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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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.

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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 |
|-------|-------|-----------|-------------|-----|-----------|---------|------------|
| Schwartz GK | 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%) |
| NCT01016015 |   |           |             |     |           |         |            |
| The Lancet 2013 |   |           |             |     |           |         |            |
| Glisson BS | 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%) |
| NCT00617734 |   |           |             |     |           |         |            |
| ASCO 2013 | II | CX plus temsirolimus | Paediatric patients with relapsed sarcoma | 43 | Response rate | No objective response | Mucositis, electrolyte disturbances and myelosuppression |
| Wagner LM | ASCO 2014 |   |           |     |           |         |            |
| NCT01614795 |   |           |             |     |           |         |            |
| Weidhardt A | I/II | CX-erlotinib | NSCLC | 18 | Safety and antitumour effect | Tolerable, 5 pts stable disease | Rash and fatigue |
| NCT00778167 |   |           |             |     |           |         |            |
| J Thorac Oncol 2012 |   |           |             |     |           |         |            |
| Naein A | I (exp) | CX-temsirolimus | Adrenocortical carcinoma | 26 | Safety and antitumour effect | Well tolerated, >40% prolonged SD | TC (38%), mucositis (58%), hypercholesterolaemia (31%), hypertiglyceridaemia (35%) and HG (31%) |
| NCT00678769 | Br J Cancer 2013 |   |             |     |           |         |            |
| Naein A | I (exp) | CX-temsirolimus | Ewing’s sarcoma | 20 | Safety and antitumour effect | 35% SD, PR or CR | TC (85%), mucositis (8%), hypercholesterolaemia (75%), hypertiglyceridaemia (70%) and HG (65%) |
| NCT00678769 | Clin Cancer Res. 2012 |   |             |     |           |         |            |
| Ma CK | I | CX-temsirolimus | Breast cancer | 26 | MTD | 15% SD | Mucositis, neutropenia and TC |
| NCT00699491 | Breast Cancer Res Treat. 2013 |   |             |     |           |         |            |
| El-Khoueiry AB | I | CX-sorafenib | Hepatocellular carcinoma | 21 | Safety, MTD | OS 13.1 | HG (10%), diarrhoea (19%), hypertension (19%), TC (14%), palmar-plantar erythrodyesthesia (10%) and fatigue (10%) |
| NCT01008566 | ASCO 2014 |   |             |     |           |         |            |
| Ko AH | 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%) |
| NCT01222689 | ASCO 2013 |   |             |     |           |         |            |
| Carter CA | II | S-erlotinib vs erlotinib | NSCLC | 78 | KRAS wt: PFS | 2.3 m vs 2.1 m, NS | Diarrhoea (23%), fatigue (23%), lymphopenia (13%), myositis (10%), dyspnoea (10%) and rash (7%) |
| NCT01229150 | ASCO 2013 |   |             |     |           |         |            |
| NCT01206140 | II | S-temsirolimus vs S-MK2206 | Soft tissue sarcoma BRAF V600-mutant melanoma | 70 | KRAS mut: ORR PFS | Ongoing | NA |
| NCT01519427 | II | S-temsirolimus | BRAF-mutant melanoma | NA | Objective response | NA | NA |
| NCT01166126 | II | S-temsirolimus | Solid tumours and KRAS-mutant colorectal cancer | 29 | Objective response MTD, tolerability | Well tolerated, 2 PR, 4 SD | Rash (20%), hyponatraemia (20%) and headache (20%) |
| NCT01287130 | ASCO 2012 |   |             |     |           |         |            |
| Dustin A | I | S-cetuximab | Solid tumours and KRAS-mutant colorectal cancer | 51 | MTD, antitumour effect MTD, safety | Well tolerated, 3 PR, 24 SD | Rash (2%), stomatitis (2%) and detached retinal pigment epithelium (2%) |
| NCT01586624 | ASCO 2012 |   |             |     |           |         |            |
| Khan KH | I | S-MK2206 | Solid tumours | 48 | ORR | 48 | NA |
| NCT01021748 | ASCO 2012 |   |             |     |           |         |            |
| NCT01364051 | II | S-cediranib | Solid tumours (exc) and NSCLC (exc) | 89 | MTD | Ongoing | NA |

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.
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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