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Abstract

Introduction: Cetuximab is a mouse-human chimeric antibody directed against the Epidermal Growth Factor Receptor (EGFR). EGFR-dependent signaling plays a crucial role in epithelial cancer biology, so several anti-EGFR agents have been developed. Cetuximab was the earliest and after about two decades it gained a place in the management of advanced colorectal and head and neck cancers, whereas it has had a tough time in Non Small Cell Lung Cancer (NSCLC), where despite statistically significant phase III trials, the clinical benefit observed was marginal and insufficient to grant cetuximab approval from regulatory bodies and a place in routine clinical practice.

Areas covered: we have retrieved literature on the role of Cetuximab in NSCLC, including preclinical studies and clinical trials, focusing on recent findings.

Expert opinion: Cetuximab currently has no role in NSCLC treatment outside of research settings. We summarize the historical developement of Cetuximab research and argue that failure to identify a predictive biomarker has so far hampered its chances to enter routine practice. We identify crucial issues that should be addressed in future research, most importantly the role of EGFR amplification as predictive biomarker.

Overview

Non Small Cell Lung Cancer (NSCLC) is among the most frequent and deadliest neoplasms in western world. According to SEER estimates, incidence for lung cancer in 2016 is around 225.000 total cases in the USA, ~13% of all new cases. NSCLC accounts for 84% cases, with adenocarcinoma and squamous cell histologies accounting for 88% of all NSCLC (1). In more than 50% of the cases NSCLC presents with locally advanced or metastatic disease, where prognosis remains dismal. For stage IIIA NSCLC, 5 year survival is about 14%, but it drops to less than 5% for IIIB and metastatic (2). When Cetuximab initiated its clinical developement in early 2000s, no targeted agent was available for NSCLC, and

research was focused on identifying the best platinum-based doublet, which remain the cornerstone of therapy for metastatic disease to date, with the addition of radiotherapy for locally advanced disease. No real consensus has been reached for the optimal platinum companion, with taxanes, pemetrexed and vinca alkaloids as first choices (3–5). Anti-angiogenic therapy with Bevacizumab or Ramucirumab can add a moderate advantage at the price of significant toxicity and can be added in selected patients (3,5–7). Targeted therapy has gained an important role in NSCLC, with the approval of two main classes of drugs. Patients with translocations involving ALK and ROS, accounting for < 5% of all NSCLC, can now be treated with oral inhibitors crizotinib, ceritinib or alectinib as monotherapy (3,5,8–10). Patients with EGFR mutations, accounting for a larger share (up to 18%, with wide variations across nations (11)) are treated with EGFR tyrosine kinase inhibitors (TKI) erlotinib, gefitinib or the 2nd generation afatinib in the first line. All these compounds provided advantages in progression-free-survival (PFS) by not overall survival (OS) compared to standard chemotherapy (3,5,12). Despite the variety of agents approved, the vast majority of locally advanced or metastatic tumors relapse and response rates in second line and more are still extremely low, with no agent able to provide significant improvements in survival over supportive care. Given its high mortality and incidence, there are ample margins of improvement. The arena of new drugs has widened significantly in recent years. Probably the most dramatic changes have been brought about by the introduction of immune checkpoint inhibitors, initially only in second line (nivolumab, pembrolizumab and atezolizumab) and more recently in the first line (pembrolizumab) (13–15). New agents for targeted therapy are currently in advanced developement or have recently been FDA-approved, including new targeted therapies against EGFR (dacomitinib, AZD9291, rociletinib, osimertinib and others) or other signaling pathways (MEK inhibitors like selumetinib, MET inhibitors like tivantinib and cabozantinib and others). Cetuximab is also not the only anti-EGFR antibody in developement. Earlier competitors like Panitumumab and Matuzumab failed in phase 2 clinical trials (16,17); Necitumumab had better success, with a recent FDA approval for the treatment of squamous cell lung cancer based on the results of the SQUIRE trial (18).

