panitumumab was administered intravenously every 2 weeks at a dose of 6 mg/kg. Primary endpoint was overall response rate (ORR) according to Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1; secondary endpoints were progression-free survival (PFS) and safety. A Simon's two-step design was chosen; 4 partial remissions (PR) in the first 32 patients were required for continuing to step two. An exploratory biomarker analysis was performed.

***Results***. Thirty-three patients were enrolled. Two patients obtained a PR for an ORR of 6%, and 15 (45%) showed stable disease (SD) for at least 2 months, resulting in a 51% disease control rate. Median PFS was 2.6 months (95% confidence interval [CI]: 1.7–3.7), while median OS was 9.7 months (95% CI: 6.3–17.2). The most frequent adverse drug reactions were cutaneous rash (64%) and hypomagnesemia (55%). Overall, 30% of patients experienced grade 3/4 adverse events. No infusion-related reactions occurred. EGFR copy number gain (CNG) was more frequent in patients who benefitted from panitumumab. Two uncommon *KRAS* mutations (G48E, T50I) and 3 canonical PIK3CA mutations (all E545K) were detected. High-risk HPV16 was found in 10 patients and EGFR CNG in 13 treated patients. EGFR CNG seems to be more frequent in individuals with at least SD compared with patients with progressive disease (59% vs. 30%). PFS for patients with EGFR CNG was 4.6 months (95% CI: 1.0–9.2 months) and 1.9 months (95% CI: 1.0–3.2 months) for patients without CNG ($p = .02$).

***Conclusion***. Panitumumab monotherapy in pretreated HNSCC patients was well tolerated but moderately active. We observed a considerable disease control rate. Future strategies with this agent comprise right patient selection through the identification of reliable biomarkers and gene signatures predicting response and, considering good tolerability and convenience, combination strategies with novel agents and immune therapeutic agents. ***The Oncologist*** 2017;22:782–e70

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## Discussion

We show activity of panitumumab in terms of disease stabilization, even though the prespecified response rate for completion of our study was not met. Panitumumab is safe and convenient in terms of schedule and toxicity. These results support a potential value of panitumumab in pretreated HNSCC as a candidate for combination strategies in future clinical trials but not as monotherapy in an unselected patient population.

In the biomarker analysis, EGFR CNG emerges as potentially predictive. Our findings confirm a correlation between skin reaction severity and overall survival while patients with lower on-treatment magnesium levels show a tendency to a higher probability of response.

The recently published PRISM trial presented efficacy data for panitumumab as monotherapy in the second-line setting [1]. There are, however, differences between the PRISM trial and our trial. We included fewer patients with oropharyngeal and oral cavity cancers and far more hypopharyngeal and laryngeal cancers. Panitumumab administration differed, as we administered 6 mg/kg intravenously every 2 weeks compared with 9 mg/kg every 3 weeks in PRISM, allowing a higher median adjusted drug exposure with our application schedule (42.9 mg/kg [range: 5.1–193.1 mg/kg] against 26.8 mg/kg [range, 8.2–198.2 mg/kg] in PRISM). Disease control rate and PFS are of greater interest if compared with novel immune therapies with anti-programmed cell death protein 1 antibodies, pembrolizumab and nivolumab, already approved by the U.S. Food and Drug Administration in recurrent or metastatic HNSCC for second-line treatment [2, 3]. Therefore, even if our study and the PRISM trial conclude that panitumumab should not be further investigated as monotherapy in unselected, pretreated HNSCC patients, given the observed low toxicity and convenience of application, panitumumab remains a potential candidate for combination strategies in future trials. In HNSCC, neither mutational status (EGFR, RAS, BRAF) nor EGFR immunhistochemistry (IHC) expression was predictive for cetuximab response. Our biomarker analysis can only be regarded as hypothesis generating (Table 1, online). EGFR CNG could potentially be a predictive biomarker for response and PFS, warranting consideration for patient selection in future clinical trials with anti-EGFR antibodies in HNSCC. In summary, we present safety and efficacy data on panitumumab in platinum-pretreated HNSCC, showing good tolerability and efficacy in terms of disease control but not for response.

