Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival

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Summary

Background Previous results from our phase 3 randomised trial showed that adding cetuximab to primary radiotherapy increased overall survival in patients with locoregionally advanced squamous-cell carcinoma of the head and neck (LASCCHN) at 3 years. Here we report the 5-year survival data, and investigate the relation between cetuximab-induced rash and survival.

Methods Patients with LASCCHN of the oropharynx, hypopharynx, or larynx with measurable disease were randomly allocated in a 1:1 ratio to receive either comprehensive head and neck radiotherapy alone for 6–7 weeks or radiotherapy plus weekly doses of cetuximab: 400 mg/m² initial dose, followed by seven weekly doses at 250 mg/m². Randomisation was done with an adaptive minimisation technique to balance assignments across stratification factors of Karnofsky performance score, T stage, N stage, and radiation fractionation. The trial was un-blinded. The primary endpoint was locoregional control, with a secondary endpoint of survival. Following discussions with the US Food and Drug Administration, the dataset was locked, except for queries to the sites about overall survival, before our previous report in 2006, so that an independent review could be done. Analyses were done on an intention-to-treat basis. Following completion of treatment, patients underwent physical examination and radiographic imaging every 4 months for 2 years, and then every 6 months thereafter. The trial is registered at www.ClinicalTrials.gov, number NCT00004227.

Findings Patients were randomly assigned to receive radiotherapy with (n=211) or without (n=213) cetuximab, and all patients were followed for survival. Updated median overall survival for patients treated with cetuximab and radiotherapy was 49·0 months (95% CI 32·8–69·5) versus 29·3 months (20·6–41·4) in the radiotherapy-alone group (hazard ratio [HR] 0·73, 95% CI 0·56–0·95; p=0·018). 5-year overall survival was 45·6% in the cetuximab-plus-radiotherapy group and 36·4% in the radiotherapy-alone group. Additionally, for the patients treated with cetuximab, overall survival was significantly improved in those who experienced an acneiform rash of at least grade 2 severity compared with patients with no rash or grade 1 rash (HR 0·49, 0·34–0·72; p=0·002).

Interpretation For patients with LASCCHN, cetuximab plus radiotherapy significantly improves overall survival at 5 years compared with radiotherapy alone, confirming cetuximab plus radiotherapy as an important treatment option in this group of patients. Cetuximab-treated patients with prominent cetuximab-induced rash (grade 2 or above) have better survival than patients with no or grade 1 rash.

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Introduction

Squamous-cell cancers of the head and neck with advanced primary lesions, with or without regional lymph-node metastases, are challenging to treat effectively while maintaining the function of vital healthy structures. Extensive surgical resection of the primary tumour and regional cervical lymphatics used to be the standard of care in the USA.[1,2] More recently, additional organ-preserving strategies using either radiation alone[3,4] or chemoradiotherapy[5] have become a treatment option for these patients, and have been the focus of much investigation.

The systematic clinical investigation of organ-preserving radiotherapy and chemoradiotherapy regimens suggested that these regimens could produce overall survival results as good as surgical resection for patients with locoregionally advanced squamous-cell cancer of the head and neck (LASCCHN),[5–9] thus radiation had become a cornerstone of treatment for patients with LASCCHN by the 1990s.[3,4] The addition of chemotherapy to radiotherapy has also been extensively investigated. A recent meta-analysis of 87 randomised trials that compared locoregional treatment with or without chemotherapy found that the addition of chemotherapy to locoregional treatment was associated with an absolute survival advantage of 4·5% at 5 years.[10] However, chemoradiotherapy is associated with increased toxicity

compared with radiotherapy alone.[8–12] Adding to the complexity of treatment decisions, altered fractionated radiotherapy has been shown to be associated with a survival advantage compared with once-daily radiotherapy,[11] but can be difficult to deliver with chemotherapy.[12] Therefore, a judicious approach to the optimal use of altered fractionated radiotherapy with or without chemoradiotherapy is warranted. Mitigating toxicity remains an important goal in developing new treatment approaches for patients with LASCCHN.[11,12]

