

Pharmacokinetics of gefitinib and erlotinib

In a Comment¹ on the OPTIMAL trial,² Tetsuya Mitsudomi suggests that differences in clinical activity between the oral kinase inhibitors erlotinib and gefitinib in *EGFR* mutation-positive non-small-cell lung cancer could be attributable to their respective areas under the serum concentration–time curve (AUC). Erlotinib has a seven-times greater AUC than does gefitinib, which might explain its better clinical activity.

However, the activities of two chemically different drugs cannot be compared based solely on their AUC (by contrast with the comparison between two chemically identical agents, such as a generic and reference drug). The AUC depicts variations of blood concentrations over time after administration of a specific drug, at a specific dose. Pharmacokinetic characteristics that might cause differences in the activities of two drugs usually relate to tissue diffusion (if the target is extravascular) and elimination. Gefitinib has a perhaps more favourable pharmacokinetic profile than does erlotinib, with a longer elimination half-life (50.5 h vs 16.5 h) and a larger tissue distribution.³ Differences in clinical activities between erlotinib and gefitinib might instead be explained by differences in their enzymatic inhibitory potential in situ and their duration of action.

I declare that I have no conflicts of interest.

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The MARS feasibility trial: conclusions not supported by data

The value of extrapleural pneumonectomy (EPP) in the context of multimodality therapy for patients with malignant pleural mesothelioma is controversial. Several phase 2 studies have been reported on the role of neoadjuvant chemotherapy, EPP, and postoperative radiotherapy. These studies have included patients with T1–3 tumours, but differed in the inclusion of N2 status and sarcomatoid histology. Around three-quarters of patients included in these trials underwent EPP and about three-fifths received postoperative radiotherapy. Median survival ranged from 16.8 to 25.5 months, and the operative mortality from EPP from 0% to 5% (table).^{1–6}

Independent assessment of the distinct components of a multimodality concept is desirable, especially of radical surgery and postoperative radiotherapy, because both have a more pronounced potential to affect survival than does chemotherapy alone. The MARS trial⁷ attempted to assess the efficacy of EPP, and an ongoing SAKK trial is assessing the value of postoperative radiotherapy after neoadjuvant chemotherapy and EPP (ClinicalTrials.gov identifier NCT00334594).

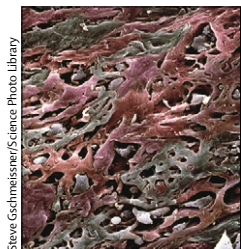
Because of the anticipated difficulty in recruitment of patients to a trial comparing EPP with a non-surgical approach, the MARS researchers designed a feasibility trial with the objective of randomly assigning 50 patients within 1 year to assess the possibility of completing a larger trial to clarify the role of EPP. The study was therefore not designed to test the benefit (or absence thereof) of EPP for patient outcome, and any conclusions are speculative. Moreover, this feasibility study failed, because it took 3 years to accrue 50 patients.

According to the investigators of the MARS trial, 670 patients would be needed to identify any significant difference in overall survival between EPP and no EPP. However, the survival results reported in *The Lancet Oncology*⁷ are based on only 30 deaths. Thus, no firm conclusion can be drawn about the effect of EPP on overall survival from these data.

	Stage	Number of patients			ITT median survival (95% CI)	EPP operative mortality
		Chemotherapy	EPP	Radiotherapy		
Weder and colleagues ¹	T1–3, N0–2	19 (100%)	16 (84%)	13 (68%)	23	0%
Weder and colleagues ²	T1–3, N0–2	61 (100%)	45 (74%)	36 (59%)	19.8 (14.6–24.5)	2.2%
Rea and colleagues ³	T1–3, N0–2	21 (100%)	17 (81%)	15 (71%)	25.5	0%
Batirel and colleagues ⁴	T1–3, N0–2	20 (100%)	16 (80%)	12 (60%)	17	5%
Krug and colleagues ⁵	T1–3, N0–2	77 (100%)	57 (74%)	44 (57%)	16.8 (13.6–23.2)	3.7%
Van Schil and colleagues ⁶	T1–3, N0–2	59 (100%)	42 (73%)	38 (64%)	18.4 (15.6–32.9)	5%

ITT=intention to treat. Median survival is in months.

Table: Prospective studies of trimodality therapy of malignant pleural mesothelioma including neoadjuvant chemotherapy, extrapleural pneumonectomy (EPP), and radiotherapy



112 patients were registered in this study and 50 (42%) were randomly assigned to treatment. Eligibility for randomisation was determined by CT restaging after chemotherapy and assessment by a multidisciplinary team. No information about the status of the 58% of patients not considered eligible for randomisation is provided in the report; however, these patients were presumably deemed to be unfit for surgery because of tumour progression or other compromising conditions. Therefore the reported survival results cannot be compared directly with results of the prospective multimodality studies in the table,¹⁻⁶ in which survival is reported by intention to treat from the start of any therapy.