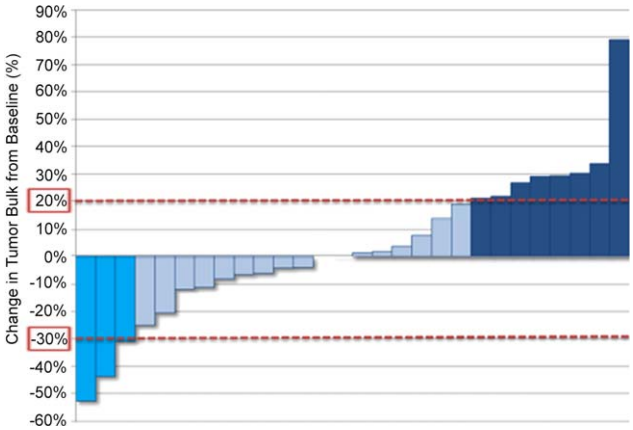


**Figure 1.** Best change in overall tumor burden from baseline ($n = 33$).

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| Trial Information | |
|---|---|
| **Disease** | Head and neck cancers |
| **Stage of Disease/Treatment** | Metastatic/advanced |
| **Prior Therapy** | 1 prior regimen |
| **Type of Study - 1** | Phase II |
| **Type of Study - 2** | Single arm |
| **Primary Endpoint** | Overall response rate |
| **Secondary Endpoint** | Progression-free survival |
| **Secondary Endpoint** | Toxicity |
| **Additional Details of Endpoints or Study Design** | |
| Study Design: Open-label, uncontrolled phase II trial performed in three Swiss tertiary cancer centers. The primary endpoint for efficacy was ORR according to RECIST version 1.1. Secondary endpoint was PFS. Evaluation of panitumumab safety profile in terms of adverse events (AEs) and adverse drug reactions was a secondary objective. AEs were coded according to Common Terminology Criteria for Adverse Events (CTCAE, version 3.0). | |
| Statistical Analyses: Simon's two-stage design was applied: 32 patients were to be enrolled requiring at least 4 partial or complete responses for trial continuation up to a total of 82 patients. The sample size was calculated based on an expected 10%–15% ORR, insufficient antitumor activity defined for an ORR below 8% (null hypothesis), and promising activity for an ORR >18% (alternative hypothesis), assuming a 5% type-I-error with 80% power. PFS and OS were estimated applying the Kaplan-Meier method. Unplanned analyses exploring the correlation between response and skin or magnesium toxicity and the potential impact of EGFR gene status on PFS and OS were performed. For the correlation between response and toxicity, the chi-square test was used for contingency tables with response categories, the nonparametric Spearman test for the overall tumor burden differences, and the Cox-model to PFS and OS, while Kaplan-Meier PFS and OS curves by EGFR gene status were compared using the log-rank test. All statistical analyses were performed using SAS software, version 9.3 (SAS Institute Inc., Cary, NC, https://www.sas.com/en_us/home.html). | |
| **Investigator's Analysis** | Evidence of target inhibition but no or minimal antitumor activity |

| Drug Information for Phase II Control Arm | |
|---|---|
| **Drug 1** | |
| **Generic/Working name** | Panitumumab |
| **Trade name** | Vectibix |
| **Company name** | Amgen |
| **Drug type** | Antibody |
| **Drug class** | EGFR |
| **Dose** | 6 milligrams (mg) per kilogram (kg) |
| **Route** | Intravenous (IV) |
| **Schedule of Administration** | Panitumumab was administered intravenously at a dose of 6 mg/kg on days 1 and 15 of a 28-day cycle. Dose reductions from 6 to 4.8 and 3.6 mg/kg were planned in case of severe adverse drug reactions. |

| Patient Characteristics for Phase II Control Arm | |
|---|---|
| **Number of patients, male** | 27 |
| **Number of patients, female** | 6 |
| **Stage** | IV |
| **Age** | Median (range): 60 (42–87) |
| **Number of prior systemic therapies** | Median (range): 1.7 |
| **Performance status: ECOG** | 0 — 16 |
| | 1 — 16 |
| | 2 — 1 |
| | 3 — |
| | unknown — |
| **Other** | Not Collected |