High levels of epidermal growth factor receptor (EGFR) expression, which have been seen in approximately 90% of squamous-cell cancers of the head and neck,[13] have been shown to correlate with worse clinical outcome,[14] decreased response to radiotherapy, and increased loco-regional recurrence following definitive radiotherapy.[15] Preclinical studies in human squamous-cell cancer of the head and neck cell lines have shown that the inhibition of EGFR results in radiosensitisation.[16–18] Cetuximab is an IgG1 monoclonal antibody that exclusively targets EGFR with high affinity, and inhibits endogenous ligand binding, thereby blocking receptor dimerisation, tyrosine kinase phosphorylation, and signal transduction.[19–23] Cetuximab has been shown to inhibit growth across various squamous-cell carcinoma cell lines, and exposure to cetuximab before or after radiation increases the radiosensitivity of such cells.[13,17,18] Furthermore, in-vitro and in-vivo studies have shown that there is synergy between cetuximab and radiotherapy, with the combination resulting in a greater reduction in cellular proliferation than either treatment alone.[13,17,18]

In 1998, based on preclinical and phase 1b and 2a clinical studies, we designed a randomised trial to test the value of adding cetuximab to radiotherapy in the definitive treatment of patients with LASCCHN.[13,16–18,24] Recruitment was completed in March, 2002, and, compared with radiotherapy alone, the addition of cetuximab was shown to be associated with a 13% absolute improvement in locoregional control at 3 years (34% vs 47%) and a 10% absolute improvement in survival at 3 years (45% vs 55%).[25] The previously published results of all trial endpoints were reported after locking the dataset to further input. After the dataset was locked, a thorough independent review was undertaken. This decision was made based on discussions with the US Food and Drug Administration (FDA). The treating sites were asked to provide only information regarding overall survival following the initiation of the independent review. Here we report an update of survival, and aim to use this updated data for subgroup analyses of patient and tumour characteristics.

Data from several studies across multiple cancers (including recurrent/metastatic squamous-cell cancer of the head and neck, colorectal, non-small cell lung cancer, and pancreatic cancer) suggest a correlation between overall survival and the presence and/or intensity of cetuximab-induced acne-like rash.[26–29] Thus, we also assess the significance of cetuximab-induced rash in the context of these updated survival data.

Methods
Patients
As previously described in detail,[25] following the approval of the protocol by the institutional review board of each participating institution, patients with stage III or IV non-metastatic, measurable cancers of the oropharynx, hypopharynx, or larynx were randomly assigned to either radiotherapy alone or radiotherapy with cetuximab. Only those patients judged to be medically suitable for definitive radiotherapy, and who had a Karnofsky performance score (KPS) of at least 60 with normal haematopoietic, hepatic, and renal function were eligible for inclusion. Investigators were not instructed to select patients on the basis of characteristics other than the stated eligibility criteria.

Procedures
Radiotherapy consisted of one of the following three regimens:[25] once-daily radiotherapy delivered at 2 Gy per day to a total dose of 70 Gy to gross disease; twice-daily radiotherapy delivered as 1·2 Gy in two separate fractions each day (separated by ≥6 h) to a total dose of 72·0–76·8 Gy; and concomitant boost radiotherapy delivered as 1·8 Gy per day for 30 fractions, with a second fraction of 1·5 Gy delivered more than 6 h after the first fraction during the last 12 days of treatment for a total dose of 72 Gy.

The radiation regimens were required to deliver at least 50–54 Gy to uninvolved nodal areas of the neck, and grossly involved neck nodes could receive the reduced gross disease dose of 60 Gy (reduced from the gross
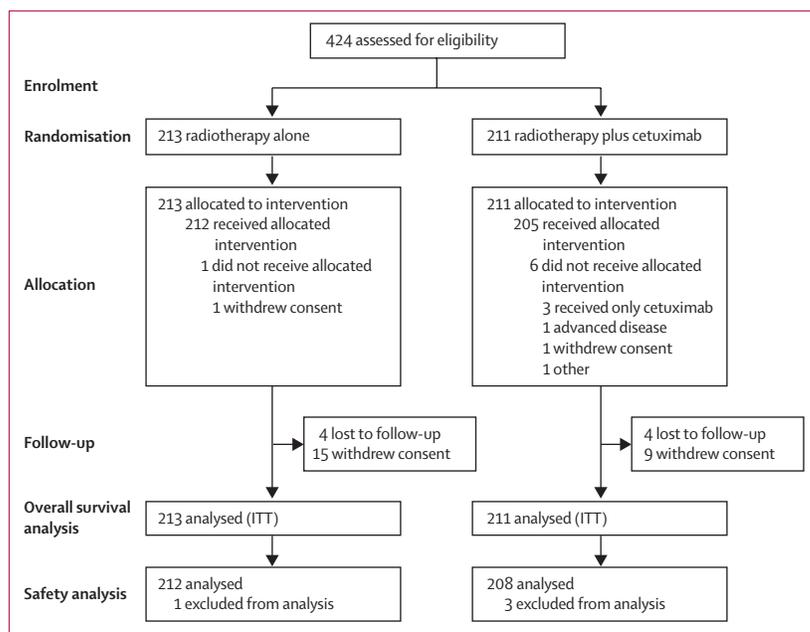