Introduction to the compound

Cetuximab began its clinical developement in the late 90s and was among the first targeted therapies to be developed in the context of NSCLC. The impetus was the observation, a decade earlier, that many lung cancer cells express EGFR at high levels and are dependent on its signaling for growth (19–22).

Chemistry

Cetuximab was obtained by chimerization with the human IgG1 constant region of the murine fraction variable regions from myeloma cell line 225, producing an antibody that blocks the ligand-binding site of the EGFR (20–25). It has an approximate molecular weight of 152 kDa.

Pharmacodynamics

Cetuximab has high affinity to the EGFR, surprisingly higher than the original murine antibody 225 (23,24,26). It inhibits ligand binding and ligand-mediated receptor phosphorylation, in particular on Mitogen-Activated Kinases (MAPK). In

addition, there is also evidence suggesting that cetuximab promotes receptor internalisation, reducing the number of receptors available for interaction with the ligand (26,27). Finally, there is in vitro evidence for antibody-dependent cellular cytotoxicity but no complement-mediated lysis (24). Cetuximab treatment enhances direct cytotoxicity from radio and chemotherapy(28). Combination with chemotherapy it was recently found to induce so-called immunogenic cell death (29).

Pharmacokinetics and metabolism

After 2-hour infusion of 250 and 400 mg/m2, maximum concentrations are reached 1hr later at 158.1 and 205 ug/mL and the elimination half lives are 71 and 75.1 hours, respectively. The volume of distribution is dose-independent and approximated the vascular space of 2 to 3 L/m2 (30). At antibody doses in the range of 200 to 400 mg/m2, systemic clearance is saturated (30,31). The PK appeared to be nonlinear in all settings analysed (30–32). Concurrent administration of chemotherapy or radiotherapy did not alter cetuximab PK (31–33). Subsequent studies did not identify patient-associated variables (age, gender, body weigh, race, etc) associated with different PK and requiring dose adjustments (34).

Clinical efficacy

Early phase I studies

Two phase 1 studies established dosing for cetuximab (31,32). The first, by Baselga et al, was in fact a combination of 3 trials in which cetuximab was explored as a single dose and weekly multiple doses with or without cisplatin. Doses ranged from 5 to 400 mg/m2, on a total of 52 patients. Overall, the frequency of grade 3 or higher cetuximab-related events was 1.6%. Disease stabilizations were observed in all studies. The study with cisplatin was limited to head and neck or non–small-cell lung cancer; 69% patients treated with antibody doses ≥ 50 mg/m2 had completed 12 weeks of therapy as planned, and 2 partial responses were observed (31). In the second study, Cetuximab was explored at doses up to 500 mg/m2 in combination with radiotherapy in patients with advanced head and neck squamous cell carcinoma. Most toxicities were associated with radiotherapy but one patient experienced grade 3 skin toxicity outside of the irradiation field at the highest dose of 500 mg/m2, which suggested the adoption of a lower dose for subsequent studies (32).
All patients achieved an objective response (13 complete, 2 partial). On the basis of these data, the recommended dose for subsequent studies was set at a loading dose of 400 to 500 mg/m2 and a maintenance weekly dose of 250 mg/m2.

Clinical developement in combination with radiotherapy for stage IIIA-IIIB NSCLC

Six phase II trials (summarized in table 1) have been conducted testing cetuximab in combination with concurrent radiotherapy with or without chemotherapy in the setting of stage III NSCLC (35–40).
Earlier single-arm studies on the addition of cetuximab to chemoradiation were promising but fairly small. However, subsequent randomized trials failed to show superiority of cetuximab addition. In the CALGB 30407 trial, 101 patients were randomized to concurrent radiochemotherapy (Pemetrexed + Carboplatin

