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Liver resection rate following downsizing chemotherapy with cetuximab in metastatic colorectal cancer: UK retrospective observational study

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Abstract

Aims: The high objective response rate to cetuximab along with chemotherapy in patients with colorectal liver metastases makes it an effective downsizing protocol to facilitate surgery in those with initially unresectable disease. Adoption of this strategy has been variable in the UK. A retrospective observational study was conducted in 7 UK specialist liver surgical centres to describe the liver resection rate following a downsizing protocol of cetuximab and chemotherapy and to evaluate the quality and efficiency of processes by which the treatment was provided.
Methods: Data were collected in 2012 by reviewing medical records of patients with colorectal metastases confined to the liver, defined as unresectable without downsizing therapy at first review by a specialist Multi Disciplinary Team (MDT).
Results: Sixty patients were included; 29 (48%) underwent liver resection following cetuximab and chemotherapy. Of the 29, 17 (59% or 28% of all patients) achieved R_0 resection and 7 (24% or 12% of all patients) R_1 resection. All treated patients were KRAS wild-type.
Conclusion: In specialist liver surgical centres, where patients are evaluated for liver resection, optimal management by MDT using KRAS testing, cetuximab and chemotherapy results in a 28% R_0 resection rate in patients with initially unresectable colorectal cancer liver metastases.

Keywords: Cetuximab; Downsizing chemotherapy; Liver resection; Colorectal cancer

Synopsis

A retrospective observational study of liver resection rates and health care processes associated with the management of patients with previously unresectable metastatic colorectal cancer treated with downsizing chemotherapy and cetuximab. Optimal outcomes are achieved with appropriate specialist management.

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Introduction

Downsizing chemotherapy to facilitate resection of otherwise unresectable liver metastases from colorectal cancer has been widely studied and is a safe and effective strategy to improve the prognosis of patients with colorectal metastases confined to the liver.[1,2]

The addition of targeted biological agents such as cetuximab to chemotherapy regimens is a promising recent development in the available therapeutic options.[3] UK Technology Appraisal bodies have recommended cetuximab for use in the National Health Service (NHS) along with chemotherapy as a downsizing treatment for patients with KRAS wild-type (wt) metastatic colorectal cancer (mCRC) and otherwise unresectable liver metastases.[4,5] Subsequent to this study being conducted, in Dec 2013 the licence for cetuximab was updated to exclude patients that harbor additional KRAS and NRAS mutations (exons 2, 3 and 4 of KRAS and NRAS) which are negative predictors of outcome to cetuximab. Cetuximab is now indicated in patients with RAS wt metastatic colorectal cancer.[6]

The technology appraisals of cetuximab for downsizing unresectable liver metastases were based on evidence from the CELIM study[7] which showed that cetuximab added to either FOLFOX or FOLFIRI regimens yielded high resection rates (34% achieved R_0 resection) and improved response rates in relation to historical controls. More recently, Ye et al. have shown improved resectability (26% R_0 resection rate), response rates and survival with the addition of cetuximab to conventional chemotherapy in a study directly comparing cetuximab plus chemotherapy with chemotherapy alone in patients with unresectable liver metastases of colorectal cancer.[8]

While robust randomized clinical trial data remains the essential basis of all evidence-based medicine, it is becoming increasingly important to supplement these studies with more broadly inclusive, contextualized 'real world' observational studies.[9] These take into account the preferences of patients and oncologists and withdrawal from chemotherapy in patients with significant side effects. Expert opinion has suggested that if provided in the usual UK context of management by multidisciplinary teams (MDTs) involving highly specialised liver surgical services, resection rates following downsizing chemotherapy combined with cetuximab could even exceed those seen in clinical trials.[4]

To date there have been no observational studies of the outcomes achieved with downsizing chemotherapy and cetuximab for colorectal liver metastases in UK clinical practice. It has been acknowledged that liver resection rate is a key outcome measure for this treatment and also recommended that patients receiving it should be managed only by MDTs that involve highly specialised liver surgical services.[4] Hence, this multi-centre retrospective observational study was conducted in 7 UK NHS specialist liver surgical centres with a primary objective of estimating the proportion of patients with unresectable liver metastases who underwent liver resection following downsizing treatment with chemotherapy plus cetuximab. A secondary objective was to evaluate the health care process by which the treatment was provided in normal UK practice.