In the MARS study⁷ a few factors can be identified that could further affect the interpretation. First, the chemotherapy delivered in MARS before randomisation was not standardised for type and dose of drugs or for number of cycles, which generates difficulties in assessing such small numbers of events. Second, no data are provided about the time from beginning of chemotherapy to EPP. In a multidisciplinary treatment approach, the time allowed between the different treatments should be fixed and as short as possible. Lastly, it is important to know whether the surgical triage of 19 of 24 patients having an attempted EPP, of whom only 16 eventually completed EPP, was related to undue treatment delays. Moreover, three patients in the non-surgical group eventually did undergo EPP and three additional patients had non-EPP surgery. These protocol violations further complicate interpretation.

EPP is the focus of the MARS feasibility trial. However, within the context of MARS the operative mortality for the 17 patients who underwent EPP per protocol was 18%. By contrast, recently reported trials for trimodality therapy including EPP

show mortality of 0–5%.¹⁻⁶ In view of the small number of patients in the MARS study, this high mortality could be a statistical anomaly, but nevertheless, is a concern.

The MARS study did not show the feasibility of doing a trial comparing chemotherapy with EPP and radiotherapy. We believe the interpretation of the study—“These data, although limited, suggest that radical surgery in the form of EPP within trimodal therapy offers no benefit and possibly harms patients”—is inappropriate, could move clinical research for mesothelioma in the wrong direction, and might be harmful to patients seeking advice.

We declare that we have no conflicts of interest.

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Authors' reply

Apart from MARS,¹ evidence relating to extra-pleural pneumonectomy (EPP) for mesothelioma comes from uncontrolled studies. Large follow-up studies report median survivals of 12, 13, and 14 months in 385, 121, and 208 patients, respectively. Small prospective studies report median survival in the range of 1–2 years, on intention to treat from the start of the planned trimodal treatment. The equivalent measure of survival in MARS was 18 months (14.4 months after randomisation plus 3.6 months from registration). These data and citations are provided in our Article along with full details and discussion about the significance of two patients in the EPP group who died within 30 days.¹

What sets MARS apart is that after completion of chemotherapy, eligible patients were randomly allocated to EPP and radical

postoperative radiotherapy to the hemithorax, or no EPP, thus providing a valid control group. A randomised control group and analysis by intention to treat are essential if the biases of case selection, reporting, and interpretation are to be circumvented.² Trials should be pragmatic and any multimodal treatment strategy should be assessed in real-life settings, including variation in treatments and respect for patients' wishes at each stage. For example, patients in our study received varying chemotherapy, but it was given before randomisation and therefore cannot have biased the EPP versus no EPP comparison.

The power calculation at the planning stage was based on reports available at the time.³ Future trials, and indeed future practice, should be based on what we know now.

Many patients will accept randomisation between EPP and no EPP; however, many clinicians are reluctant to offer it. A large study with longer follow-up would be needed to provide reliable evidence of mortality patterns and long-term survival. But without a willingness to move on from non-randomised phase 2 studies, recruitment of the required numbers of patients would be difficult, and probably impossible, even in an international trial. In the absence of any reliable evidence of benefit, or the prospect of obtaining such evidence, we can only repeat our conclusion that "these data, although limited, suggest that radical surgery in the form of EPP within trimodal therapy offers no benefit and possibly harms patients".

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Pitfalls in the assessment of prognostic factors

Kenneth O'Byrne and colleagues¹ examined whether candidate biomarkers were predictive for the efficacy of chemotherapy plus cetuximab for advanced non-small-cell lung cancer. Patients with tumours expressing PTEN who were given chemotherapy plus cetuximab had a median survival of 11.4 months (95% CI 8.6-13.6) versus 6.8 months (5.9-12.7), for those with tumours not expressing PTEN (hazard ratio

[HR] 0.80, 95% CI 0.55-1.16, $p=0.24$). For patients given chemotherapy without cetuximab, the median survival was 11.0 months (9.2-12.6) for patients with tumours expressing PTEN versus 9.3 months (7.6-11.9) for patients with tumours not expressing PTEN (HR 0.77, 0.54-1.10, $p=0.16$).

In addition to the high p values, the 95% CIs show large overlaps and contained values both above and below 1.0. Therefore, whether the prognostic factor was favourable or unfavourable is unclear. Because of several problems in the study design and data analysis, the results cannot show whether PTEN expression is a potential indicator of good prognosis.

PTEN staining was assessed by subjective grading with four score values from 0 to 3 which were badly defined. Terms such as moderate average staining are subjective, and not reproducible. Furthermore, values were dichotomised without further explanation. Dichotomised prognostic factors, derived from the use of cutoffs, provoke threshold effects with substantial loss of information. Efficiency, reliability, and test power are diminished. Type I or type II errors and even paradoxical results might be obtained.^{2,3} Furthermore, definition of cutoff values varies widely between and within laboratories, thus comparisons made between results of different reports are often difficult.²

Computer-assisted quantitative morphology has substantially increased the information that can be obtained from histological or cytological slides.⁴ Computerised analysis of the immunohistochemical reaction product by measurement of the integrated optical density would be a more accurate and reproducible method for assessment of PTEN expression in this study. Robertson and colleagues⁵ showed that the mean optical density of histological astrocytoma slides obtained automatically by a computer