and radiotherapy (60 Gy) with or without Cetuximab. No significant difference was demonsrated between the two arms in terms of failure-free survival (12.3 vs 12.6 months) and OS (25.2 vs 21.2) (35). Another similarly sized randomized study, where 102 patients were randomized to receiving or not cetuximab in combination with cisplatin and radiotherapy (66Gy), also showed no benefit (40). More recently, cetuximab was tested as addition to cisplatin and vinorelbin and concurrent individualized, isotoxic accelerated radiotherapy in a single-arm phase 1 trial (41). Results were in line with previous studies, with a median OS of 21.0 months (95% CI 19.0–22.8 months). The final word on the issue was spelled out by the RTOG 0617 trial, the largest to date. Two hypotheses were tested at the same time: whether RT dose intensification to 74 Gy was superior to standard 60 Gy and whether addition of cetuximab to the carboplatin and paclitaxel backbone was superior. Recruitment for the RT intensification hypothesis was terminated earlier due to futility but recruitment for cetuximab met its accrual endpoint and 465 patients wer available for analysis (42). Confirming the results of the earlier phase 2 trials, no OS improvement was observed with cetuximab (25·0 months [95% CI 20·2–30·5] vs 24·0 months [19·8–28·6]; two-sided p=0·58; HR 0·94 [95% CI 0·74–1·19]).
An alternative approach that deserves consideration, so far tested only in 2 small nonrandomized studies, is the use of cetuximab alone with radiotherapy, in patients unfit to receive chemoradiotherapy. Jatoi et al administered cetuximab concomitant to 60 Gy RT (39), whereas Jensen et al administered cetuximab concomitant to 66 Gy IMRT and for subsequent 13 weeks (38). Median OS were 15.1 and 19.6 months respectively, which favorably compares to historical controls of similar populations treated with radiotherapy alone (43). If this approach resists the test of randomized trials, it may have some benefit in this difficult to treat population.

Clinical developement for stage IIIB-IV

Phase II studies

The first trials specifically investigating activity of cetuximab in the context of NSCLC were two small (n=31-35) phase I/II trials, in combination with either paclitaxel/carboplatin (44) or gemcitabine/carboplatin (45) in the first line stage IV setting. Response rates of 26% and 29% and median OS of 11.0 and 10.2 months appeared promising. The Lung Cancer Cetuximab Study (LUCAS) was the first trial testing cetuximab in a randomized fashion, coupling it to the regimen that would later be tested for its registration study (33). Patients were randomized to receive cisplatin/vinorelbine with or without cetuximab, administered weekly at 250 mg/m2 after a loading dose of 400 mg/m2 (a schedule that has remained the standard in most studies), in 3-week cycles for a maximum of 8 cycles. The study was conducted on 86 patients without prior sample size calculation; these results appeared again moderately promising, with better response rates (33% vs 28%), median PFS (5.0 vs 4.6, HR = 0.71, 95% CI 0.4–1.2) and median OS (8.3 vs 7.3 months, HR=0.71, 95% CI 0.5–1.1). However, unsurprisingly, no efficacy parameter was statistically significant.
An additional randomized phase II study on 131 patients (BMS100) tested the addition of cetuximab to gemcitabine + cisplatin or carboplatin. Again, there were signs of moderate efficacy for the addition of cetuximab, with better

response rate (27.7%, 95%CI 17.3 - 40.2 vs 18.2%, 95% CI 9.8 - 29.6), median PFS (5.09 months, 95%CI 4.17 - 5.98 vs 4.21 months, 95%CI 3.81 - 5.49) and OS (11.99 months, 95%CI 8.80 - 15.18 vs 9.26 months, 95%CI 7.43 - 11.79) (46).
A more recent, single arm study explored combining cetuximab to cisplatin and pemetrexed for 4-6 cycles, followed by maintenance with cetuximab and pemetrexed until progression or unacceptable toxicity. The study yielded slight improvements over past combinations in terms of ORR (38.5%) and PFS (5.8 months) and similar OS (11.3 months) (47).
A further improvement was observed in the SWOG S0536 single-arm phase II study on 110 patients, in which both bevacizumab and cetuximab were added to carboplatin and paclitaxel for 6 cycles, with both antibodies kept for maintenance until progression. ORR was 56%, PFS 7 months (95% CI: 6–8 months) and median OS was 15 months (95% CI: 11–21 months); toxicity profile was deemed acceptable, although there were 4 treatment-related deaths, 2 of which due to pulmonary hemorrhage, a well-known bevacizumab-related toxicity (48). This study was the basis for designing the ongoing phase III SWOG S0819 trial testing cetuximab plus carboplatin and paclitaxel, with or without bevacizumab (49).
Cetuximab was also studied as a single-agent in heavily pretreated NSCLC, obtaining a response rate of 4.5%, in line with that of other antiblastics and EGFR inhibitors tested in the same setting (50).

