IMMUNOTHERAPY

ICI for resected stage IV melanoma

Immune-checkpoint inhibition (ICI) is an approved treatment approach for both unresectable and completely resected advanced-stage melanoma; however, patients with completely resected stage IV disease have been under-represented in clinical trials to date. In particular, the efficacy of dual PD-1 and CTLA4 ICI in this subgroup is unclear. Now, data from the phase II IMMUNED trial address these knowledge gaps.

In IMMUNED, 167 patients with stage IV cutaneous melanoma and no evidence of disease after surgery and/or radiotherapy were randomly assigned (1:1:1) to receive adjuvant nivolumab plus ipilimumab (nivo+ipi), nivolumab alone (nivo) — both at the approved dosages — or placebo. At a median follow-up duration of 28.4 months, the median relapse-free survival (RFS) duration was not reached in the nivo+ipi group (HR 0.23, 97.5% CI 0.12–0.45; $P<0.0001$) and was 12.4 months in the nivo group (HR 0.56, 97.5% CI 0.33–0.94; $P=0.011$), versus 6.4 months with placebo. At 1 year and 2 years, RFS was 75% and 70%, respectively, in the nivo+ipi group, with a plateau on the Kaplan–Meyer curve out to 42 months. These rates were 52% and 42% with nivo alone, and 32% and 14% with placebo. The benefits of nivo+ipi and nivo alone over placebo were similar across all pre-specified subgroups; tumour PD-L1 expression <5%, *BRAF* mutation or CNS involvement did not seem to diminish efficacy.

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"Our findings clearly demonstrate greatly improved disease control with ICI than with observation alone. Furthermore, our study provides strong evidence that dual ICI enables much better disease control than PD-1 ICI as monotherapy," principal investigator Dirk Schadendorf summarizes. Indeed, in an exploratory analysis of RFS with nivo+ipi versus nivo, the HR was 0.40 (97.5% CI 0.20–0.79). "This effect was seen despite the fact that 50% of patients in the nivo+ipi group only received ≤2 doses of the combination (owing to toxicities). Importantly, this raises questions regarding how intensely and for how long we need to treat patients, particularly in the adjuvant setting," adds Schadendorf. The investigators plan to examine these aspects, as well as predictive biomarkers, to optimize patient management.

The rates of treatment-related grade 3–4 adverse events were 71% with nivo+ipi versus 27% with nivo, most commonly increased levels of serum liver enzymes, amylase and/or lipase, and autoimmune disorders (including hepatitis); the treatment discontinuation rates were 62% versus 13%. However, no deaths were deemed treatment related.

These results support the use of single-agent ICI in the adjuvant treatment of resected stage IV melanoma. The data might lead to a shift towards dual ICI in this setting.

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In the news

LUNG CANCER AT ASCO20 VIRTUAL

As is common in ASCO Annual Meetings, the lung cancer track in ASCO20 Virtual included numerous relevant studies. Some of the most promising results presented this year were from trials of targeted agents.

Tepotinib is a highly selective orally administered MET tyrosine-kinase inhibitor (TKI). Primary efficacy data from the phase II VISION trial of tepotinib in patients with metastatic non-small-cell lung cancer (NSCLC) harbouring *MET* exon 14 skipping alterations were presented and simultaneously published. In patients with ≥9 months of follow-up ($n=99$), the objective response rate (ORR) was 46%, and the median progression-free survival (mPFS) duration was 8.5 months. In patients with brain metastases (11 of 99), the ORR was 55% and the mPFS duration was 10.9 months. The frequency of grade ≥3 treatment-related adverse events (TRAEs) was 28%.

Several presentations focused on combinatorial approaches involving TKIs. A phase I/II trial is testing concurrent treatment with the EGFR TKIs osimertinib and gefinitib to delay emergence of acquired mutations at second sites in *EGFR*. At a median follow-up of 14.8 months, the ORR was 88.9%, and the disease control rate was 100.0% in 27 evaluable patients. In a phase III trial involving 133 patients with untreated oligometastatic NSCLC (<6 lesions), stereotactic body radiotherapy plus a TKI improved outcomes over treatment with a TKI alone: the mPFS duration was 20.2 months versus 12.5 months (HR 0.62, 95% CI 0.39–0.97; $P<0.001$), and the median overall survival (mOS) duration was 25.5 months versus 17.4 months (HR 0.68, 95% CI 0. 47–1.00; $P<0.001$). Grade 3–4 TRAEs were more frequent with combination therapy.

Use of TKIs in the adjuvant setting in patients with *EGFR*-mutated NSCLC was another important theme. In the phase III ADJUVANT-CTONG1104 trial involving 111 patients, mOS durations were numerically, but not significantly, longer with gefitinib versus doublet chemotherapy (75.5 months versus 62.8 months; HR 0.92, 95% CI 0.62–1.36; $P=0.67$). In the phase III ADAURA trial, 2-year disease-free survival was higher with osimertinib versus placebo (90% versus 44%; HR 0.17, 95% CI 0.12–0.23; $P<0.0001$).

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Therapeutic approaches based on HER2 targeting are being tested in patients with NSCLC. Interim data of the phase II DESTINY-Lung01 trial of the antibody–drug conjugate trastuzumab deruxtecan revealed an ORR of 61.9% and grade ≥3 TRAEs in 52.4% of patients.

Trials of immune-checkpoint inhibitors were also discussed. The OS benefit of nivolumab plus ipilimumab (with or without chemotherapy) over chemotherapy in the metastatic setting was confirmed in CheckMate 227 and CheckMate 9LA. Results after 5 years of follow-up as well as those from biomarker analyses are eagerly awaited.

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