Ramucirumab plus pembrolizumab: can we make the maths work?

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A 2015 analysis from The Cancer Genome Atlas[1] identified gastroesophageal adenocarcinoma, non-small-cell lung cancer, and urothelial carcinomas as types of tumours with increased antigenic mutations, highlighting their predicted potential to respond to immunotherapy. Since 2015, the treatment of advanced gastroesophageal adenocarcinoma, non-small-cell lung cancer, and urothelial carcinoma has been fundamentally changed with the approval of immune checkpoint inhibitors such as PD-1 inhibitors. Anti-PD-1 and anti-PD-L1 antibodies have shown single-drug activity in these tumours in later-line settings, and antitumour activity when given as a combination therapy in all three cancer types in the JVDF trial presented by Roy Herbst and colleagues in *The Lancet Oncology*.[2] Although patients with gastroesophageal adenocarcinoma, non-small-cell lung cancer, and urothelial carcinoma have varying responses and durations of responses to immune checkpoint inhibitors, objective responses according to Response Evaluation Criteria in Solid Tumors occur in few patients, albeit often characterised by durable and clinically relevant benefit. Several trials of combinatorial approaches seeking to expand the proportion of responders to immune checkpoint inhibitors are ongoing, and combinations of immune checkpoint inhibitors with anti-angiogenic therapies, including bevacizumab and the small molecule antiangiogenic multi-kinase inhibitor axitinib, have shown meaningful activity in larger trials.[3,4]

In their phase 1a/b JVDF trial,[2] Herbst and colleagues present the results of a combination of the IgG4 PD-1 antagonist pembrolizumab with the IgG1 anti-VEGFR-2 antibody ramucirumab in 41 previously treated patients with advanced gastric or gastro-oesophageal junction adenocarcinoma, 27 with non-small-cell lung cancer, and 24 with urothelial carcinoma. The trial was well designed and clinically relevant because ramucirumab is already well studied in different combinations for each tumour type (eg, ramucirumab plus paclitaxel in gastro-oesophageal adenocarcinoma; and ramucirumab plus docetaxel in non-small-cell lung cancer and in bladder cancer). Patients with non-small-cell lung cancer could have had previous therapy with treatments targeting VEGF or VEGFR; for all other patients, previous therapy with drugs targeting the VEGF–VEGFR, PD-1–PDL-1, or PD-1–PDL-2 signalling pathways was not permitted. Information about patients' PD-1 and PD-L1 status was collected but not required for eligibility. Roughly 40% of patients had received one previous line and 50% two previous lines of therapy across cohorts. All patients (except cohort A with gastric or gastro-oesophageal junction adenocarcinomas) received standard-dose pembrolizumab (200 mg intravenously) every 3 weeks given concurrently with intravenous ramucirumab 10 mg/kg on day 1 of a 21-day cycle (patients in cohort A received standard-dose pembrolizumab every 3 weeks and intravenous ramucirumab 8 mg/kg on days 1 and 8). In terms of the toxicity profile, 22 (24%) of 92 patients had one or more grade 3 or worse treatment-related adverse event; these findings were similar to values for monotherapy data for each drug and synergistic toxicity was not clearly apparent.

With imaging done every 6 weeks for the first 24 weeks, the proportion of patients who achieved an overall response was modest across cohorts (7% of those with gastric or gastro-oesophageal junction adenocarcinoma, 30% with non-small-cell lung cancer, and 13% with urothelial carcinoma). Progression-free survival results were encouraging compared with previous trials of anti-PD-1 or anti-PD-L1 monotherapy, although sample sizes were small for each cohort. In an exploratory analysis of efficacy outcomes by PD-L1 status, PD-L1-positive patients seemed to have better outcomes than those with PD-L1-negative disease across tumour types (for example, in the urothelial carcinoma cohort, confirmed objective responses were only recorded in patients with PD-L1-positive disease). How do we place these hypothesis-generating results in the context of each tumour type to guide further development strategies?

Several ongoing trials, including the first-line cohorts from Herbst and colleagues' study, might help to refine the optimal patient for treatment with VEGF plus immune checkpoint inhibitor combinations. VEGF blockade can regulate expression of inhibitory immune checkpoint receptors, affect myeloid immunosuppression, and increase T-cell trafficking

to tumours, and anti-VEGF therapies might help to adjust the tumour microenvironment toward a more immunosupportive phenotype.[5,6] Beyond potentially complementary mechanisms, preclinical studies using anti-mouse VEGF-A and anti-mouse PD-L1 antibodies have suggested synergistic activity in small-cell lung cancer models.[7] Within the more immunoresponsive tumour types of non-small-cell lung cancer and urothelial carcinoma in the study, the heterogenous patient populations limited the investigators' ability to examine which subsets benefitted from the addition of ramucirumab beyond what would have occurred with pembrolizumab alone. Correlates from a prospective three-arm phase 2 trial (sunitinib *vs* atezolizumab *vs* atezolizumab plus bevacizumab) suggested that patients with high T-cell effector expression and high myeloid inflammation gene signatures derived the most benefit from the addition of bevacizumab beyond atezolizumab alone.[4] Unfortunately, in the JVDF study, baseline biomarker analyses are not presented, and on-treatment or progression biopsies were not included in the trial protocol, limiting detailed examination of responders.