Figure 1: Trial profile

disease dose) if the investigators planned a neck dissection after radiotherapy. For patients who received concomitant cetuximab with radiotherapy, an initial loading dose of 400 mg/m² was delivered over 120 min, 1 week before the start of radiotherapy. These patients then received seven weekly infusions of 250 mg/m² of cetuximab during radiotherapy. The details of the infusions and the radiotherapy quality assurance have been outlined previously.[25]

Patients were assessed at regular intervals after the completion of radiotherapy. Follow-up assessments began 4 weeks after the completion of radiotherapy and included history taking, physical examination, and CT imaging of the head and neck. Following an 8-week assessment, follow-up examinations were done every 4 months for 2 years, and every 6 months thereafter. More frequent visits were at the discretion of the individual investigator. The treatment sites were asked to provide only survival information after the dataset had been locked: before this time, patients were assessed for recurrence and toxicities by the Radiation Therapy Oncology Group (RTOG) criteria.[30] The prognostic significance of human papillomavirus (HPV) status has only become clear over the past 5 years, and therefore no HPV testing was done in this trial.

Randomisation and masking

The trial was not blinded because cetuximab was known to cause an acneiform rash. After discussions with the FDA, it was felt that physician and patient blinding was not possible. An interactive voice response system (IVRS) enabled individual sites to obtain a randomisation number and treatment group for a given patient. This process was done by PharmaNet medical monitors (Princeton, NJ, USA). Authorised individuals at each institution called the IVRS system (using a pass code) and responded to certain prompts. The system then faxed the institution with details of the assigned treatment group. Randomisation was done using a minimisation technique, which used an adaptive balancing algorithm.[31] Patients were stratified according to their KPS (60–80 vs 90–100), nodal involvement (N0 vs N+), tumour stage (T1–3 vs T4), and radiotherapy fractionation.

Statistical analysis

The sample size was determined using a two-sided log-rank test and the hypothesis that the addition of cetuximab to radiotherapy would increase locoregional control at 1 year from 44% to 57% based on historical studies and phase 2 assessments with cetuximab and radiotherapy in this setting. 208 patients per group were required to detect this difference with a 90% power and 5% significance level. This analysis was based on an expected accrual period of 18 months and an additional follow-up period of 12 months (two-sided log-rank test). This sample size would provide an 80% power to detect a

	Radiotherapy (N=213)	Radiotherapy plus cetuximab (N=211)
Age (years; median [range])	58 (35–83)	56 (34–81)
Sex (male/female)	169 (79)/44 (21)	171 (81)/40 (19)
KPS (90–100/60–80/unknown)	141/71/1 (66/33/1)	147/63/1 (69/30/1)
N stage (N0/N+)	41/172 (19/81)	43/168 (20/80)
T stage (T1–3/T4)	153/60 (72/28)	152/59 (72/28)
Radiotherapy fractionation		
Concomitant boost	119 (56)	118 (56)
Once a day	57 (27)	54 (26)
Twice a day	37 (17)	39 (18)
Primary tumour site		
Oropharynx	135 (63)	118 (56)
Hypopharynx	27 (13)	36 (17)
Larynx	51 (24)	57 (27)
AJCC (stage III/IV)	51/161 (24/76)	55/156 (26/74)
EGFR status		
Detectable	170 (80)	166 (79)
Non-detectable	3 (1)	0
Unknown	40 (19)	45 (21)
Neck dissection	53 (25)	51 (25)
Salvage surgery	25 (12)	29 (14)
Secondary radiation	12 (6)	13 (6)
Secondary chemotherapy	44 (21)	37 (18)

Data are n (%). KPS=Karnofsky performance score. AJCC=American Joint Committee on Cancer. EGFR=epidermal growth factor receptor.