Phase III studies

The pivotal phase III trial leading to FDA approval in NSCLC was FLEX (51). 1125 patients were randomized to receiving Cisplatin and Vinorelbin plus or minus Cetuximab (no placebo, open label); cetuximab was continued until progression or unacceptable toxicity. Importantly, patients were required to have IHC-demonstrated EGFR expression, but the cutoff chosen for positivity was very low (at least one postive tumor cell). The study showed a small but statistically significant OS improvement (1.2 months, 11.3 vs 10.1 months, HR=0.871, p=0.044) at the price of worse toxicity profile (higher febrile neutropenia, rash, diarrhea and infusion-related reactions). The study spurred controversy in its aftermath. Despite the trial meeting its primary endpoint (OS), neither FDA nor EMA granted approval for NSCLC, given the marginal benefit and the use of a suboptimal comparator arm. Concerns grew as a subsequent trial (BMS099 (52)) in which cetuximab failed to demonstrate significant benefit when added to a possibly more effective chemotherapy. Chemotherapy-naive (n=676) patients were randomized to receiving chemotherapy (carboplatin + a taxane at physician's choice) with vs without cetuximab. PFS, the primary endpoint, did not differ (4.4 vs 4.24 months, HR=0.902, 95% CI 0.761- 1.069, p=0.24); OS showed a trend favouring the cetuximab arm but the trial was not powerful enough to demonstrate such small OS improvement (9.7 vs 8.4 months, HR=0.890 95% CI 0.754- 1.051; p=0.17). Metanalyses pooling data from all four randomized trials described above (LUCAS, BMS100, BMS099 and FLEX) confirmed the modest but statistically significant advantage in OS of adding cetuximab to chemotherapy (53–55). Randomized studies are summarized in table 2.
There is some evidence supporting the use of cetuximab maintenance in monotherapy in patients free of disease after first line therapy with platinum-

based CT. This trial (NEXT) was designed to test weekly vs bi-weekly cetuximab administration but recruitment was halted pematurely because of the EMA negative ruling on cetuximab (56). Results were nevertheless published and showed good OS of 12.6 months , comparable to other studies in the same setting, with no significant differences between the two adinistration schedules. Cetuximab was also tested in the second line setting after failure of platinum-based therapy, in combination with docetaxel or pemetrexed, but no significant improvement was observed (57).

The search for predictive biomarkers

Much research has attempted to identify genetic biomarkers predictive of response to anti-EGFR antibodies. These efforts have generated practice-changing results in colorectal cancer, but in the context of NSCLC things have been more difficult. Retrospective analyses of the FLEX and BMS099 trials showed no evidence that K-ras mutations or PTEN deletions mediate resistance to cetuximab (58–60). Also, the presence of an EGFR mutation is not predictive, as summarized in a Cochrane review (12). Instead, mounting evidence points to EGFR gene amplification and/or overexpression as a good predictive biomarker. In FLEX, cases with an elevated immunohistochemistry score (31% of enrolled patients) had better survival when treated with the addition of cetuximab (median survival of 12.0 vs 9.6 months, HR 0·73, 95% CI 0·58–0·93; p=0·011). A retrospective analysis of 2 phase II trials suggested better but marginally significant benefits from FISH-evaluated high EGFR copy number (48,61). Preliminary results from the SWOG S0819 testing cetuximab with bevacizumab and chemotherapy confirmed this association (62). In apparent contrast with these findings, EGFR amplification showed no predictive power in FLEX (58). With a more careful look at the data, survival and response was possibly superior in FISH-positive patients treated with cetuximab (11.6 vs 9.9 months), but the number of samples analysed (25% of the original 1125) was certainly too small to confer sufficient power (p=0.44). Interestingly, in FLEX the percentage of patients FISH-positive is similar to those scored as high by IHC (37% vs 31%), suggesting that the two tests may infact identify a largely overlappig population. This is confirmed by analysing data from The Cancer Genome Atlas, where it is clearly visible that EGFR amplification is associated with significant increase in EGFR mRNA expression (figure 1, data retrieved from cBioportal (63) on provisional lung adenocarcinoma and provisional squamous lung cancer on 14 october 2016)

