

Addition of nivolumab to chemotherapy in patients with advanced gastric cancer: a relevant step ahead, but still many questions to answer



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Among the most relevant highlights of the European Society of Medical Oncology (ESMO) 2020 virtual meeting were several important advances for the treatment of gastro-oesophageal cancers, which were presented and discussed at the third presidential session. Two phase III randomised trials studied the addition of Nivolumab to standard chemotherapy in patients with advanced gastro-oesophageal adenocarcinomas, including gastric, junctional and lower third oesophageal locations in the CheckMate649 trial¹ and only gastric and junctional locations for the ATTRACTION-4 study.² In both trials, at least one primary endpoint was met and therefore, we should consider them as positive studies. However, their practical consequences, implying modifications in clinical practice and adoption as standard of care require a careful analysis of all details in both studies.

Both studies share a similar design but they also differ in some relevant aspects. CheckMate649 is a global study which accrued patients from all over the world, while ATTRACTION-4 did only so in Japan, Korea and Taiwan. Both had similar stratification factors including tumour cell PD-L1 expression $\geq 1\%$ vs $\leq 1\%$ and compared the addition of Nivolumab to conventional platinum-based chemotherapy (CAPOX or FOLFOX for CheckMate649 and CAPOX or S1 plus oxaliplatin for ATTRACTION-4) with the same co-primary end points: centrally assessed progression-free survival (PFS) and overall survival (OS), although for a biomarker selected group only (PD-L1 Combined Positive Score (CPS) ≥ 5) in CheckMate-649). Nivolumab was able to increase response rate and PFS in both studies. However, OS was only significantly prolonged for patients allocated to the Nivolumab plus chemotherapy arm in CheckMate649. In CheckMate-649, median OS exceeded 12 months in the experimental arm for the first time in a global clinical trial for HER2 negative patients. After many years of clinical

research in advanced gastro-oesophageal adenocarcinomas, we cannot ignore this relevant step forward.

We may speculate on the potential reasons for the positive OS results in CheckMate-649 and the apparent discrepancy with ATTRACTION-4. Median survival in the Asian study was over 17 months in both arms of the trial and post-progression therapy was given to more than 66% of patients, while in CheckMate649, only 39% of progressing patients received further treatment, indicating the disparity between the use of second and further lines of treatment in Western and Asian countries. Also, a higher proportion (27%) of control arm patients in ATTRACTION-4 received post-trial immunotherapy. Second and further lines of therapy may increase survival on first progression, and it is possible but not confirmed that a more proactive treatment approach could balance the lack of use of nivolumab in first line. On the other hand, the phase III randomised KEYNOTE-062 failed to show superiority of the addition of Pembrolizumab, another checkpoint inhibitor, to chemotherapy versus chemotherapy alone in a similar subset of high PD-L1 CPS score patients.³ This makes CheckMate649 the only positive trial improving survival in this setting.

Another point for discussion is the use of biomarkers and their predictive potential in these trials. Two different drivers may facilitate antitumour response to checkpoints inhibitors: a high mutational burden with an increased number of different neoantigens, able to elicit a significant immune response against the tumour or, the presence of effector immune cells with potential to act and eventually kill the tumour.⁴ Both CheckMate649 and ATTRACTION-4 stratified patients according to tumour PD-L1 expression. However, the primary endpoint in CheckMate-649 is based on PD-L1 CPS which accounts for PD-L1 on tumour and tumour associated immune cells. In contrast, no distinction

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in endpoints according to biomarker assessment was made in ATTRACTION-4. In ATTRACTION-4, 84% of randomised patients were tumour PD-L1 <1% and only 16% were $\geq 1\%$ PD-L1, and tumour PD-L1 expression did not appear to significantly impact on the magnitude of PFS or OS benefit. The picture of PD-L1 expression according to CPS among CheckMate649 patients was very different. Of note, 60% of patients included in CheckMate649 were part of this primary target population (CPS ≥ 5) and only 18% were CPS<1%. Although CPS and tumour PD-L1 staining are different methods and cannot be compared, it could be the case that the Asian trial selected a population which was less sensitive to Nivolumab for the primary endpoint analysis CheckMate649. As we stated once for refractory patients, it looks like checkpoints inhibitors are not for all advanced gastro-oesophageal adenocarcinoma patients, and biomarker selection is required for patient benefit.⁵

However, before accepting Nivolumab added to chemotherapy as standard of care, many questions are emerging regarding the validation of CPS as a biomarker in advanced gastro-oesophageal adenocarcinomas. Why and how was the 5% cut-off was established to define the primary target population in CheckMate 649? If Nivolumab is approved for this specific indication in patients whose tumours bear a CPS $\geq 5\%$, how will quality control be implemented when pathologists across different institutions in general practice have to perform and interpret this test to guarantee the right patient selection? Will these results be applicable if a different PD-L1 immunohistochemistry assay is used? Should CPS be done in archival biopsies or in recent ones? Finally, are the results applicable when only small endoscopic samples are available?

Another way of assessing the potential impact in clinical practice of CheckMate649 is to apply the Magnitude of the Clinical Benefit Score (MCBS) developed by the ESMO.⁶ In table 1, a summary of the data needed to calculate the MCBS score in diseases with control arm survival of less than 12 months is demonstrated. As the follow-up in CheckMate649 is not yet mature, the maximum MCBS score cannot be

assigned as this requires an improvement in OS at 24 months. Acknowledging that these numbers could change with longer follow-up, we can use the inferior limit of the 95% CI for the OS HR, as well as the quantitative difference in months for median OS. Interestingly, this calculation demonstrates that the highest MCBS scores are associated with the CPS ≥ 5 population, with incrementally lower MCBS scores allocated to CPS ≥ 1 and all patient populations. We are curious of what could have happened to those patients with CPS lower than 5 and more than 1, which are in the middle, but this information has not been made available thus far.

In summary, the data presented from these two randomised trials at ESMO 2020 offer the tantalising possibility of adopting first line immunotherapy for patients with gastric and gastro-oesophageal adenocarcinoma; however, relevant questions regarding biomarker selection may need to be addressed before adopting this treatment as a standard of care.

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Table 1 Data to calculate ESMO MCBS in three different subsets of patients according to PD-L1 CPS in the CheckMate649 trial

Population selected according to CPS score (% patients)	Lower limit 95% Hazard Ratio for OS	Increased median OS in the experimental arm	ESMO MCBS
CPS $\geq 5\%$ (60%)	0.59	3.3 months	4
CPS $\geq 1\%$ (82%)	0.64	2.7 months	3
All patients (100%)	0.68	2.2 months	2

Data on proportions of patients alive at 24 months are not provided. ESMO MCBS are calculated for median OS of standard treatment below 12 months. See Ref. 5. CPS, Combined Positive Score; ESMO MCBS, European Society for Medical Oncology Magnitude of the Clinical Benefit Score; OS, overall survival.