Methods

Prior to commencement of the study at each centre, local NHS Trust Research and Development (R&D) management approval was obtained. Approval from an Independent Ethics Committee (IEC) was not required due to new Governance Arrangements for UK Department of Health Research Ethics Committees, effective from September 2011.[10] These allow studies involving the use of anonymised data collected by clinicians who already have access to identifiable records without IEC review or explicit patient consent.[11]

All patients meeting the inclusion/exclusion criteria were selected for inclusion in the study, by clinicians involved in their care within each centre, from clinical records and databases. There was no random sampling of subjects. Patients were included if: they had mCRC with metastases confined to the liver, defined as unresectable at first review by the specialist MDT; the specialist MDT review was after publication of NICE TA176 in August 2009 and they received downsizing chemotherapy and cetuximab, starting cetuximab between Oct 2009–Apr 2012. Patients were excluded if they had been enrolled in a clinical trial or had received privately funded healthcare, as these patients would not represent normal clinical practice in the NHS.

Data on patient and disease characteristics, resection rates, concomitant chemotherapy and response rates were collected retrospectively from medical records and hospital databases at each participating hospital. Where necessary, missing data were requested from other healthcare providers, most commonly referral centres and satellite centres providing chemotherapy administration, for details of chemotherapy and cetuximab prescribing.

For the evaluation of the health care process by which downsizing chemotherapy with cetuximab was managed, the participating centres were each asked to provide a service profile to describe the MDT structure, including specialist representation and workload.

Data collection was undertaken by members of the clinical team at each centre from February to November 2012. Prospective follow-up is ongoing to determine 5 year survival.

Results

Study centres

Service profiles were provided by all seven centres. Six described their MDT structure as hepatobiliary or hepatopancreatobiliary; three held hepatobiliary MDT meetings

and three hepatopancreatobiliary MDT meetings; all seven MDTs met weekly. In addition, all centres provided MDT review dates for all patients in the study. The median number of referral centres per MDT was 11.0 (Interquartile range (IQR) 6.3–14.3). Only one centre performed liver transplants. The median annual number of liver resections performed for mCRC per centre was 80.0 (IQR 70.0–100.0), representing 44%–93% of all liver resections performed annually.

Study sample

Anonymised data were received for 64 patients. Four patients were excluded: one for metastases not confined to the liver, one due to enrollment in a clinical trial and two due to private healthcare for mCRC. Hence 60 patients were included in the study (range 5–12 per centre).

Seventy-five percent (45/60) of the study sample were male and the mean (SD) age at first downsizing chemotherapy infusion was 62 (11) years. Seventy-seven percent (46/60) had synchronous presentation of CRC and mCRC. In 52% (31/60) the primary tumour had been resected prior to MDT review (Table 1).

Primary endpoint

Resection rate

Twenty-nine (48%) patients underwent liver resection following downsizing treatment including cetuximab (95% CI 36–61%). Five of 11 patients who received irinotecan-based chemotherapy and 24/49 of those who received oxaliplatin-based chemotherapy underwent liver resection.

Secondary endpoints

Resection outcome

Of the 29 resected patients 17 (59%, or 28% of the whole sample, 95% CI 17–40%) had complete resection with an R_0 (clear/negative margins) outcome. A further 7 (24% or 12% of the whole sample, 95% CI 4–23%) had a R_1 outcome (presence of microscopic tumour invasion of the resection margin (tumour-free margin 0 mm)[12]) (Table 2).

Table 1
Patient characteristics.

Characteristic	Result (total n = 60)
N (%) Males	45 (75%)
Mean (SD) age at first infusion of downsizing chemotherapy (years)	62 (11)
Presentation:	
Metachronous	8 (13%)
Synchronous	46 (77%)
Unknown	6 (10%)
Primary tumour site:	
Colon	30 (50%)
Rectosigmoid	15 (25%)
Rectum	15 (25%)
N (%) with primary tumour resected prior to specialist MDT review	31 (52%)

Table 2
Resection rate and outcome.