| Primary Assessment Method for Phase II Control Arm | |
|---|---|
| **Number of patients screened** | 38 |
| **Number of patients enrolled** | 33 |
| **Number of patients evaluable for toxicity** | 33 |
| **Number of patients evaluated for efficacy** | 33 |
| **Response assessment CR** | $n = 0$ (0%) |
| **Response assessment PR** | $n = 2$ (6%) |
| **Response assessment SD** | $n = 15$ (46%) |
| **Response assessment PD** | $n = 11$ (33%) |
| **Response assessment OTHER** | $n = 5$ (15%) |
| **(Median) duration assessments PFS** | 2.6 (95% CI 1.7–3.7) months |
| **(Median) duration assessments OS** | 9.7 (05% CI 6.3–17.2) months |
| **Phase II Control Arm Adverse Events** | Treatment-related adverse events with incidence $\geq$10% and/or of grade 3–4 severity. |

| Adverse Event | | | |
|---|---|---|---|
| | Maximum grade by patient ($n = 33$), $n$ (%) | | |
| **Adverse Event (MedDRA PPT)** | **Any grade** | **Grade 3** | **Grade 4** |
| Rash | 21 (63.6) | — | — |
| Dry skin | 6 (18.2) | 1 (3) | — |
| Dermatitis acneiform | 4 (12.1) | 1[a] (3) | — |
| Hypomagnesaemia | 18 (54.50 | 1 (3) | 4 (12.1) |

| | | | |
|---|---|---|---|
| Blood calcium decreased | 11 (33.3) | 1 (3) | 1 (3) |
| Blood potassium decreased | 8 (24.2) | 1 (3) | 1 (3) |
| Alveolitis | 1 (3) | — | 1[b] (3) |
| Cheilitis | 3 (9.1) | 1 (3) | — |
| Stomatitis | 3 | 1 (3) | — |

[a]Leading to treatment withdrawal at cycle 5.
[b]Fatal outcome at cycle 1.
Abbreviation: —, no data; MedDRA, medical dictionary for regulatory activities; N, number of patients; PPT, primary preferred term.

## Assessment, Analysis, and Discussion

| | |
|---|---|
| **Completion** | Study completed |
| **Pharmacokinetics/Pharmacodynamics** | Not collected |
| **Investigator's Assessment** | Evidence of target inhibition but no or minimal antitumor activity |

We show activity of panitumumab in terms of disease stabilization, even though the prespecified response rate for completion of our study was not met. Panitumumab is safe and convenient in terms of schedule and toxicity. As with other targeted agents, the response rate in unselected patients may not be the best endpoint for evaluating clinical activity. We confirm the observation that a subgroup of patients respond well to anti-epidermal growth factor receptor (EGFR) antibody treatment. These results support a potential value of panitumumab in pretreated head and neck squamous cell cancer (HNSCC) as a candidate for combination strategies in future clinical trials but not as monotherapy in an unselected patient population.

In the biomarker analysis, EGFR copy number gain (CNG), besides being a known prognostic marker, emerges as potentially predictive, because only 3 out of 14 patients with CNG showed initial progression. The advent of a cutaneous rash and an early onset of hypomagnesaemia has been repeatedly discussed as a predictive biomarker for responses to anti-EGFR antibodies and cetuximab in particular [1, 2]. Our findings confirm a correlation between skin reaction severity and overall survival (OS) while patients with lower on-treatment magnesium levels show a tendency toward a higher probability of response.