New combinations with biological agents

Based on the laboratory finding that NSCLC with acquired resistance to erlotinib and gefitinib remain dependent on EGFR for growth (64,65), several labs began testing combinations of alternative EGFR inhibitors for use after failure of TKI therapy. The combination of cetuximab and afatinib, a second generation TKI, proved effective on mouse models (66). This led to the design of a phase 1b trial with a dose finding phase and two subsequent expansion phases exploring concurrent afatinib + cetuximab or afatinib +cetuximab initiated after failure of afatinib alone (67). In departure from previous schedules, cetuximab was administered as 500 mg/m2 every 2 weeks. 201 patients progressing to TKI for an EGFR-mutated NSCLC were enrolled, of which 126 were treated at the MTD of

both drugs. ORR was 29%, a good improvement from the 7-8% observed in trials with afatinib or cetuximab alone on similar populations (68). Interestingly, cetuximab seems to also synergize with a novel allosteric EGFR inhibitor (EAI045) and the combination potently inhibits growth in mouse models of lung cancer driven by EGFR mutants resistant to all EGFR TKIs (69).
Other combinations with biologicals, such as with cilengitide (an integrin inhibitor)(70) or with cixutuxumab (IGF1R inhibitor) (71) did not give good results.

Safety and tolerability

The most characteristic toxicity associated with cetuximab is an acne-like rash, tha develops in up to 90% of patients and is dose-related (72,73). It usually manifests within the first 2 weeks of therapy and is characterized by a maculopapular eruption localized to face and trunk, areas with high density of seborrheic glands. The rash is classified as G1-G2 in most cases, with a much smaller incidence of G3 or more events. However, since it is chronic and disfigurating, it is often a reason for treatment discontinuation. Also, there is a clear subjective bias for evaluating cetuximab rash severity, with oncologists systematically giving lower scores compared to dermatologists (74). The severity of rash is potentially increased when cetuximab is co-administered with radiotherapy (75), given the role of EGFR in the repair of skin lesions. However, the incidence of grade ≥3 was similar in the phase 3 trials with chemo alone or chemoradiotherapy (10% in FLEX, 9% in RTOG 0617) (42,51). Combination of cetuximab with other EGFR inhibitors does not lead to increased severity of cutaneous toxicity (76). The rash may complicate with bacterial superinfections. Other skin toxicities are also common but rarely high grade with cetuximab, including xerosis, paronychia, hair growth abnormalities including alopecia and trichomegaly of the eyelashes/hypertrichosis of the face, and telangiectasias (72,77). Topical or oral antibiotics (macrolides, clindamycin or tetracyclines), topical corticosteroids and vitamin K creams can be employed to control severity (72).
Other common toxicities are fatigue, fever, nausea, diarrhea, which are probably unrelated to dose or number of cycles administered (73). Less common are electrolyte imbalances, particularly hypomagnesemia (17), which may occur weeks or even months after cetuximab interruption and for which periodic monitoring during treatment and up to at least 8 weeks after treatment end is advised (73). In the two trials in which Quality of Life (QoL) measurements were reported (51,52), no statistically significant differences were observed. Toxicity data as collected for the Cochrane metanaysis (55) is summarized in table 3.