Liver resection outcomes	No. of patients	% (n = 60)	SE	95% CI	
R_0	17	28%	5.8%	17%	40%
R_1	7	12%	4.1%	4%	23%
R_2	1	2%	1.7%	0%	10%
Other	2	3%	2.3%	0%	12%
Unknown	2	3%	2.3%	0%	12%
No resection	31	52%	6.5%	39%	64%
Total	**60**	**100%**			

Range of downsizing chemotherapy regimens

Forty-nine (82%) patients received an oxaliplatin-based chemotherapy regimen and in 11 (18%) chemotherapy was irinotecan-based (Table 3).

Dose density of cetuximab

Of the 18 patients with complete cetuximab dosing data, the median total dose of cetuximab administered was 5180 mg (IQR 4049–7175). The median weekly dose of cetuximab administered was 207 mg/m^2 (IQR 176–230), excluding the loading dose.

Duration of downsizing

In the 27 patients with first and last chemotherapy infusion dates recorded, median duration of chemotherapy was ten weeks (IQR 9–20) and in the 35 patients with first and last cetuximab infusion dates recorded, median duration of cetuximab was 11 weeks (IQR 8–16).

Complete response (CR) following downsizing

In the 33 patients for whom a pathologic response was recorded, nine (27%) patients had a complete response and 24 (73%) did not.

Time to surgical intervention

In the 29 patients who underwent liver resection, median time from first infusion of cetuximab until liver resection was 23 weeks (IQR 19–30). Only 13 patients who underwent liver resection had complete cetuximab dosing data; median time from last infusion of cetuximab until liver resection in these patients was 15 weeks (IQR 11–18). Median time from first cetuximab infusion to first 'resectable' scan result was 12 weeks (IQR 9–17) (n = 26 with scans indicating liver resectable).

KRAS testing

All 60 patients underwent KRAS testing. The median time from blood sampling to receipt of the KRAS result was eight days (IQR 7–13) (n = 27 with complete dates).

Table 3
Chemotherapy regimens.

Chemotherapy regimen	No. of patients	% (n = 60)	SE	95% CI	
FOLFOX4	10	17%	4.8%	7%	26%
FOLFOX6	3	5%	2.8%	1%	14%
FOLFOX6 modified	14	23%	5.5%	13%	34%
FOLFIRI	8	13%	4.4%	6%	24%
Other, specified	26	43%	6.4%	31%	56%

Note: Chemotherapy regimens are not mutually exclusive, 1 patient received FOLFOX4 followed by FOLFOX6.

Other includes:

- Irinotecan monotherapy **(2 patients)**
- Irinotecan modified de Gramont **(1 patient)**

} 3 irinotecan based

- FOLFOX6 modified with calcium folinate, not leucovorin **(8 patients)**
- Oxaliplatin modified de Gramont **(6 patients)**
- Capecitabine + oxaliplatin **(2 patients)**
- FOLFOX **(2 patients)**
- Capecitabine + oxaliplatin (1 cycle) then oxaliplatin + 5-FU **(1 patient)**
- Capecitabine + oxaliplatin (3 cycles) then FOLFOX6 modified (with calcium folinate, not leucovorin) **(1 patient)**
- Raltitrexed + oxaliplatin **(1 patient)**
- Oxaliplatin + 5-FU **(1 patient)**
- Oxaliplatin + 5-FU + folinic acid (non-standard regimen) **(1 patient)**

} 23 oxaliplatin based

All 60 patients had KRAS wild-type so cetuximab was appropriate in all cases. Use of cetuximab in KRAS wt patients was appropriate at this time, the licence was subsequently updated to use of cetuximab in RAS wt patients only.

Overall survival

The 24 month survival of the entire patient group is shown in Fig. 1 based on whether patients were resected. Twenty-nine patients underwent liver resection; of these 19 (66%) were alive at this time. Among all 60 patients who received cetuximab and chemotherapy, there was one death within 15 weeks of the first dose of cetuximab (ie within four weeks of the median end of cetuximab treatment), in a patient who received FOLFOX6 modified chemotherapy with cetuximab. The patient who died suffered a post-operative bleed. Thirty-one patients did not undergo liver resection; of these 13 (42%) were alive at 24 months. The apparent difference between the two observed proportions (66% vs 42%, p = 0.0577) (Fisher's exact test), at 24 months does not quite reach statistical significance due to the small sample sizes.