***Table 1:* Patient and tumour characteristics**

50% increase in median survival. Details of the analysis have been previously published.[25] Additional follow-up regarding locoregional control was not captured after our previous reports; therefore, this endpoint is not updated. Survival was assessed as a standard stratified log-rank comparison of the two treatment groups on an intention-to-treat basis,[32] and a forest plot made as previously described.[33]

The primary endpoint was the duration of locoregional control, which was defined as the time without progression of locoregional disease or death. Secondary endpoints of survival, and quality of life were assessed. The best response during the first year was used in the assessment of response and has been previously reported.[25] Quality of life has also been previously reported.[34] Information regarding late toxicities was not collected.

Patients who received cetuximab were assessed for an acneiform rash, which was defined by the Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART) as acne; rash; maculopapular rash; and exfoliative dermatitis. In a previous publication,[25] pustular rash and dry skin were included, but further review with the investigators suggested that these terms were not being used for acneiform rash. Patients who had either no rash or grade 1 rash were classed as having mild rash. Patients who developed a grade 2–4 rash were classed as having prominent rash. A backward stepwise Cox regression analysis was done to control for potential

	Radiotherapy (N=212)			Radiotherapy plus cetuximab (N=208)		
	All grades	Grade 3/4	Grade 4	All grades	Grade 3/4	Grade 4
Skin reaction*	200 (94·3%)	45 (21·2%)	3 (1·4%)	204 (98·1%)	73 (35·1%)‖	4 (1·9%)
Mucositis/stomatitis†	199 (93·9%)	110 (51·9%)	9 (4·2%)	194 (93·3%)	116 (55·8%)	13 (6·3%)
Dysphagia	134 (63·2%)	63 (29·7%)	3 (1·4%)	136 (65·4%)	54 (26·0%)	1 (0·5%)
Xerostomia‡	150 (70·8%)	6 (2·8%)	0 (0%)	150 (72·1%)	10 (4·8%)	0 (0%)
Acneiform rash§	21 (9·9%)	3 (1·4%)	0 (0%)	174 (83·7%)‖	35(16·8%)‖	1 (0·5%)
Infusion reaction¶	4 (1·9%)	0 (0%)	0 (0%)	32 (15·4%)‖	6 (2·9%)‖	2 (1·0%)

*Skin reaction includes all Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART) terms in the Skin and Appendages body system. †Mucositis/stomatitis includes COSTART terms aphthous stomatitis; gingivitis; glossitis; mouth ulceration; mucous membrane disorder; stomatitis; and ulcerative stomatitis. ‡Xerostomia is COSTART term dry mouth. §Acneiform rash includes COSTART terms acne; rash; maculopapular rash; exfoliative dermatitis. ¶Infusion reaction includes COSTART terms allergic reaction; anaphylactoid reaction; and/or fever; chills; or dyspnoea on the first day of treatment. ‖Statistically significant (p<0·05) difference between the treatment groups; Fisher's exact test.
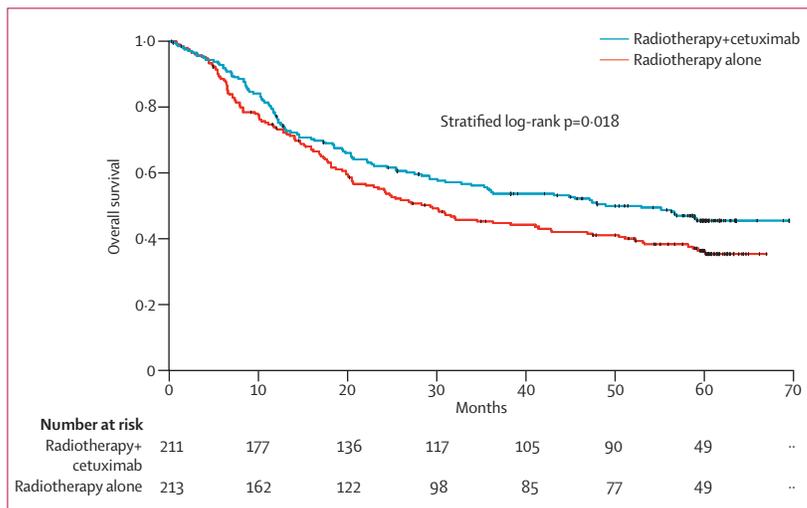
Table 2: Most common adverse events

