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Immunotherapy in the treatment of advanced gastric cancer — more limitations than potential

It is obvious that the introduction of modern immunotherapy has significantly changed oncological practice. Despite the fact that immunotherapeutic drugs have become the standard care in several types of cancer, for most solid tumours the change is limited. In some cancers, such as pancreatic ductal adenocarcinoma, currently used immune checkpoint inhibitors (ICIs) have no activity. For other cancer types, such as colon cancer, the benefit of ICIs is limited to a particular, well defined sub-population (patients with microsatellite instability). A few cancer types, such as melanoma and lung cancer, are especially susceptible to ICIs, and here the immunotherapy is a real breakthrough. From this perspective, gastric cancer can be seen as a specific entity. The last decade brought limited improvement in gastric cancer treatment (limited mostly to the introduction of ramucirumab, a VEGF2 inhibitor, for second-line treatment and development of trifluridine/tipiracil combination as a salvage therapy). Simultaneously, despite promising results of phase I and II trials [1], which led to registration of pembrolizumab for the treatment of patients with advanced gastric cancer by the Food and Drug Administration (FDA), available phase III trial data are disappointing. On the one hand, it is clear that ICIs possess some activity in the treatment of gastric cancer (with 10–20% response rate achieved with ICIs monotherapy). On the other hand, there is only a single positive phase III trial, which assessed activity of nivolumab as a salvage treatment of gastric cancer in an Asian population. Two other phase III trials, which evaluated pembrolizumab and avelumab, are negative. The question regarding the role of ICIs in the treatment of gastric cancer remains open. Nevertheless, available phase III data will provide a base for further research, which justifies more detailed analysis.

The first of the aforementioned trials was published on 6th October 2017 by Kang et al. [2] in "The Lancet". ATTRACTION-2 was a randomised, double-blinded, phase III trial that compared nivolumab with placebo as a salvage treatment for patients with advanced gastric cancer. The trial included 493 patients from Japan, South Korea, and Taiwan, randomised in a 2:1 ratio to nivolumab or placebo, respectively. The primary end-point was overall survival (OS), and the secondary end-point was progression-free survival (PFS). Patients recruited to the trial had very good or good performance status (ECOG 0 or 1) and progressed after at least two lines of systemic treatment. After a median follow-up of 8.87 months in the nivolumab arm and 8.59 months in the placebo arm, the primary end-point was met. The achieved median OS was significantly longer in patients receiving nivolumab, reaching 5.26 months (95% confidence interval [CI] 4.60–6.37) compared to 4.14 months (95% CI 3.42–4.86) in patients receiving placebo. The hazard ratio (HR) for the OS difference was 0.63 (95% CI 0.51–0.78; $p < 0.0001$). The achieved effect was independent of the length of nivolumab treatment and remained significant in most of the analysed sub-groups. Additionally, the secondary end-point of PFS was also met, with median PFS of 1.61 in the nivolumab arm (95% CI 1.52–2.30) and 1.45 in the placebo arm (95% CI 1.45–1.54), which resulted in an HR of 0.60 (95% CI 0.49–0.75; $p < 0.0001$). The objective response rate was also in favour of nivolumab (11.2% *vs.* 0%). Rates of all adverse events (91% *vs.* 84%), all treatment-related adverse events (43% *vs.* 27%), grade 3 and 4 treatment-related adverse events (10% *vs.* 4%), serious adverse events (10% *vs.* 5%), and adverse events that led to death (2% *vs.* 1%) were numerically higher in the nivolumab arm compared to the placebo arm. The OS benefit associated with nivolumab was independent of programmed death-ligand 1 (PD-L1) expression, but these results were not available for all patients. The described trial led to the registration of nivolumab in the treatment of patients with advanced gastric cancer in several Asian countries (including Japan). Because pre-clinical data suggest that gastric cancer presents more immunogenicity in non-Asian patients, the trial raised high expectations for similar results in different populations.

The outcomes of the next study, KEYNOTE-061, were published on 4th June 2018 in "The Lancet" by Shitara et al. [3]. KEYNOTE-061 was a randomised, non-blinded, phase III trial that compared pembrolizumab with paclitaxel in the second-line treatment of advanced gastric cancer. The study included patients