Discussion

This was a retrospective observational study of the processes and outcomes associated with downsizing chemotherapy plus cetuximab in the treatment of patients with initially unresectable colorectal liver metastases. The results show that almost half (48%) of the patients who

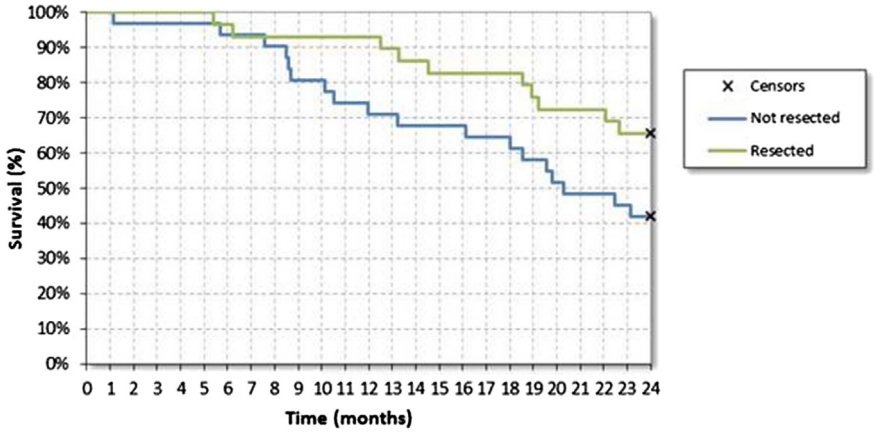

Figure 1. Kaplan Meier Survival Plot: survival to 24 months from start of downsizing therapy.

received downsizing treatment with chemotherapy and cetuximab underwent liver resection, on average after 12 weeks' treatment. Over half of these (59% of those undergoing resection or 28% of all the patients) had a R_0 outcome of resection, which is similar to the results of the CELIM interventional study[7] in which 34% (36/106) (95% CI 25–44) had a R_0 outcome and a randomized controlled trial[8] with 26% (18/70) R_0 outcomes. All three studies are relatively small, producing results with wide confidence intervals, but taken together, the similarity of the results would suggest that chemotherapy and cetuximab can facilitate a curative resection in a quarter to one third of patients whose liver metastases were initially deemed unresectable by a specialist MDT. Stratification of resection rate by chemotherapy regimen received was not planned due to the small size of the study. However, post-hoc comparison of resection rate in the small group of patients treated with irinotecan-based chemotherapy with those treated with oxaliplatin-based chemotherapy did not add support to previous work suggesting that cetuximab with oxaliplatin-based chemotherapy may be an undesirable combination.[13]

To date 24 months' survival data are available for our study and with this relatively short follow up and the small sample size the apparent difference between patients who did and did not undergo liver resection does not quite achieve statistical significance, with 66% and 42% of patients respectively surviving at 24 months from the first chemotherapy infusion. Survival at two years was higher (85%) in patients who underwent resection in a much larger, National Cancer Data Repository study.[14] However, this covered patients undergoing liver resection for colorectal metastases and measured survival from colorectal tumour resection not from downsizing chemotherapy as in our study, it is unclear whether it included patients receiving downsizing chemotherapy for previously unresectable disease. In that study more patients who underwent liver resection survived for 24 months than those who did not (85% vs 24% respectively); at five years the difference was even more marked (45% vs 9% respectively) and survival of resected patients was similar to patients with stage III disease (45% vs 42% respectively). More recently, five year survival results of the CELIM study showed that 46% of patients who had a R_0 resection following downsizing chemotherapy and cetuximab survived for five years compared with only 19% of those who did not have an R_0 resection.[15] These results support the case for ensuring that all those who could undergo resection are offered it, and our preliminary survival results further support the inclusion of those who require downsizing chemotherapy to achieve resection. The results apply to patients with initially unresectable liver-limited metastases and should not be extrapolated to patients with operable disease in whom the use of biological agents is not recommended.