Figure 2: Overall survival by treatment: 5-year update (median follow-up 60 months)

countries in Europe, North America, Africa, and Oceania. 213 patients were randomly assigned to radiotherapy alone, and 211 were assigned to receive radiotherapy and cetuximab (figure 1). The treatment groups were well balanced with respect to stratification factors, other potential prognostic factors, and additional therapies such as elective neck dissections and other treatments (table 1). Although the median follow-up has been updated by less than 1 year since the last analysis, additional survival information has been obtained for 40% (76 patients) of the 188 patients who were alive at the time of the last analysis.[25]

Median overall survival in the radiotherapy-alone group was 29·3 months (95% CI 20·6–41·4), compared with 49·0 months (32·8–69·5) in the cetuximab group. 5-year overall survival was 36·4% and 45·6%, respectively (hazard ratio [HR] 0·73, 95% CI 0·56–0·95; p=0·018; figure 2). In subgroup analyses, median overall survival values for patients who received cetuximab and radiotherapy versus radiotherapy alone were: American Joint Committee on Cancer (AJCC) T1–3 (69·5 *vs* 41·4 months, HR 0·66, 95% CI 0·48–0·92), AJCC N1–3 (53·0 *vs* 26·9 months, HR 0·71, 0·54–0·95), AJCC stage II–III (69·5 *vs* 46·9 months, HR 0·79, 0·47–1·35), and AJCC stage IV (43·2 *vs* 24·2 months, HR 0·76, 0·57–1·02).

We also assessed the potential associations of various patient and tumour factors with the effect of cetuximab on overall survival. A forest plot[33] was done to assess whether certain patient groups had an increased or decreased likelihood of improved survival with the addition of cetuximab to radiotherapy (figure 3). Patients with oropharyngeal tumours, early AJCC T stage (T1–3), treatment in the USA, concomitant boost, advanced AJCC N stage (N1–N3), high KPS (90–100), male sex, and age less than 65 years were factors associated with a potential increased benefit from cetuximab combined with radiotherapy versus radiotherapy alone. However, the trial was not powered for this subgroup analysis, and therefore these data should be interpreted with caution.

As expected, patients who received cetuximab had a greater number of grade 3 and 4 infusion reactions (3%) than did those who received radiotherapy alone, and more acneiform skin reactions (table 2). Information regarding late toxicity was not collected. Figure 4 shows the timing of the onset of the rash in the 174 patients from the cetuximab group who developed it. The cetuximab-induced rash began within 35 days of the initiation of treatment in 95% (167/174) of patients. Of the 208 patients who received cetuximab, 94% (195) received at least 7 doses, and 90% (187) received at least 1800 mg/m². There was no association between cumulative dose and rash (data not shown). Of the patients who received cetuximab, patients with a prominent rash had significantly longer overall survival compared with those with mild rash (68·8 months *vs* 25·6 months; HR 0·49, 0·34–0·72; p=0·002; figure 5).

confounding variables when assessing the relation between rash and survival.[35] The trial is registered at www.ClinicalTrials.gov, number NCT00004227.

Role of the funding source

Funding was provided for cetuximab treatments, data collection, statistical analysis, and the production of figures. The sponsors worked with the study chair (JAB) to develop the initial plan for randomisation. The plan was slightly modified to accommodate input from the initial meeting with potential investigators. The study chair (JAB) wrote the protocol. The sponsors contracted PharmaNet to provide clinical trial support involving stratification of patients and collection of data. The corresponding author had full access to all the data and final responsibility to submit the manuscript for publication.