Expert opinion

Cetuximab is currently not approved for NSCLC treatment in Europe nor in the USA. It remained on ASCO and NCCN guidelines for some years but it was removed from both documents in 2016 (3,5). Despite statistically significant results from the registration studies, routine cetuximab use failed to gain consensus because of its high cost-benefit ratio: the price in both monetary and toxicity terms is cosidered too high for a marginal gain of 1.2 months in OS (78,79). Thus, interest in this molecule has waned and remains confined to research setting. We think that the main reason for its failure lies in the inability

to identify a clear predictive biomarker early during drug developement. The current emphasis on precision oncology based on genetic markers may carve a niche for cetuximab resurrection. Cetuximab-responsive NSCLC do exist out there, but they are likely to be a small and defined fraction of all NSCLC. Had such biomarker been identified *before* clinical developement, we might have seen a Herceptin-like story. In fact, we think that most efforts should be focused on consolidating the role of EGFR amplification as a predictive biomarker. Current evidence from the SWOG S0819 is still preliminary but deserves to be invested on.

A second possible niche is in the treatment of metastatic EGFR-mutated NSCLC in combination with new generation TKIs, hoping to slow down or temporarily revert the acquisition of genetic resistance. Recent data from preclinical and phase 1b studies (67,69) is promising. This strategy is currently being explored in randomized trials, on TKI-naïve patients (NCT02438722, NCT02716311) and on patients with acquired resistance (NCT00716456).

Lastly, in the context of locally advanced NSCLC, further research should investigate its role as adjunct to radiotherapy in patients unfit to undergo chemoradiation. This approach has gained some following in the context of Head and Neck cancer (80), but in NSCLC the evidence in favour of this approach is so far represented only by small nonrandomized studies (38,39). The impact on quality of life, if demonstrated noninferior to chemoradiation, might be high.

Conclusion

Cetuximab demonstrated improved efficacy over standard therapy in both locally advanced and metastatic NSCLC, but the absolute survival gain in unselected populations is very small and so far deemed unjustifiable in light of the chronic toxicity. Further research is required to identify highly selected patient subsets where cetuximab may still have a beneficial impact

Article highlights

- Cetuximab provides statistically significant but clinically marginal OS gain in unselected NSCLC
- It is currently not a viable therapeutic option in routine practice
- EGFR amplification is a likely predictive biomarker
- Combining cetuximab to EGFR TKIs may be effective in cases of primary or acquired TKI resistance
- Its role as adjunct to radiotherapy in stage IIIA patients unfit for chemoradiation should be explored

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Table 1: Trials combining cetuximab with (chemo)radiation

	Year	study type	n Pts	Patient stage	Chemotherapy regimen	RT (Gy)	OS (months)	2-yrs OS
N0422, Jatoi et al	2010	phase 2, single arm	58	IIIA 59%, IIIB 49%	Concurrent Cetuximab	60	15.1	22 %
NEAR, Jensen et al	2011	phase 2, single arm	30	II 7%, IIIA 57%, IIIB 37%	Concurrent Cetuximab followed by maintenance Cetuximab	66	19.5	35 %
SATELLITE, Hallqvist et al	2011	phase II, single arm	71	IIIA 37%, IIIB 63%	Induction Docetaxel and CDDP followed by concurrent Cetuximab	68	17	37 %
RTOG 0324, Blumenschein et al	2011	phase II, single arm	87	IIIA 46%, IIIB 54%	Concurrent CBDCA, Paclitaxel and Cetuximab followed by Consolidation CBDCA and Paclitaxel	65	22.7	49 %
CALGB 30407, Govindan et al	2011	phase II, randomized	101	IIIA 55%, IIIB 42%	Concurrent CBDCA and Pemetrexed followed by consolidation Pemetrexed	70	21.2	
					Concurrent CBDCA and Pemetrexed + Cetuximab followed by consolidation Pemetrexed		25.2	
van den Heuvel et al	2014	phase II, randomized	102	II 8%, IIIA 51%, IIIB 41%	Concurrent Cisplatin	66	n.a. (HR =1)	58 %
					Concurrent Cisplatin + Cetuximab			62 %
RTOG 0617, Bradley et al	2015	phase III, randomized	465	IIIA 65%, IIIB 35%	Concurrent and consolidation CBDCA and Paclitaxel	60 or 74	24 (19.8 - 28.6)	50.10 %
					Concurrent and consolidation CBDCA and Paclitaxel + cetuximab		25 (20.2 - 3056)	52.30 %