Our study was not designed to compare survival of patients who received downsizing chemotherapy and cetuximab but who did not go on to resection, with survival of similar patients not offered downsizing or resection. Previous work has shown that addition of cetuximab to the chemotherapy regimens commonly used for downsizing resulted in longer progression-free survival among patients with KRAS wild-type.[15] The 24 month survival of 42% of unresected patients in our study compares favourably with the results of the previous studies and suggests that patients embarking on a downsizing regimen are not disadvantaged if they do not proceed to resection.

A secondary objective of this study was to evaluate the health care processes associated with delivery of downsizing chemotherapy and cetuximab. In particular whether the need for KRAS testing to determine the suitability of cetuximab for each patient due to receive downsizing chemotherapy was causing delay in chemotherapy initiation. However, we found that KRAS testing was routinely and efficiently conducted, not delaying chemotherapy and cetuximab start.

A further previously recognized[4] important factor for ensuring optimal management of these patients is specialist MDT involvement in decision making regarding resectability and the need for downsizing treatment. Patients included in this study were managed by a specialist MDT, meeting frequently, with routine, efficient KRAS testing at the time the study was conducted (now RAS testing) to ensure appropriate of cetuximab treatment. Our study has shown this 'package' results in a resection rate similar to that achieved in clinical trials. This reflects a previous study in one centre[16] which showed that management of patients without the involvement of a specialist liver MDT leads to patients being denied potentially curative treatments as some who could undergo resection are not referred if decisions are taken by non-specialists.

Study limitations

The retrospective design of this study relies on the completeness of clinical records with respect to the study dataset. Complete study data was not available for all patients and as we have not attempted to impute missing data, several analyses have been conducted on data from fewer than half the patients in the study. This obviously raises the possibility of misleading results arising from this incomplete data if those with missing data are different from those with evaluable data. Data were missing especially for chemotherapy and cetuximab prescribing, which was commonly undertaken at referring or satellite centres from whom requested data sharing was incomplete. However data were available for the primary endpoint for all patients in the study.

Only a relatively short duration of survival follow up is available to date due to the recent introduction of cetuximab into use outside clinical trials: we recognize that the use of resection rate as our main endpoint is a surrogate for the outcome which is most meaningful to patients and

we continue to follow up patients prospectively with the aim of reporting five year survival in due course.

The licence for cetuximab was updated in December 2013 from KRAS wt to RAS wt, which means that there may have been a number of patients that received cetuximab treatment in this study that may not have benefitted. Approximately 10% of the total population have been found to harbor additional KRAS and NRAS mutations in addition to KRAS exon 2 mutations.[17–19] Further refinement of the patient population to RAS wt would give a more accurate reflection of the results.

Our study did not include any assessment of patients' quality of life (QoL) associated with the interventions studied (which may be a more meaningful endpoint for patients even than survival) due to the retrospective design and the lack of a routinely-used measure of QoL. This is particularly important since 52% of patients did not proceed to resection and did not therefore receive potentially curative treatment. This could be addressed with a prospective observational study.

In spite of these limitations, we nevertheless believe that the results we report here offer a worthwhile insight into the outcomes of downsizing with chemotherapy and cetuximab.

Conclusion

In specialist liver surgical centres, where patients are evaluated and prepared for liver resection, optimal management by a specialist (either hepatobiliary or hepatopancreatobiliary) MDT using KRAS testing (now RAS testing), cetuximab and oxaliplatin- or irinotecan-based chemotherapy results in outcomes comparable with those achieved in clinical trials.

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Conflict of interest statement

Mr Malik is an advisor to Terumo (unconnected to this study); Dr Byrne is employed by Merck Serono, sponsors of the study; Dr Thompson was employed by Merck Serono, sponsors, at the time of the study; Ms Pulfer is employed by pH Associates Ltd, study management company; Professor Davidson, Mr Khan, Professor Berry, Mr Cameron, Mr Pope, Mr Sherlock and Mr Helmy have no commercial interests to declare.