Results

The trial recruited 424 patients between April, 1999, and March, 2002, at 73 centres in the USA and 14 other

This difference remained significant after stepwise Cox regression adjustments were made for KPS, age, and location of treatment.[35] The difference also remained significant after a sensitivity analysis excluding early deaths within 2 months of randomisation (data not shown). The small number of patients in the radiotherapy-alone group who developed acneiform rashes showed no survival difference compared with patients without rashes (data not shown). Since the cetuximab-induced rash showed a fairly consistent relation with survival across most subgroups, the rash was assessed in the group of patients with the worst prognosis: those with a KPS less than 90 (of the 61 patients who received cetuximab and had a KPS less than 90, 33 had mild rash and 28 had prominent rash). Even in this group, there was a suggestion (not significant) that the rash may be associated with longer survival (HR 0·67, 95% CI 0·38 1·17, p=0·15). Similar results were seen for patients aged >65 years (data not shown).

Discussion

Previously reported results from this trial showed better survival and locoregional disease control associated with cetuximab plus radiotherapy in patients with LASCCHN, relative to radiotherapy alone, and these differences were not associated with reduced quality of life or increased radiation-induced mucositis or dysphagia.[25,34] This updated analysis was done to assess additional 5-year overall survival results. The long-term results corroborate the earlier findings that the addition of cetuximab to radiotherapy improved the survival of patients with LASCCHN. There was a difference of about 9% in absolute survival for the addition of cetuximab to radiotherapy compared with radiotherapy alone (36·4% vs 45·6%). Additionally, the subgroup analyses showed that patients given cetuximab who developed a prominent cetuximab-induced acneiform rash (grade 2–4) had better overall survival compared with patients given cetuximab who developed a mild or no rash (grade 0–1). The overall survival benefit associated with the addition of cetuximab to radiotherapy, relative to radiotherapy alone, is remarkably similar to that seen in the 3-year analysis (45% vs 55%),[25] which supports the validity of 3-year overall survival as a surrogate for long-term overall survival.

These updated survival results provide further support for considering the combination of cetuximab and radiotherapy as a standard option in the treatment of LASCCHN. Our previous report provided the impetus for the inclusion of cetuximab and radiotherapy as a treatment option for LASCCHN in the 2007 National Comprehensive Cancer Network (NCCN) guidelines.[36] Depending on the stage of disease, these guidelines include three treatment options that include radiotherapy as the cornerstone of treatment: radiotherapy alone, radiotherapy with concomitant systemic treatments such as cetuximab or cytotoxic chemotherapy, or
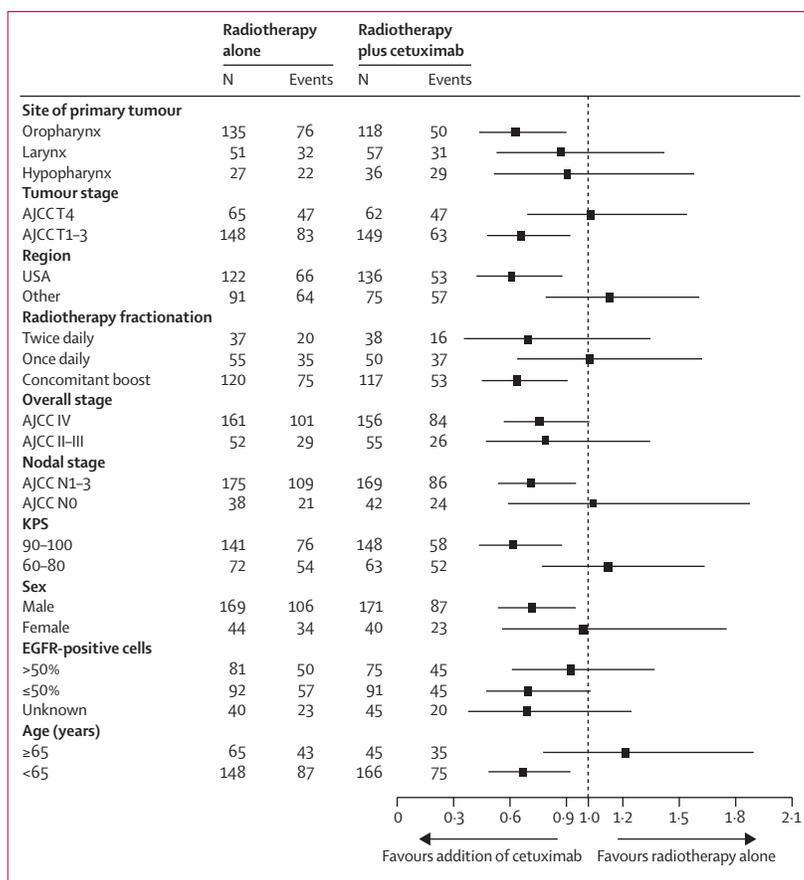