Table 2. Randomized trials in stage IIIB-IV NSCLC

Reference	Year	study type	Patient number	Therapy regimen	OS months (95% CI)	PFS months (95% CI)	ORR
FLEX, Pirker et al	2009	phase 3	1125	Cetuximab+cisplatin+vinorelbine	10.5 (9.2-12.0)	4.8 (4.2-5.3)	36%
				cisplatin+vinorelbine	9.1 (8.2-10.1)	4.8 (4.4-5.3)	29%
BMS 099,	2010	phase 3	676	Cetuximab+carboplatin+taxane	9.69 (8.28-11.5)	4.4 (4.11-5.06)	25.70%
				carboplatin+taxane	8.38 (7.33-9.62)	4.24 (3.94-4.63)	17.20%
BMS 100, Butts et al	2007	phase 2	130	Cetuximab+platinum+gemcitabine	11.99 (8.8-15.18)	5.09 (4.17-5.98)	27.70%
				platinum+gemcitabine	9.26 (7.43-11.79)	4.21 (3.81-5.49)	18.20%
Lung Cancer Cetuximab Study, Rosell et al	2008	phase 2	86	Cetuximab+cisplatin+vinorelbine	8.3 (6.1-9.9)	5 (4.5-5.8)	35%
				cisplatin+vinorelbine	7.3 (5.6-9.5)	4.6 (2.5-6.0)	28%

Table 3: Toxicity (as reported in Yang et al 2014, Cochrane Review)

	Cetuximab+Chemo	Chemo alone	Relative Risk	95% CI
acneiform rash	11.2	0.3	37.37	10.66-130.95
hypomagnesemia	5.3	0.8	6.57	1.13-38.12
infusion reaction	3.9	1.1	3.5	1.76-6.94
diarrhea	4.8	2.3	2.1	1.26-3.48
hypokalemia	6.3	3.6	1.74	1.02-2.99
febrile neutropenia	10.6	7.6	1.4	1.1-1.77
leukopenia	58.1	42.7	1.36	1.17-1.58

Figure legend

Figure 1: relationship between EGFR expression, copy number and point mutations. Data obtained for provisional Lung Adenocarcinoma (left) and provisional Lung Squamous Carcinoma from the TCGA through cBioPortal

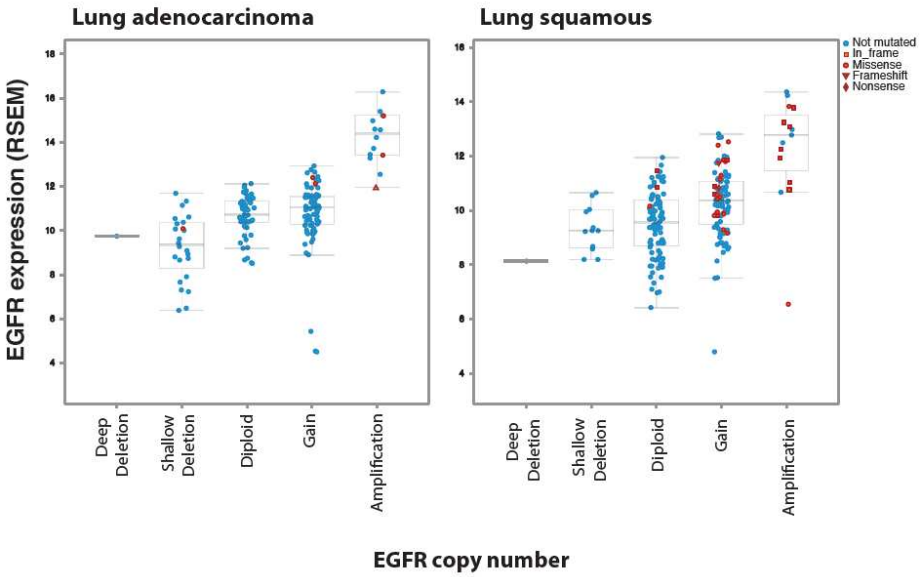

Figure 1