Anti-EGFR antibodies are active in different tumors. In HNSCC, cetuximab is established in first-line treatment and was able to show a response rate of 13% and disease stabilization in 33% of patients, with a median progression-free survival (PFS) of 2.3 months as monotherapy for platinum-refractory HNSCC [3]. The recently published PRISM trial was a phase II trial with panitumumab as second-line therapy and presented efficacy data [4]. There are some differences between PRISM and our trial, which are worth pointing out. Inclusion criteria were similar, but we included fewer patients with oropharyngeal and oral cavity cancers and far more with hypopharyngeal and laryngeal cancers. Panitumumab administration differed, as we administered 6 mg/kg intravenously every 2 weeks compared with 9 mg/kg every 3 weeks in PRISM, allowing a higher median adjusted drug exposure with our application schedule (42.9 mg/kg [range: 5.1–193.1 mg/kg] against 26.8 mg/kg [range, 8.2–198.2 mg/kg] in PRISM). A further important difference was the timing of first response assessment (6 weeks in PRISM and 8 weeks in our trial). We observed patients with initial slight progression but formally stable disease according to Response Evaluation Criteria In Solid Tumors criteria who showed stabilization or even regression in subsequent tumor assessments. Even 8 weeks could be too early for response assessment, excluding some patients who could potentially benefit from longer treatment duration. Median PFS was 1.4 months (95% CI: 1.3–2.4 months) and median OS 5.1 months (95% CI: 4.3–8.3 months), markedly lower than our estimates of 2.6 months (95% CI: 1.7–3.7 months) for PFS and 9.7 months (95% CI: 6.3–17.2 months) for OS. A higher susceptibility to anti-EGFR antibodies for non-oral cavity and oropharyngeal cancers and a higher median adjusted drug exposure could account for this observation. Later observation could be a further reason why adding panitumumab to a platinum-based chemotherapy failed to show an OS benefit in a randomized phase III trial called the SPECTRUM trial, because the panitumumab schedule was identical to the one chosen by PRISM investigators and not based on sound phase II data. Whereas another anti-EGFR antibody, cetuximab, was able to improve OS in a pivotal phase III trial, if associated to a backbone platinum-based chemotherapy, the EXTREME trial.

The EXTREME trial comprised a maintenance treatment with cetuximab. The observed survival advantage with cetuximab together with maintenance treatment could mostly be driven by patients whose tumors were susceptible to anti-EGFR therapy. Our observation that durable response was achieved in platinum-refractory disease supports this hypothesis and confirms that there is a need for further understanding activity of anti-EGFR antibodies in HNSCC.

Disease control rate and PFS are of notice if compared with novel immune therapies with anti-programmed cell death protein 1 antibodies, pembrolizumab and nivolumab, already approved by the U.S. Food and Drug Administration in recurrent or metastatic HNSCC for second-line treatment [5, 6]. For instance, PFS was 2.0 months (95% CI; 1.9–2.1 months) for nivolumab with a median OS of 7.5 months (95% CI: 5.5–9.1 months) in a pivotal phase III trial.

Therefore, even if our study and the PRISM trial conclude that panitumumab should not be further investigated as monotherapy in unselected, pretreated HNSCC patients, for individuals who are anti-EGFR antibody-naïve, panitumumab and other EGFR antibodies remain a viable treatment option, given the observed low toxicity and convenience of application, and they

remain potential candidates for the study of combination strategies in this entity.

None of the investigated biomarkers in HNSCC was identified to be predictive for panitumumab activity. In colorectal cancer, the presence of KRAS mutation was predictive for lack of anti-EGFR antibody treatment benefit [7]. In non-small cell lung cancer, EGFR IHC score, within the FLEX trial, was predictive for response to cetuximab treatment in a non prespecified analysis, whereas for EGFR, KRAS, and BRAF mutations, no predictive value has been shown [8]. In HNSCC neither mutational status (EGFR, RAS, BRAF) nor EGFR IHC expression was predictive for cetuximab response. Our biomarker analysis can only be regarded as hypothesis-generating. EGFR CNG could potentially be a predictive biomarker for response and PFS, warranting consideration for patient selection in future clinical trials with anti-EGFR antibodies in HNSCC, even if it was not shown to be predictive for cetuximab in a sub-analysis of patients included in the EXTREME trial [9]. So far, only retrospectively generated gene signatures were able to show differential outcomes with anti-EGFR antibodies [10]. Identifying and, by doing so, selecting patients with a higher probability for a clinical benefit with anti-EGFR antibodies should be the future approach and could justify further investigation of anti-EGFR antibodies in HNSCC patients. Therefore, making best use out of our patients' tissue, we plan to validate in our samples the gene signature developed by the group at the National Cancer Institute in Milan [10].

In summary, we present safety and efficacy data on panitumumab in platinum pretreated HNSCC, showing good tolerability and efficacy in terms of disease control but not for response.

Studies defining the role of biologic agents in specific cancers are useful to help designing future treatment combinations. This will potentially integrate new classes of drugs, including immune therapies such as checkpoint inhibitors and tailored vaccines. Panitumumab, considering its good tolerability and convenience, could be an ideal combination partner. Strategies to improve its efficacy could be to recognize the mechanisms of resistance to anti-EGFR antibodies and to define the subset of patients with a high probability of response by the use of reliable biomarkers.