	Radiotherapy alone		Radiotherapy plus cetuximab	
	N	Events	N	Events
Site of primary tumour				
Oropharynx	135	76	118	50
Larynx	51	32	57	31
Hypopharynx	27	22	36	29
Tumour stage				
AJCC T4	65	47	62	47
AJCC T1–3	148	83	149	63
Region				
USA	122	66	136	53
Other	91	64	75	57
Radiotherapy fractionation				
Twice daily	37	20	38	16
Once daily	55	35	50	37
Concomitant boost	120	75	117	53
Overall stage				
AJCC IV	161	101	156	84
AJCC II–III	52	29	55	26
Nodal stage				
AJCC N1–3	175	109	169	86
AJCC N0	38	21	42	24
KPS				
90–100	141	76	148	58
60–80	72	54	63	52
Sex				
Male	169	106	171	87
Female	44	34	40	23
EGFR-positive cells				
>50%	81	50	75	45
≤50%	92	57	91	45
Unknown	40	23	45	20
Age (years)				
≥65	65	43	45	35
<65	148	87	166	75

Figure 3: **Overall survival by pre-treatment characteristics: 5-year update**
AJCC=American Joint Committee on Cancer. KPS=Karnofsky performance score. EGFR=epidermal growth factor receptor.
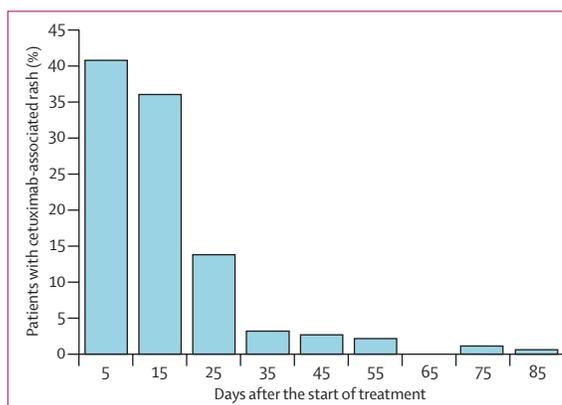

Figure 4: **The onset of cetuximab-induced rash following the initiation of first treatment**

sequential treatment of induction chemotherapy followed by concomitant chemoradiotherapy. The guidelines suggest that the intensity of treatment should be increased as the severity, or tumour burden, of LASCCHN increases. Further study is warranted to determine whether or not these severity-based
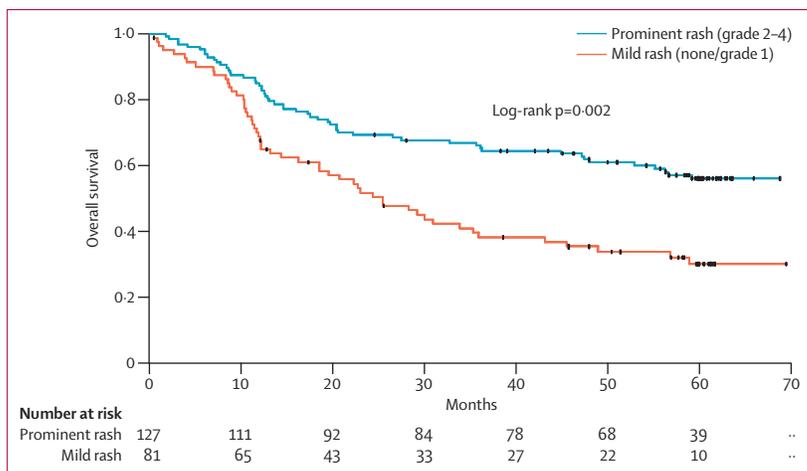
Figure 5: Overall survival by severity of rash in cetuximab-treated patients

recommendations are appropriate. To this end, a phase 3 RTOG 0522 trial assessing concurrent accelerated radiation and cisplatin versus concurrent accelerated radiation, cisplatin, and cetuximab for stage III and IV head and neck carcinomas recently closed to patient enrolment. Data from this trial will provide definitive information regarding cetuximab in combination with chemoradiation in the locally advanced disease setting, and provide the rationale for further exploration in earlier stages of disease.