References

1. Lam VW, Spiro C, Laurence JM, et al. A systematic review of clinical response and survival outcomes of downsizing systemic chemotherapy and rescue liver surgery in patients with initially unresectable colorectal liver metastases. *Ann Surg Oncol* 2012 Apr;**19**(4):1292–301.
2. Lehmann K, Rickenbacher A, Weber A, Pestalozzi BC, Clavien PA. Chemotherapy before liver resection of colorectal metastases: friend or foe? *Ann Surg* 2012 Feb;**255**(2):237–47.
3. Nordlinger B, Adam R, Arnold D, Zalcberg JR, Gruenberger T. The role of biological agents in the resection of colorectal liver metastases. *Clin Oncol R Coll Radiol* 2012 Aug;**24**(6):432–42.
4. National Institute for Health and Clinical Excellence. *Colorectal cancer (first line) – cetuximab (TA176)* June 2009. http://publications.nice.org.uk/cetuximab-for-the-first-line-treatment-of-metastatic-colorectal-cancer-ta176. [accessed 03.12.13].
5. Scottish Medicines Consortium. *SMC advice: cetuximab (Erbitux)* 8 Feb 2010. Available at: http://www.scottishmedicines.org.uk/SMC_Advice/Advice/543_09_cetuximab__Erbitux_/cetuximab__Erbitux_1. [accessed 03.12.13].
6. Merck Serono. Summary of Product Characteristics, Erbitux 5 mg/ml solution for infusion. Available at: https://www.medicines.org.uk/emc/medicine/19595 [accessed 14.08.14].
7. Folprecht G, Gruenberger T, Bechstein WO, et al. Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomised phase 2 trial. *Lancet Oncol* 2010;**11**:38–47.
8. Ye L-C, Liu T-S, Ren L, et al. Randomized controlled trial of cetuximab plus chemotherapy for patients with KRAS wild-type unresectable colorectal liver-limited metastases. *J Clin Oncol* 2013;**31**(16):1931–8.
9. Garrison Jr LP, Neumann PJ, Erickson P, Marshall D, Mullins CD. Using real-world data for coverage and payment decisions: the ISPOR Real-World Data Task Force report. *Value Health* 2007 Sep-Oct;**10**(5):326–35.
10. Health Research Authority. *Governance arrangements for research ethics committees (GAfREC)* May 2011. Available at: http://www.nres.nhs.uk/nres-publications/news/governance-arrangements-for-research-ethics-committees/. [accessed 03.12.13].
11. Data Protection Act. *s33 research exemption* 1998. Available at: http://www.legislation.gov.uk/ukpga/1998/29/section/33. [accessed 03.12.13].
12. Ayez N, Lalmahomed ZS, Eggermont AM, et al. Outcome of microscopic incomplete resection (R1) of colorectal liver metastases in the era of neoadjuvant chemotherapy. *Ann Surg Oncol* 2012 May;**19**(5):1618–27.
13. Primrose J, Falk S, Finch-Jones M, et al. Systemic chemotherapy with or without cetuximab in patients with resectable colorectal liver metastasis: the new EPOC randomised controlled trial. *Lancet Oncol* 2014 May;**15**(6):601–11.
14. Morris EJA, Forman D, Thomas D, et al. Surgical management and outcomes of colorectal cancer liver metastases. *Br J Surg* 2010;**97**:1110–8.
15. Folprecht G, Gruenberger T, Bechstein W, et al. Cetuximab and chemotherapy in the treatment of patients with initially "nonresectable" colorectal (CRC) liver metastases: long-term follow-up of the CELIM trial. *J Clin Oncol* 2013;**31**. [suppl; abstr 3538].
16. Jones RP, Vauthey JN, Adam R, et al. Effect of specialist decision-making on treatment strategies for colorectal liver metastases. *Br J Surg* 2012 Sep;**99**(9):1263–9.
17. Douillard J-Y, Oliner KS, Siena S, et al. Panitumumab–FOLFOX4 treatment and *RAS* mutations in colorectal cancer. *N Engl J Med* 2013;**369**:1023–34.
18. Ciardiello F, Lenz HJ, Kohne CH, et al. Effect of *KRAS* and *NRAS* mutational status on first-line treatment with FOLFIRI plus cetuximab

in patients with metastatic colorectal cancer (mCRC): new results from the CRYSTAL trial. *J Clin Oncol* 2014;**32**. [suppl 3; abstr LBA443].

19. Heinemann V, von Weikersthal LF, Decker T, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2014;**15**:1065–75. http://dx.doi.org/10.1016/S1470-2045(14) 70330-4.