In PD-L1-positive patients (those with a combined positive score of 1 or higher), studies of single-drug pembrolizumab in second and third-line gastric or gastro-oesophageal junction adenocarcinoma have been associated with 10–15% of patients achieving an overall response and progression-free survival of 1·5 and 2·0 months respectively.[8,9] Although cross-trial comparisons of progression-free survival are confounded by differences in eligibility criteria and patient characteristics, the duration of progression-free survival in the gastric or gastro-oesophageal junction adenocarcinoma cohort in Herbst and colleagues' study was 2·5 months (95% CI 1·5–4·2), (and 4·6 months [2·3–8·5] in PD-L1-positive patients), similar to results from the gastric or gastro-oesophageal junction adenocarcinoma cohort in a phase 1b durvalumab plus ramucirumab trial (median progression-free survival of 2·6 months). Additionally, the phase 3 REGARD trial of single-drug ramucirumab in patients with advanced gastric or gastro-oesophageal junction adenocarcinoma showed a median progression-free survival of 2·1 months in a second-line population.[10] There were further confounding complexities across the JVDF study cohorts including an unknown proportion of patients with PD-L1 expression of more than 10%, a group known to derive greater benefit from PD-1 drugs. Overall, it was unclear if the combination of pembrolizumab and ramucirumab was clinically additive or synergistic, although the combination seemed to be safe.

As we move toward precision immunotherapy, it is increasingly relevant to understand the patient molecular phenotype, especially in combination studies. For example, does a patient with gastric or gastro-oesophageal junction adenocarcinoma and PD-L1 expression of more than 10% derive additional benefit from combination with ramucirumab, or is this patient more likely to resemble the population of patients with a high T-cell effector signature and low myeloid inflammation signature in which the addition of bevacizumab to atezolizumab did not seem to improve upon atezolizumab alone?[4] Ultimately, randomised trials to determine the true contribution of each drug are needed to address this unresolved oncology maths problem.

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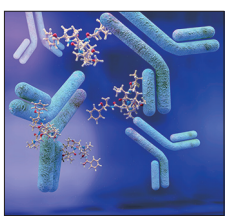
A new agent in the family of antibody–drug conjugates

Amplification of the *HER2* gene occurs in approximately 15% of breast cancers, defining HER2-positive disease. Patients whose tumour overexpresses the HER2 receptor derive benefit from trastuzumab-based treatments.[1] The emergence of antikinase treatments (eg, neratinib and lapatinib) and other antibodies (eg, pertuzumab) that target the HER2 receptor have enhanced this class of drugs and have substantially improved outcomes for patients with HER2-positive breast cancer.

HER2-positive breast cancers are heterogeneous. Genetic analysis has established that these tumours do not represent an intrinsic subtype but rather are distributed along the whole breast cancer spectrum,[2] which helps to explain why no predisposing factors for HER2-positive breast cancer have been detected.[3] Reported genome alterations accord with the luminal-to-basal phenotype. *HER2* amplification initially arises as a genetic incident from unknown causes, but the mechanism implicated in HER2 amplification has been identified in most cases as the breakage–fusion–bridge cycle.[2] However, the observed focal amplification suggests that other mechanisms might also be involved, such as formation of double-minute chromosomes. In some cases, several breakpoints associated with interchromosomal events indicate that amplification might have occurred on other chromosomes. Rarely, deleterious mutations could also cause HER2 overexpression without any amplification-supporting processes. Thus, the various mechanisms that lead to a HER2-positive status, combined with the heterogeneity of associated genetic breast cancer subtypes, suggests the need for tailored therapeutic strategies.

The most recent evolution in targeted treatment is antibody engineering, which permits a paradigm that might work independently of HER2 positivity or breast cancer subtypes. The chemical conformation of trastuzumab allows a cytotoxic agent to be linked to the antibody without affecting its ability to bind to HER2. Internalisation of the HER2 receptor triggered by binding of the antibody–drug conjugate allows delivery of the cytotoxic agent inside the cell—an innovative approach to target cancer. Trastuzumab emtansine was the first-in-class named antibody–drug conjugate available for routine use in patients with breast cancer.[4] The agent includes DM1—a microtubule inhibitor derived from maytansine—conjugated to trastuzumab via a stable linker. Randomised trials have shown that trastuzumab emtansine improves clinical outcomes for patients with HER2-positive metastatic breast cancer and has a more acceptable safety profile than standard treatment regimens.[5] Although standard trastuzumab-containing regimens in a neoadjuvant setting did not lead to pathological complete responses in patients with early-stage breast cancer, a switch to trastuzumab emtansine instead of pursuing adjuvant trastuzumab showed a survival benefit.[6] How trastuzumab emtansine could become the backbone of anti-HER2 treatment strategies is still a matter of debate.

Trastuzumab emtansine binds to HER2-expressing cells with similar affinity to trastuzumab alone. Both molecules can inhibit the PI3K signalling pathway and HER2 extracellular domain shedding and can elicit an antibody-dependent cellular cytotoxicity response on binding of the Fab region to HER2 on cancer cells and binding of the Fc region to FcγRs on immune-effector cells. The contributions of each mechanism to the efficacy of trastuzumab can be highly variable, due to the therapeutic partners (if any), the host predisposition, or the diversity of tumour subtypes. Trastuzumab emtansine provides a lower exposure to trastuzumab than does the antibody alone, which might reduce the magnitude of the previously described effects. However, the option of direct delivery of the cytotoxic agent needs to be added to the existing mechanisms of delivery. Based on the contribution of each mechanism to the



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