PROSTATE CANCER

^{68}Ga-PSMA-11 PET enables accurate detection of recurrent disease

Retrospective studies have shown that ^{68}Ga-labelled prostate-specific membrane antigen PET (^{68}Ga-PSMA-11 PET) imaging improves metastasis detection compared with conventional imaging (CT, MRI and bone scintigraphy) in biochemically recurrent prostate cancer. Findings from the first prospective trial in this setting have now been reported.

The single-arm multicentre trial enrolled 635 men with biochemically recurrent prostate cancer to undergo ^{68}Ga-PSMA-11 PET imaging. The final efficacy analysis included patients with adequate follow-up for lesion validation via histopathological analysis ($n = 93$) or a composite reference standard ($n = 223$; comprising conventional imaging and serum PSA follow-up).

The overall detection rate was 75%, and detection significantly increased with rising PSA, although PSA doubling time and nadir were not associated with detection rate. Both per-patient and per-region positive predictive values (PPVs) were 0.84 (95% CI 0.75–0.90 and 0.76–0.91, respectively) by histopathological validation (the primary end point) and 0.92 (both 95% CI 0.88–0.95) by composite validation. The per-patient and per-region sensitivity by histopathological validation was 0.92 (95% CI 0.84–0.96) and 0.9 (95% CI 0.82–0.95), respectively. Regarding secondary end points, inter-reader agreement was substantial across regions and no grade ≥2 adverse events occurred.

These data illustrate the promise of ^{68}Ga-PSMA-11 PET for localization of recurrent disease, and data from an ongoing study (NCT03515577) comparing ^{68}Ga-PSMA-11 PET with the FDA-approved ^{18}F-fluciclovine PET modality are eagerly awaited.

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ORIGINAL ARTICLE Fendler, W. P. et al. Assessment of ^{68}Ga-PSMA-11 PET accuracy in localizing recurrent prostate cancer: a prospective single-arm clinical trial. *JAMA Oncol.* https://doi.org/10.1001/jamaoncol.2019.0096 (2019)

IMMUNOTHERAPY

bTMB is a promising predictive biomarker

Tumour mutational burden (TMB) is a promising biomarker of a response to immune-checkpoint inhibitors, independent of programmed cell death 1 ligand 1 (PD-L1) status. TMB is usually measured in DNA from tumour tissue samples through whole-exome sequencing (WES) or sequencing of cancer gene panels (CGPs). New data support the use of plasma cell-free DNA to determine the blood TMB (bTMB) as a less invasive and more convenient alternative.

A novel CGP for TMB assessment was developed and validated virtually using The Cancer Genome Atlas WES data from 9,205 specimens of 33 different cancer types. This CGP panel, NCC-GP150, encompasses the entire exonic regions of 150 rationally selected genes and had a correlation with the WES data similar to that of established CGPs (such as MSK-IMPACT and F1CDx). When NCC-GP150 was applied to a published data set comprising 34 patients with non-small-cell lung cancer (NSCLC) treated with anti-programmed cell death 1 (PD-1) antibodies, a greater than median TMB was associated with better progression-free survival (PFS; HR 0.36, 95% CI 0.14–0.93; $P = 0.03$).

Assessment of matched tumour tissue and plasma samples from 48 patients with advanced-stage NSCLC using WES and NCC-GP150, respectively, resulted in a Spearman correlation coefficient between tissue TMB and bTMB of 0.62. At the median tissue TMB (75), the optimal bTMB threshold was ≥6, with a sensitivity and specificity of 0.88 and 0.71, respectively.

In an independent cohort of 50 patients with advanced-stage NSCLC treated with anti-PD-(L)1 antibodies, those with a bTMB ≥6 ($n = 28$) had superior objective response rates (39.3% versus 9.1%; $P = 0.02$) and PFS (HR 0.39; 95% CI 0.18–0.84; $P = 0.01$). These relationships held upon multivariate analysis. In keeping with previous evidence for tissue TMB, bTMB and PD-L1 status were not correlated.

These findings warrant testing of bTMB as a biomarker in prospective trials.

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ORIGINAL ARTICLE Wang, Z. et al. Assessment of blood tumor mutational burden as a potential biomarker for immunotherapy in patients with non-small cell lung cancer with use of a next-generation sequencing cancer gene panel. *JAMA Oncol.* https://doi.org/10.1001/jamaoncol.2018.7098 (2019)

LUNG CANCER

Pembrolizumab improves OS across PD-L1 subgroups

In 2016, KEYNOTE-024 established the superior efficacy of first-line pembrolizumab over chemotherapy for metastatic non-small-cell lung cancer (NSCLC) with a programmed cell death 1 ligand 1 (PD-L1) tumour proportion score (TPS) ≥50%. Now, overall survival (OS) data from the second interim analysis of KEYNOTE-042, which investigated the efficacy of pembrolizumab in patients with a lower PD-L1 TPS, have been reported.

The phase III trial enrolled 1,274 patients with previously untreated, PD-L1-positive (TPS ≥1%), locally advanced or metastatic NSCLC without a sensitizing *EGFR* or *ALK* alteration. Patients were randomized 1:1 to receive pembrolizumab or platinum-based chemotherapy. The primary end point was OS across three predefined subgroups (TPS ≥50%, ≥20% and ≥1%).

At a median follow-up duration of 12.8 months, OS was significantly longer in patients receiving pembrolizumab than in those receiving chemotherapy across all PD-L1 subgroups (TPS ≥50% HR 0.69, 95% CI 0.56–0.85, $P = 0.0003$; TPS ≥20% HR 0.77, 95% CI 0.64–0.92, $P = 0.0020$; TPS ≥1% HR 0.81, 95% CI 0.71–0.93, $P = 0.0018$). Median OS for pembrolizumab versus chemotherapy was 20.0 versus 12.2 months, 17.7 versus 13.0 months and 16.7 versus 12.1 months for the TPS ≥50%, ≥20% and ≥1% subgroups, respectively.

Any grade (63% versus 90%) and grade ≥3 (18% versus 42%) treatment-related adverse events (TRAEs) were lower with pembrolizumab. In each arm, TRAEs led to death in 2% and to treatment discontinuation in 9% of patients.

Overall, these findings have led the FDA to extend the indication for pembrolizumab to patients with a PD-L1 TPS as low as 1%.

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ORIGINAL ARTICLE Mok, T. S. K. et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. *Lancet.* https://doi.org/10.1016/S0140-6736(18)32409-7 (2019)