(as opposed to overexpression or amplification) seems to be sufficient for trastuzumab deruxtecan to induce meaningful tumour responses.[6] These and other advances suggest an expanded spectrum of HER2 druggable alterations encompassing HER2-activating mutations, supra-physiological HER2 expression, addiction to HER2 amplification, the presence of molecular resistance mechanisms to specific compounds, and tumour and patient immune status. This complex scenario will require adequate testing in rationally designed clinical trials, which is the greatest challenge for the immediate future.

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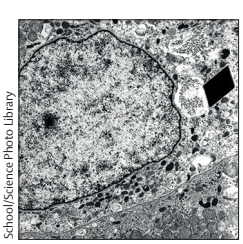
Personalised management of alveolar soft part sarcoma: a promising phase 2 study



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Medical oncologists have identified approximately 100 different histological subtypes of sarcoma, each of which exhibit specific characteristics and outcomes and require a tailored approach. Accordingly, an accurate biopathological diagnosis of sarcoma is a mandatory first step towards personalised treatment.[1] However, approximately a third of sarcomas are misdiagnosed before the solicitation of an expert second opinion. In *The Lancet Oncology*, Breelyn A Wilky and colleagues[2] report on the remarkable results of a clinical trial assessing the combined activity of axitinib plus pembrolizumab for advanced sarcoma. The study cohort included 12 patients with alveolar soft part sarcoma (ASPS), which is one of the rarest subtypes of sarcoma and accounts for only 48 (0·5%) of 10 262 sarcomas in the French Nationwide NetSarc database as of December 2014.[3]

ASPS is usually diagnosed in adolescents and young adults and is associated with a high risk of lung and brain metastasis. Long-term follow-up is required because ASPS can relapse even several decades after initial treatment. For special cases, surgery or focal treatment during the oligometastatic stage might be feasible; otherwise, close monitoring is acceptable, given the spontaneous and indolent disease course and good survival prognosis (5-year overall survival exceeding 70% in many large case series).[4]

Although ASPS is considered refractory to classical chemotherapy, it is a so-called targetable sarcoma. This subtype is characterised by a persistent unbalanced translocation der(17)t(X;17)(p11;q25) and two mutually exclusive variants of the inherent chimeric fusion protein ASPSCR1-TFE3. In everyday practice, fluorescent in-situ hybridisation confirmation of this translocation

is extremely important to a final diagnosis of ASPS. The fusion variants induce immunosuppression in the tumour microenvironment, hepatocyte growth factor receptor (MET) overexpression, and angiogenesis via hypoxia-inducible factor 1-α (HIF-1α) overexpression. These specific biological features have encouraged the successful exploration of antiangiogenic drugs (eg, pazopanib, cediranib, axitinib), a MET inhibitor (crizotinib), and immune-stimulating drugs. In a large retrospective study of ASPS,[5] pazopanib elicited one (3%) objective response in 29 patients and a progression-free survival of 13 months. In a formal phase 2 trial assessing pazopanib activity,[6] one (17%) of six patients with ASPS had an objective response, and in a dedicated phase 2 trial,[7] cediranib induced objective responses in 15 (35%) of 43 ASPS patients. Crizotinib, a potent MET inhibitor, induced responses in two (4%) of 45 patents with ASPS in a phase 2 trial,[8] and an ancillary analysis showed that most of patients with ASPS (40 [89%] of 45) overexpressed MET. Finally, some ASPS case reports describe dramatic tumour shrinkage in response to immune checkpoint inhibitors.[9] Consequently, clinical trials of atezolizumab (NCT03141684) or pembrolizumab (NCT03012620) are currently recruiting patients with ASPS.

Wilky and colleagues[2] report the findings from a non-randomised phase 2 study assessing the activity and safety of a combination of axitinib (an antiangiogenic drug) plus pembrolizumab (an immune-stimulating checkpoint inhibitor). 12 (33%) of 36 enrolled patients with sarcoma had ASPS, and of those with ASPS 55% (six of 11 assessable patients) achieved an objective response. This outcome surpasses those of the studies previously mentioned[5–9] and suggests an additive or synergistic effect of antiangiogenic and immune-stimulating drugs for this sarcoma subtype. Accordingly, the investigators have indicated that they believe this combination has preliminary activity in ASPS.

The design and performance of a clinical trial for a highly rare disease is very challenging. Accordingly, the study by Wilky and colleagues was limited to a subgroup analysis of patients with ASPS, rather than a dedicated trial. The primary endpoint (3-month progression-free survival) was also of restricted relevance, given the indolent course of ASPS. Finally, the statistical hypothesis for sample size calculation is usually applied to common histological sarcoma subtypes (eg, liposarcoma, leiomyosarcoma) after a lack of response to doxorubicin-based chemotherapy, hence use of this threshold might not be appropriate for patients with ASPS.