## Acknowledgments

Amgen Europe B.V., Breda, Netherlands supplied panitumumab and provided financial support for the conduct of the trial in the form of an unrestricted grant with no further involvement. The Clinical Trial Unit of Ente Ospedaliero Cantonale (CTU-EOC) was in charge of data management, monitoring, and trial coordination.

## Disclosures

**Martin Früh:** Novartis, BMS (RF). The other authors indicated no disclosures.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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## Figures and Tables

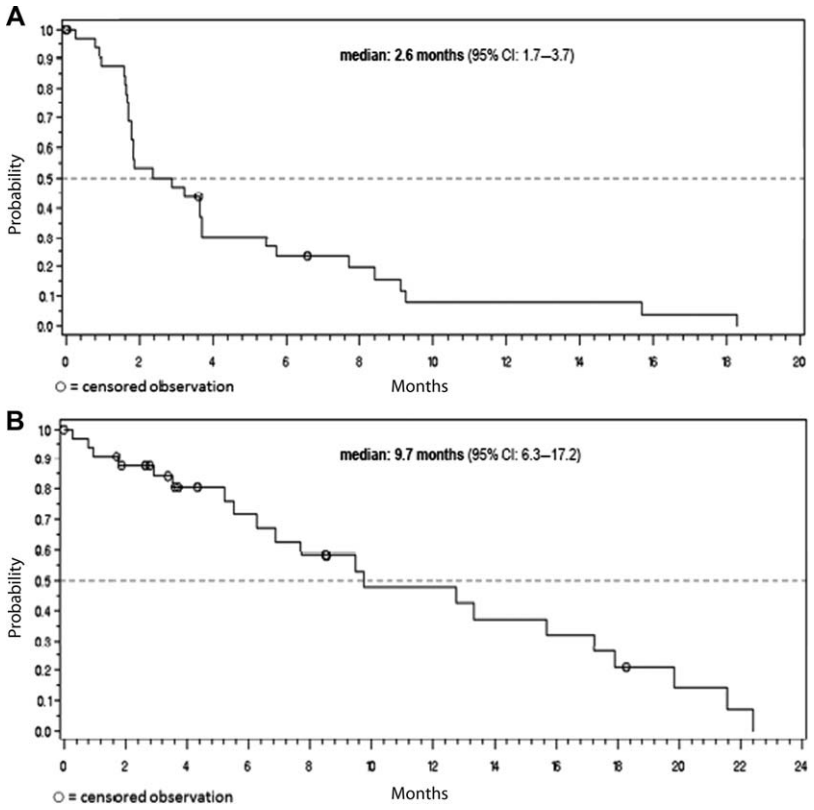


**Figure 2.** Progression-free survival **(A)** and overall survival **(B)**; $n = 33$.
Abbreviations: CI, confidence interval.

