IMMUNOTHERAPY

## NEOADJUVANT PD-1 BLOCKADE IN NSCLC

Immune-checkpoint inhibitors targeting the PD-1–PD-L1 axis have improved the outcomes of patients with advanced-stage non-small-cell lung cancer (NSCLC), including after definitive chemoradiotherapy for unresectable stage III disease. However, whether these agents are effective in patients with resectable stage I–IIIA NSCLC — for whom therapeutic advances have been limited — remains unknown. Now, data from a pilot neoadjuvant study provide new insights.

In this study, 22 patients were allocated to receive 2 doses of the anti-PD-1 antibody nivolumab (3 mg/kg every 2 weeks) starting ~4 weeks before resection of stage I (19%), stage II (48%), or stage IIIA (33%) NSCLC. After receiving one dose, one patient was deemed ineligible and another had grade 3 pneumonia and proceeded to surgery without receiving a second dose. Four other patients had grade 1–2 adverse events. Importantly, treatment did not delay surgery for any patient and of the 21 primary tumours removed, 20 were completely resected.

Of the patients with complete resection, nine (45%) had a major pathological response (≤10% viable residual tumour cells), including three complete responses (15%), and eight (40%) had disease downstaging. At a median of 1 year after surgery, recurrence-free survival was 80%: three patients had lymph-node or metastatic recurrence (one died and two had responses to salvage therapies lasting >1 year); one patient without recurrence had died of an unrelated injury.

Major and complete pathological responses occurred irrespective of tumour PD-L1 status before treatment. By contrast, the percentage of viable residual tumour was inversely correlated with pretreatment tumour mutation burden ($r_s$ −0.75, $P$ = 0.008) and predicted neoantigen load ($r_s$ −0.78, $P$ = 0.005). Moreover, expansion of peripheral blood and intratumoural T cells, including some neoantigen-specific clones that were undetectable before treatment, was detected after PD-1 blockade.

These results demonstrate the feasibility and promising activity of neoadjuvant PD-1 blockade in patients with early stage NSCLC; further testing of this approach is warranted.

*David Killock*

**ORIGINAL ARTICLE** Forde, P. M. et al. Neoadjuvant PD-1 blockade in resectable lung Cancer. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa1716078 (2018)

HAEMATOLOGICAL CANCER

# Targeted combination has synergy in MCL

Both the BTK inhibitor ibrutinib and the BCL-2 antagonist venetoclax have impressive efficacy in patients with B cell malignancies. Now, results of the phase II AIM study in patients with mantle-cell lymphoma (MCL) show that these agents can be combined safely to enhance clinical responses.

This historically controlled trial included 23 patients with relapsed and/or refractory MCL and one with untreated disease, 75% of whom had a high-risk prognostic score. Ibrutinib monotherapy was commenced at 560 mg daily, with venetoclax added after 4 weeks followed by weekly dose escalation to 400 mg daily, in order to avoid tumour-lysis syndrome (TLS). The primary end point was the complete remission (CR) rate after 16 weeks of treatment.

"True to preclinical models, ibrutinib and venetoclax seem to be synergistic in the clinic with a final CR rate of 71% and >80% of patients in CR achieving minimal residual disease negativity," states lead investigator Constantine Tam, emphasizing that "these results are significantly better than those of either drug alone." Indeed, the CR rate at week 16 was already 42%, double that observed previously with long-term continuous use of either agent alone (21%). In the historical control group from the phase II PCYC-1104-CA study, the CR rate to ibrutinib monotherapy at 16 weeks was 9% ($P$ < 0.001). Importantly, 78% of responses to the combination therapy were ongoing at 15 months. Common adverse events were generally of a low grade, and included diarrhoea, fatigue, and nausea or vomiting; although, TLS occurred in two patients (8%).

"This study sets a new platform of combination targeted therapies for MCL and related diseases, including chronic lymphocytic leukaemia (CLL); multiple large phase II and III confirmatory studies of this combination are now underway in MCL and CLL," Tam explains. "Ultimately, this combination could provide an effective chemotherapy-free treatment of limited duration, rather than the current standard of indefinite single-agent targeted therapy."

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**ORIGINAL ARTICLE** Tam, C. S. et al. Ibrutinib plus venetoclax for the treatment of mantle-cell lymphoma. *N. Engl. J. Med.* **378**, 1211–1223 (2018)

TARGETED THERAPIES

# Poziotinib for uncommon *ERBB* mutations

Patients with *EGFR*-mutant non-small-cell lung cancer (NSCLC) with insertions in exon 20 (1–2% of all patients with NSCLC) generally do not respond to approved EGFR tyrosine kinase inhibitors (TKIs). A similar situation occurs for *HER2* exon 20 mutations, which are detected in another ~2% of patients with NSCLC. In a study with results now published, John Heymach and colleagues searched for inhibitors that could benefit these patients.

"Using structural modelling, we observed that exon 20 insertions created a 'bulge' in the drug-binding pocket that prevented the interaction with approved EGFR TKIs. We hypothesized that smaller and more-halogenated TKIs would have greater activity," explains Heymach, adding "We tested the candidate poziotinib against a panel of cells with insertions in exon 20 of *EGFR* or *HER2*, observing potent activity."

The investigators then conducted a phase II trial of poziotinib in patients with NSCLC harbouring insertions in exon 20 of *EGFR*. At 6.6 months, the first 11 patients had an objective response rate (ORR) of 64%, and the median progression-free survival (PFS) duration had not been reached. These results contrast with ORRs of <10% and PFS durations of <2 months observed when such patients have received approved EGFR TKIs.

"Our improved understanding of the structure of different exon 20 insertions should enable us to find or design even more specific drugs that work for some of the tougher-to-treat mutations," comments Heymach. Other avenues that are being further explored include two large studies with poziotinib in patients with NSCLC harbouring insertions in exon 20 of *EGFR* or *HER2*, as well as the response of patients with other cancer types harbouring these alterations (such as breast cancer, glioblastoma, or anal cancer) to poziotinib. Finally, an aspect that Heymach wants to highlight is that many of the patients involved in the study have been in touch with each other to share their experiences.

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**ORIGINAL ARTICLE** Robichaux, J. P. et al. Mechanisms and clinical activity of an EGFR and HER2 exon 20-selective kinase inhibitor in non–small cell lung cancer. *Nat. Med.* https://doi.org/10.1038/s41591-018-0007-9 (2018)