EDITORIAL

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Combining targeted therapeutics in the era of precision medicine

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We have now entered the era of precision medicine, armed with an armamentarium of novel antitumour agents against a range of critical oncogenic drivers (Tsimberidou *et al*, 2014). Although there have been noteworthy successes, patient benefit with single agent targeted therapies has been generally modest (Yap *et al*, 2013). The reasons for this are multifactorial and well described; they include the disruption of feedback loops, development of crosstalk and other escape mechanisms observed with signalling pathway inhibitors, as well as other issues such as intratumoural heterogeneity. The co-development of investigational targeted agents is thus arguably one of the most important challenges in cancer medicine today.

In the article by Wilky and colleagues, the investigators present findings from a phase I study assessing the vertical blockade of MEK1/2 and insulin growth factor-1 receptor (IGF-1R) with the small molecule selumetinib (AstraZeneca, Macclesfield, UK) and monoclonal antibody cixutumumab (ImClone Systems Inc., Bridgewater, NJ, USA), respectively (Wilky *et al*, 2014). Both selumetinib and cixutumumab had modest antitumour activity as single agents, providing the impetus for this and other targeted combination strategies (Table 1) (Rothenberg *et al*, 2007; Banerji *et al*, 2010). To our knowledge, this is the first published trial of a combination involving IGF-1R and MEK inhibitors, which aims to minimise the effects of feedback loops that may lead to the development of drug resistance (Flanigan *et al*, 2013).

The authors should be commended for this well-conducted study involving two investigational agents from different pharmaceutical companies. The primary objectives of safety and tolerability were achieved, and the maximum tolerated combination dose was 50 mg twice daily of selumetinib and 12 mg kg^{-1} of cixutumumab given every 2 weeks; these were also the starting doses of both drugs in this study. The single agent maximum tolerated dose (MTD) of selumetinib was previously established at 75 mg twice daily, whereas cixutumumab monotherapy demonstrated safety at 15 mg kg^{-1} every 2 weeks (Rothenberg *et al*, 2007; Banerji *et al*, 2010). In view of the relatively high starting doses, it is not surprising that the combination MTD was established after a single dose escalation using a conventional 3 + 3 phase I study design. Other phase I trial designs that could also be considered for such targeted combination studies include a bidirectional-dosing plan, determined by a rule-based up-and-down design (Gandhi *et al*, 2014). This could potentially lead to the identification of two different MTDs: a selumetinib-high and/or a cixutumumab-high dose. Alternatively, model-based designs that use statistical models to establish a dose–outcome relationship to guide the dose-finding process may also be pursued (Mandrekar, 2014). Such a model-based strategy enables more patients to be treated at doses closer to the MTD, reducing the number of patients required on study. Intra-patient dose escalation of one or both drugs in all patients is another combination strategy that could be considered (Yap *et al*, 2013).

The DLTs of ophthalmic symptoms in two of seven patients treated at the second dose level, and ophthalmic adverse events in 40% of patients were likely to be a manifestation of the well-described selumetinib-related mechanism-based ocular toxicities (Banerji *et al*, 2010). Other important adverse events observed with this combination include rash (77%), mucositis (53%), gastrointestinal symptoms and hyperglycaemia. Although not DLTs, such toxicities may ultimately limit the chronic use of these drugs in combination and impact patient benefit in late phase clinical trials.

Although the single agent MTD of selumetinib was not reached in this trial, data from the monotherapy study suggest that the dose of 50 mg twice daily is biologically active (Banerji *et al*, 2010). In addition, Wilky and colleagues report a correlation between the plasma drug PK levels and decreases in tumour ERK and S6 phosphorylation by immunohistochemistry, albeit in a small number of patients. Although the suppression of phosphorylated S6 in post-treatment tumour biopsies may indicate that the PI3K-AKT pathway was potentially modulated, S6 phosphorylation is not a direct readout of IGF-1R inhibition, in contrast to other markers such as IGF-1R expression or total and free IGF-1 (Larsson *et al*, 2007). It would also have been interesting to conduct detailed biomarker studies to evaluate the effects of the combination treatment on feedback loops along the IGF-1R-MEK signalling axis.

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Table 1. Cixutumumab and selumetinib clinical trials in combination with other targeted therapies