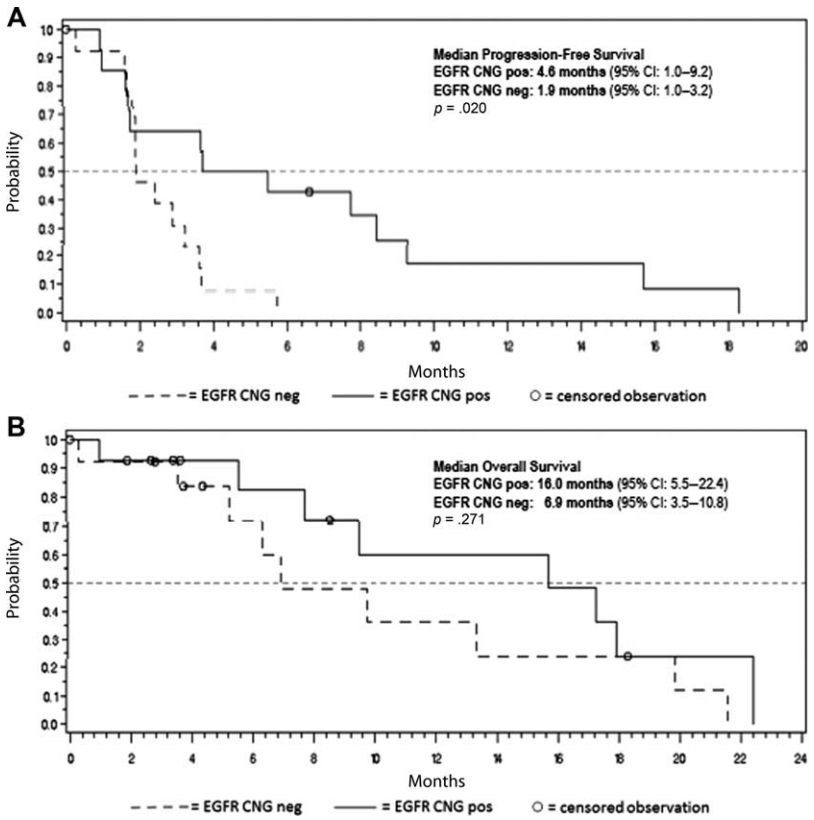


**Figure 3.** Progression-free **(A)** and overall **(B)** survival of patients with EGFR copy number gain versus patients without EGFR copy number gain ($n = 29$).
Abbreviations: CI, confidence interval; CNG, copy number gain; EGFR, epidermal growth factor receptor; neg, negative; pos, positive.

**Table 1.** Biomarker Analysis Table

| Best response | EGFR gene amplifica tion | Chr7 polysomy | FISH | KRAS | NRAS | HRAS | BRAF | PIK3CA | HPV |
|---|---|---|---|---|---|---|---|---|---|
| PD | no | no | FISH- | wt | wt | wt | wt | wt | HR16 |
| PD | no | no | FISH- | wt | wt | wt | wt | wt | HR16 |
| SD | no | yes | FISH+ | wt | wt | wt | wt | wt | neg |
| SD | no | no | FISH- | wt | wt | wt | wt | wt | neg |
| SD | no | no | FISH- | wt | wt | wt | wt | wt | HR16 |
| SD | no | yes | FISH+ | T50I | wt | wt | wt | wt | neg |
| NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| PR | no | yes | FISH+ | wt | wt | wt | wt | wt | neg |
| NA | yes | yes | FISH+ | G48E | wt | wt | wt | wt | HR16 |
| NA | NA | NA | NA | wt | wt | wt | wt | wt | neg |
| PD | no | no | FISH- | wt | wt | wt | wt | wt | neg |
| PD | no | no | FISH- | wt | wt | wt | wt | wt | HR16 |
| SD | no | yes | FISH+ | wt | wt | wt | wt | wt | HR16 |
| SD | no | yes | FISH+ | wt | wt | wt | wt | wt | HR16 |
| PD | no | yes | FISH+ | wt | wt | wt | wt | wt | neg |
| SD | no | no | FISH- | wt | wt | wt | wt | wt | neg |
| SD | no | no | FISH- | wt | wt | wt | wt | wt | neg |
| PD | no | no | FISH- | wt | wt | wt | wt | wt | neg |
| SD | yes | yes | FISH+ | wt | wt | wt | wt | wt | neg |
| PD | no | yes | FISH+ | wt | wt | wt | wt | wt | HR16 |
| SD | yes | yes | FISH+ | wt | wt | wt | wt | wt | neg |
| SD | no | yes | FISH+ | wt | wt | wt | wt | wt | neg |
| SD | yes | yes | FISH+ | wt | wt | wt | wt | wt | neg |
| PD | yes | yes | FISH+ | wt | wt | wt | wt | wt | neg |
| SD | no | no | FISH- | wt | wt | wt | wt | E545K | neg |
| SD | no | yes | FISH+ | wt | wt | wt | wt | wt | neg |
| PD | no | no | FISH- | wt | wt | wt | wt | E545K | HR16 |
| PR | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| PD | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| NA | no | no | FISH- | wt | wt | wt | wt | E545K | HR16 |
| NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| PD | no | no | FISH- | wt | wt | wt | wt | wt | neg |
| SD | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |

Abbreviations: EGFR, epidermal growth factor receptor; FISH, fluorescence in situ hybridization; NA, not assessable/not assessed; neg, negative; PD, progressive disease; PR, partial remission; SD, stable disease; wt, wild-type.