In the news

FROM MOLECULAR TARGETS AND CANCER THERAPEUTICS

In October 2019, the AACR, NCI and EORTC held their joint International Conference on Molecular Targets and Cancer Therapeutics in Boston, MA, USA. This annual event, which has been held for 30 years, provides a key opportunity to keep abreast of the busy field of translational oncology, and this year's programme did not disappoint.

The conference started with an insightful educational session in which Jaap Verweij, Elizabeth Fox and Michael Heinrich reflected on the successes and failures of targeted therapies over the past 20 years. Despite covering different cancer types, the presenters agreed on the need for appropriate preclinical models and the importance of joining resources for conducting clinical trials.

Both a keynote lecture and a dedicated session focused on targeted protein degradation with agents exploiting the cereblon–E3 ligase interaction as well as proteolysis-targeting chimeras (PROTACs). The studies presented addressed the biochemical principles guiding interactions that result in the degradation of oncogenic proteins. This knowledge has been gained from decades of study of the mode of action of lenalidomide. Major excitement surrounds these therapeutic approaches; however, their incorporation in clinical studies remains limited.

In 'spotlight' sessions, the authors of ten submitted abstracts were given the opportunity to present the results of ongoing early phase clinical trials. The agents tested in these studies are targeted at a variety of biological processes that are dysregulated in cancer, such as DNA repair, RNA splicing, interactions with immune cells or oncogenic RAS signalling. Great excitement surrounds the latter target, with recent advances in this area also being discussed in a dedicated session.

Not surprisingly, targeting DNA repair was a common theme in many presentations. The success of this therapeutic approach typically depends on exploiting cancer-specific dependencies, such as synthetic lethality, genome instability or oncogene-induced replication stress.

Bissan Al-Lazikani, Adam Dicker and Sean Khozin provided a comprehensive view of how preclinical and clinical data can be integrated to provide optimal patient-centred care. Practical examples include designing tailored treatments, evaluating treatment-related quality of life or identifying patterns of response to treatment in large patient populations.

The variety of topics covered is one of the strengths of this year's programme; important areas that cannot be summarized herein include immuno-oncology and liquid biopsies. In summary, the complex network of mechanisms that are dysregulated in cancer cells and their environment was highlighted at the conference. The good news is that joint research efforts are enabling the development of approaches to target these mechanisms, some with promising results in early phase trials. We look forward to next year's meeting in Barcelona, at which additional novel targeted therapies are likely to be presented.

Diana Romero

Credit: Simon Bradbrook/ Springer Nature Limited

TARGETED THERAPIES

Two new agents target KRAS G12C

Attempts to therapeutically target the products of the *RAS* oncogenes, frequently mutated in cancer, have had disappointing results thus far. The small molecules MRTX849 and AMG 510, from two independent drug discovery programmes, covalently bind to KRAS G12C, keeping it predominantly in an inactive state. Two articles now describe the activity of these drugs in preclinical models and initial clinical responses in patients with *KRAS*^{G12C}-mutant cancers.

Following promising findings in cell-line based studies, MRTX849 and AMG 510 inhibited 2D and 3D cell growth of *KRAS*^{G12C}-mutant cancer cell lines to variable degrees. Both agents inhibited the growth of mouse xenograft tumours derived from *KRAS*^{G12C}-mutant human cell lines or patient-derived xenograft tumours in a dose-dependent manner with a toxicity profile deemed tolerable. Tumour regression was observed with both agents at the highest doses tested. Of note, treatment with 200 mg/kg AMG 510 led to complete regression of tumours derived from CRISPR-generated *KRAS*^{G12C}-mutant syngeneic CT-26 cells in 8 of 10 immune-competent mice, but not in mice lacking T cells.

MRTX849 and AMG 510 are currently being tested in first-in-human clinical trials (NCT03785249 and NCT03600883, respectively) involving patients with *KRAS*^{G12C}-mutant solid tumours, mostly non-small-cell lung carcinoma (NSCLC) or colorectal carcinoma. The results of these trials were presented at the 2019 ASCO Annual Meeting (AMG 510) and at the 2019 AACR–NCI–EORTC joint conference (MRTX849). The majority of 17 patients receiving MRTX849 had grade 1–2 treatment-related adverse events (TRAEs), and one patient had grade 3 fatigue. Twelve patients were evaluable for response: four had partial responses (PRs) and eight had stable disease (SD). All patients who had PRs received a dose of 600 mg twice daily; one with NSCLC had a 43% reduction of the target lesion and one with CRC had a 47% reduction, both 6 weeks after starting treatment. A total of 35 patients received AMG 510; 28 events of grade 1–2 TRAEs were reported and 29 patients were evaluable for response: 5 PR, 18 SD and 6 patients had progressive disease. In two patients with NSCLC who had PRs, reduction of the target lesion was 34% and 67% after 6 weeks of treatment with doses of 180 mg and 360 mg, respectively.

Owing to the role of T cells in the response of mice to AMG 510, this agent was tested in combination with anti-PD-1 antibodies in immunocompetent mice harbouring *KRAS*^{G12C}-CT-26 tumours, leading to complete and durable responses in 9 of 10 mice. "We are dissecting the effect of AMG 510 on the immune phenotype to determine which treatment combinations might be the most effective in tumour elimination", comments investigator Jude Canon. MRTX849 is also being explored in combination, although investigator James Christensen believes that these agents could be used as monotherapies in some patients: "we need to understand *KRAS* mutations in a broader genetic context in treated patients to determine if there is a refined way to select patients for monotherapy."

The optimal treatment strategy for these agents is only one of several aspects that remain to be determined. The results of large, prospective randomized trials designed to determine the degree and duration of clinical benefit from these agents, their toxicities, and mechanisms of resistance, are eagerly awaited.

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ORIGINAL ARTICLES Hallin, J. et al. The KRASG12C inhibitor, MRTX849, provides insight toward therapeutic susceptibility of KRAS mutant cancers in mouse models and patients. *Cancer Discov.* https://doi.org/10.1158/2159-8290.CD-19-1167 (2019) | Canon, J. et al. The clinical KRAS(G12C) inhibitor AMG 510 drives anti-tumour immunity. *Nature* **575**, 217–223 (2019)