Trial	Phase	Compounds	Tumour type	Pts	End point	Results	Toxicities
Cixutumumab							
Schwartz GK NCT01016015 The Lancet 2013	II	CX-temsirolimus	Bone and soft tissue sarcoma	174	PFS at 12 weeks	33%	Anaemia (9%), HG (10%), hypophosphataemia (9%), lymphopenia (14%) and mucositis (11%)
Glisson BS NCT00617734 ASCO 2013	II	CX *vs* CX plus cetuximab	R/M-SCCHN	97	PFS	1.9 m *vs* 2.0 m	Fatigue (61.4%), rash (63.6%), nausea (34%), weight decreased (29.5%), HG (29.5%) and vomiting (20.5%)
Wagner LM NCT01614795 ASCO 2014	II	CX plus temsirolimus	Paediatric patients with relapsed sarcoma	43	Response rate	No objective response	Mucositis, electrolyte disturbances and myelosuppression
Weickhardt A NCT00778167 J Thorac Oncol 2012	I/II	CX-erlotinib	NSCLC	18	Safety and antitumour effect	Tolerable. 5 pts stable disease	Rash and fatigue
Naing A NCT00678769 Br J Cancer 2013	I (exp)	CX-temsirolimus	Adrenocortical carcinoma	26	Safety and antitumour effect	Well tolerated, >40% prolonged SD	TC (38%), mucositis (58%), hypercholesterolaemia (31%), hypertriglyceridaemia (35%) and HG (31%)
Naing A NCT00678769 Clin Cancer Res. 2012	I (exp)	CX-temsirolimus	Ewing's sarcoma	20	Safety and antitumour effect	35% SD, PR or CR	TC (85%), mucositis (8%), hypercholesterolaemia (75%), hypertriglyceridaemia (70%) and HG (65%)
Ma CX NCT00699491 Breast Cancer Res Treat. 2013	I	CX-temsirolimus	Breast cancer	26	MTD	15% SD	Mucositis, neutropenia and TC
El-Khoueiry AB NCT01008566 ASCO 2014	I	CX-sorafenib	Hepatocellular carcinoma	21	Safety, MTD	OS 13.1	HG (10%), diarrhoea (19%), hypertension (19%), TC (14%), palmar-plantar erythrodysesthesia (10%) and fatigue (10%)
Selumetinib							
Ko AH NCT01222689 ASCO 2013	II	S-erlotinib	Pancreatic cancer	46	OS	OS 7.5 m, PFS 2.6 m	Rash (21%), hypertension (13%), anaemia (11%), diarrhoea (9%) and emesis (9%)
Carter CA NCT01229150 ASCO 2013	II	S-erlotinib *vs* erlotinib	NSCLC	78	KRAS wt: PFS KRAS mut: ORR	2.3 m *vs* 2.1 m, NS 0% *vs* 7%, NS	Diarrhoea (23%), fatigue (23%), lymphopenia (13%), myositis (10%), dyspnoea (10%) and rash (7%)
NCT01206140	II	S-temsirolimus *vs* S	Soft tissue sarcoma	70	PFS	Ongoing	
NCT01519427	II	S-MK2206	BRAF V600-mutant melanoma	NA	Objective response	NA	
NCT01166126	II	S-temsirolimus	BRAF-mutant melanoma	NA	Objective response	NA	
Dustin A NCT01287130 ASCO 2012	I	S-cetuximab	Solid tumours and KRAS-mutant colorectal cancer	29	MTD, tolerability	Well tolerated, 2 PR, 4 SD	Rash (20%), hyponatraemia (20%) and headache (20%)
Khan KH NCT01021748 ASCO 2012	I	S-MK2206	Solid tumours	51	MTD, antitumour effect	Well tolerated, 3 PR, 24 SD	Rash (2%), stomatitis (2%) and detached retinal pigment epithelium (2%)
NCT01586624	I	S-vandetanib	Solid tumours (esc) and NSCLC (exp)	48	MTD, safety	Ongoing	
NCT01364051	II	S-cediranib	Solid tumours	89	MTD	Ongoing	

Abbreviations: CX = cixutumumab; esc = escalation; exp = expansion results; HG = hyperglycaemia; MTD = maximum tolerated dose; NA = not available; NS = no statistically significant; NSCLC = non-small cell lung cancer; ORR = objective response rate; P = planned; PFS = progression free survival; Pts = patients; R/M-SCCHN = recurrent or metastatic squamous cancer of head and neck; S: Selumetinib; TC = thrombocytopenia.

Only 9 of 30 (30%) patients had *BRAF* mutation status available for this combination treatment involving a MEK inhibitor. In light of the multiple next-generation sequencing (NGS) technologies currently available in the clinic, should all patient tumours have been tested? In such a phase I trial involving patients with different cancers, context dependency between tumour types remains a critical issue. Nevertheless, for signal-searching phase I studies where biologically active doses of drugs are used in patients from the outset, it may be useful to use multiplexed targeted NGS platforms to investigate a range of 'hot-spot' mutations and other aberrations as putative predictive biomarkers of response and resistance. This is especially important when no analytically validated predictive biomarkers of response have been established for a combination treatment. There is certainly now an increased impetus to undertake such NGS studies in both sequential tumour and circulating plasma DNA specimens in early phase trials for retrospective correlation with antitumour responses.

On the basis of the preliminary antitumour activity observed in this study, the investigators suggest head and neck squamous cell carcinoma, as well as thyroid and colorectal cancers as promising tumour types to explore. However, due to the limited sample size and antitumour responses in this study, it remains to be seen if these malignancies will truly represent ideal targets for this combination. An alternative molecularly-driven cancer to consider may be *KRAS*-mutant non-small cell lung carcinoma (NSCLC). The combination of IGF-1R and MEK inhibitors has been shown to enhance inhibition of *KRAS*-mutant cell lines and improve effectiveness in autochthonous mouse models of *Kras*-induced NSCLC, providing the rationale for this approach (Molina-Arcas *et al*, 2013).

In conclusion, selumetinib and cixutumumab appear to be a well tolerated and biologically active combination. In this age of precision medicine, the identification of both tumour types and molecular subtypes that are likely to benefit from the simultaneous blockade of IGF-1R and MEK with this novel combination now need to be urgently explored.

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