The development of an acneiform rash is a toxicity that is frequently associated with cetuximab and not radiotherapy alone. Data from several studies across multiple cancers suggest a correlation between overall survival and the presence and/or intensity of cetuximab-induced acne-like rash.[26–29] The present analysis examined the significance of acneiform rash in patients treated primarily with radiotherapy, since it has been associated with better survival in other treatment settings.[26] The characteristic cetuximab-induced acneiform rash arises during treatment and generally resolves completely in the first weeks following the cessation of therapy.[37] Of the 208 patients who received cetuximab and had information regarding skin toxicity, 174 (84%) patients had rash, and this incidence was similar to previous reports of cetuximab alone.[38] 127 patients had prominent rash, the remaining 81 patients had mild rash or none. Patients with prominent rash had more than 2·5 times longer overall survival than did patients with mild rash. It is possible that the acneiform rash is a biomarker of an immunological response that is conducive for optimal outcome. Further work will be necessary to determine the mechanistic significance of the acneiform rash. In the future, the presence or absence of a cetuximab-induced rash to identify patients who might benefit from more prolonged treatment with cetuximab or treatment with other agents. Preliminary investigations have assessed the use of maintenance cetuximab therapy.[39]

The forest plot analysis (figure 3) of the effect of cetuximab in various subgroups showed some interesting associations that should be explored further in the future. Cetuximab seemed to provide the most benefit for patients with oropharyngeal tumours, T1–3 tumours, treatment in the USA, concomitant boost, advanced nodal stage, and high KPS. These subgroups represent small numbers of patients, and therefore the results might represent spurious findings. However, further work should be done to test the consistency of these results. Historically, patients with low KPS have done poorly with most treatments, and there was no suggestion that cetuximab benefited these patients. This finding has discouraged the use of cetuximab in these patients, as outlined by the National Institute for Health and Clinical Excellence in the UK.[40] However, even this most unfavourable population showed a suggestion that patients who achieved a prominent cetuximab rash did better than those who did not. Therefore, it might be possible to ascertain certain biological parameters of even the most unfavourable patient groups that could direct personalised treatment.

Since the publication of a meta-analysis[10] comparing chemoradiotherapy with radiotherapy alone, and other subsequent trials, the use of chemoradiotherapy has become a popular treatment option for patients with LASCCHN. However, the addition of cytotoxic chemotherapy to radiotherapy is not the ideal treatment for all patients. Patients must be able to tolerate the potential chemotherapy-induced side-effects and an exacerbation of radiation-induced mucositis and dysphagia. Cetuximab does not increase radiation-induced toxicities.[39,41] A single institutional comparison of cetuximab and radiotherapy versus chemoradiotherapy in the treatment of patients with LASCCHN showed comparable survival results after correcting for potential confounding factors.[42] These retrospective results confirm the need for a randomised trial comparing the efficacy and quality of life of the two treatments. Recently, preliminary results were presented from a randomised phase 2 trial that examined induction chemotherapy followed by radiotherapy with either concomitant chemotherapy (cisplatin) or concomitant cetuximab.[43] The preliminary results suggested no difference in local progression between the two therapeutic approaches, but cetuximab treatment was better tolerated than cisplatin. Future studies will be designed to help provide a pathway to individualised patient treatments. The analysis of molecular markers in the context of treatment outcomes will help refine our ability to select the patients who will benefit from the addition of various systemic treatments to radiotherapy.

In summary, these updated survival results show that cetuximab provides a long-term and clinically significant survival advantage (9% absolute survival advantage at 5 years) relative to radiotherapy alone for the

management of LASCCHN. These findings provide additional support for the recent inclusion of cetuximab in the NCCN Guidelines[36] as an accepted standard systemic therapy for patients with locoregionally advanced head and neck cancer.

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