What steps might be next? A follow-up study to confirm the clinical benefit of this combination will require international collaboration, ideally in the form of a comparative phase 2 or higher randomised trial. A phase 3 trial comparing axitinib alone versus axitinib plus pembrolizumab would require approximately 50 patients, assuming the proportion of patients who have a response (primary endpoint) is 10% with axitinib alone and 40% in combination, and two-sided α and β thresholds of 10%. An international collaboration would enable researchers to determine the feasibility of axitinib plus pembrolizumab combination therapy for this rare sarcoma subtype. Importantly, a single-country group successfully completed a phase 3 trial of 80 patients with very rare desmoid tumours,[10] hence practice-changing randomised trials are possible for rare diseases. In summary, the existing information illustrates the continuum encompassing the accurate diagnosis of rare malignancies, knowledge of tumour biology, identification of potential targets, management by expert centres using innovative approaches, and finally the development of dedicated trials of personalised treatment. The era of a one-size-fits-all approach to sarcoma therapy appears to be over.

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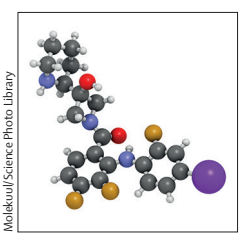
MEK and PD-L1 inhibition in colorectal cancer: a burning blaze turning into a flash in the pan



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Immunotherapy has revolutionised the treatment landscape of a wide variety of tumours. In DNA mismatch repair-deficient or high microsatellite instability metastatic colorectal cancer, single-drug or double-drug immune checkpoint inhibition have shown notable activity in both the chemotherapy-naive and chemorefractory setting. Pembrolizumab, nivolumab, and nivolumab plus ipilimumab are now approved by the US Food and Drug Administration for patients with mismatch repair-deficient or high microsatellite instability metastatic colorectal cancer who have been previously treated with standard chemotherapy. By contrast, no benefit has been observed with these drugs in patients with DNA mismatch repair-proficient, low microsatellite instability, or microsatellite-stable tumours, who account for 95% of patients with metastatic colorectal cancer and are characterised by a low number of tumour mutations, neoantigens, and infiltrating immune effector cells.

Studies have suggested that inhibition of the MAPK signalling pathway could tackle the immune resistance of mismatch repair-proficient microsatellite-stable tumours by upregulating HLA molecule expression, downregulating immunosuppressive factors, and increasing tumour-infiltrating CD8+ cytotoxic T cells.[1,2] To confirm preclinical observations and early clinical findings of synergistic activity between anti-MEK drugs and immune checkpoint inhibitors,[1–3] Cathy Eng and colleagues[4] did an international, open-label, randomised phase 3 trial of atezolizumab plus or minus cobimetinib versus regorafenib in patients with chemotherapy-refractory metastatic colorectal cancer (IMblaze370), the results of which are reported in *The Lancet Oncology*.

The trial, which enrolled 363 patients, 333 (92%) of whom had microsatellite-stable tumours, did not meet its primary endpoint, with a median overall survival of 8·87 months (95% CI 7·00–10·61) with atezolizumab plus cobimetinib (stratified hazard ratio [HR] *vs* regorafenib 1·00 [95% CI 0·73–1·38]; p=0·99) and 7·10 months (6·05–10·05) with atezolizumab alone (stratified HR *vs* regorafenib 1·19 [0·83–1·71]; p=0·34), compared with a median overall survival of 8·51 months (6·41–10·71) for standard treatment with regorafenib. Treatment effect did not differ by clinical or molecular characteristics, including microsatellite instability, *RAS* mutation status, and programmed cell death ligand 1 (PD-L1) expression. Similarly, no differences between treatment groups were observed in terms of progression-free survival, and less than 2% of patients with microsatellite-stable tumours in either investigational group achieved an objective response. The addition of cobimetinib to atezolizumab doubled the frequency of grade 3 or worse adverse events compared with atezolizumab alone (109 [61%] of 179 patients in the combination group *vs* 28 [31%] of 90 in the atezolizumab monotherapy group) and serious adverse events (71 [40%] of 179 *vs* 15 [17%] of 90).

There is great disappointment for the negative results of the IMblaze370 trial because of the scientific interest and general enthusiasm for the underlying biological rationale and supportive preliminary clinical findings, which endured throughout the study recruitment period and led to an impressively rapid accrual of just 6 months. Dwelling on potential reasons for such an unexpected failure is therefore imperative.

The IMblaze370 trial was based on intriguing data from in-vitro experiments and preclinical models. It should be noted though that controversy exists around the immunomodulatory effects of MEK inhibition, with some studies actually reporting suppression of T lymphocyte proliferative response and antigen-specific expansion and impairment of