after progression on platinum-based first-line treatment from both Asian and non-Asian countries. Patients were randomised in a 1:1 ratio to either pembrolizumab or paclitaxel, with primary end-points of OS and PFS assessed in patients with PD-L1 combined positive score (CPS) equal to or higher than 1. Altogether, 592 patients were recruited, from whom 395 had PD-L1 CPS equal to or higher than 1. After median follow-up of 8.5 months in the PD-L1 CPS-positive population, the study failed to meet its primary endpoints of both OS and PFS. Median OS in the pembrolizumab arm reached 9.1 months (95% CI 6.2–10.7) compared to 8.3 months (95% CI 7.6–9.0) in the paclitaxel arm, with HR equal to 0.82 (95% CI 0.66–1.03; one-sided p = 0.0421). OS results were consistent in all analysed sub-groups, with a more pronounced benefit from pembrolizumab seen in patients with very good performance status (ECOG 0) and in patients with primary tumour arising from the gastro-oesophageal junction (GEJ). Similarly to other trials comparing immunotherapy with chemotherapy, survival curves were better for chemotherapy during the first six months of the trial and then crossed favouring immunotherapy. This was confirmed by 12-month and 18-month survival rates (respectively, 40% and 26% in the pembrolizumab arm and 27% and 15% in the paclitaxel arm). In the subgroup of patients with PD--L1 CPS lower than 1 OS was 4.8 months (95% 3.9–6.1) in the pembrolizumab arm and 8.2 months (95% CI 6.8–10.6) in the paclitaxel arm (HR 1.20; 95% CI 0.89–1.63). Median PFS in the CPS-positive population was 1.5 months (95% CI 1.4–2.0) in patients receiving pembrolizumab and 4.1 months (95% CI 3.1–4.2) in patients receiving paclitaxel, with HR of 1.27 (95% CI 1.03–1.57). Similarly as with OS, patients with PD-L1 CPS lower than 1 receiving pembrolizumab had worse PFS than patients receiving paclitaxel (HR 2.05; 95% CI 1.50–2.79). Response rates achieved in patients with PD-L1 CPS equal to or higher than 1 were similar in both arms (16% in the pembrolizumab arm *vs*. 14% in the paclitaxel arm). In post-hoc analysis of patients with microsatellite instable tumours, pembrolizumab was associated with significantly higher response rate (47% *vs.* 17%), noticing low numbers of such patients. The rate of treatment-related adverse events was 53% among patients receiving pembrolizumab and 84% in patients receiving chemotherapy, with grade 3–5 adverse events rates of, respectively, 14% and 35%. The rate of adverse events that led to treatment discontinuation was 3% in the pembrolizumab arm and 5% in paclitaxel arm. Treatment-related deaths occurred in three patients (1%) in the pembrolizumab arm and in one patient (< 1%) in the paclitaxel arm. About 10% of patients in the paclitaxel arm received ICIs in subsequent treatment lines. Unfortunately, the published results did not include a quality-of-life comparison between arms. It more than obvious that the results of the KEYNOTE-061 trial were, and still are, a considerable disappointment for immunotherapy enthusiasts. Despite the limitation of primary end-point analysis to the subgroup of patients with higher probability of response to immunotherapy, pembrolizumab was not superior when compared with paclitaxel as a second-line treatment for advanced gastric cancer. At the same time, available data from the population with low PD-L1 CPS, albeit numerically limited, suggests superior results achieved with standard chemotherapy in this subgroup. This result strongly suggests that proper selection of patients will be crucial for ICI success in the treatment of gastric cancer.

Data from the last of the mentioned trials were published on 24th July 2018 by Bang et al. [4] in "Annals of Oncology". JAVELIN Gastric 300 was a randomised, open-label phase III trial that compared avelumab with the investigators' choice of chemotherapy (either irinotecan or paclitaxel in monotherapy) or best supportive care (BSC) in the third-line treatment of advanced gastric cancer. The trial included 371 patients, randomised in a 1:1 ratio to both arms, with a primary end-point of OS. In the control arm, only three patients (1.6%) received BSC instead of chemotherapy. PD-L1 expression, defined as the presence of immunohistochemical staining on at least 1% of cancer cells, was present in 29.3% of patients in the avelumab arm and 24.4% of patients in the chemotherapy arm. After a median follow-up of 10.6 months, the study failed to meet its primary end-point. Median OS was 4.6 months (95% CI 3.6–5.7) in the avelumab arm and 5.0 months (95% CI 4.5–6.3) in the chemotherapy arm, with an HR of 1.1 (95% CI 0.9–1.4; p = 0.81). The lack of difference in OS was consistent in all analysed subgroups. No difference was seen between patients assigned to paclitaxel and irinotecan. Median PFS was 1.4 months (95% CI 1.4–1.5) in patients receiving avelumab and 2.7 months (95% CI 1.8–2.8) in patients receiving chemotherapy (HR 1.73; 95% CI 1.4–2.2; p > 0.99), with results in favour of chemotherapy in all analysed subgroups. The achieved response rate was low in both arms, with only 2.2% response rate in the avelumab arm and 4.3% response rate in the chemotherapy arm. Treatment-related adverse events occurred — 48.9% of patients receiving avelumab and 74% of patients receiving chemotherapy, with grade 3 and higher in, respectively, 9.2% and 31.6% of patients. Only seven patients (3.8%) in the avelumab arm and nine patients (5.1%) discontinued the treatment due to adverse events. No deaths due to adverse events were noted in the avelumab arm. However, a significant difference in the rate of infusion-related adverse events was seen — 21.2% in the avelumab arm and only 2.8% in the chemotherapy arm. Subsequent treatment with immunotherapy was reported in two patients (1%) receiving avelumab and eight patients

(4.3%) receiving chemotherapy. Results of JAVELIN Gastric 300 trials was, just as results of KEYNOTE-061, a disappointment. Avelumab activity in the third-line treatment of gastric cancer was marginal, and clinical outcomes were numerically inferior to conventional chemotherapy. Therefore, despite a favourable toxicity profile, it is difficult to recognise avelumab as a valuable treatment option.

The results of the three described phase III trials define the current role of immunotherapy in the clinical management of advanced gastric cancer. The ATTRACTION-2 trial confirms the benefit from nivolumab as a salvage treatment after failure of standard chemotherapy in an Asian population. However, considering the difference in tumour biology and drug metabolism in other populations, these results cannot be extrapolated to non-Asians. For European and North American patients, pembrolizumab might be more appropriate option, as approved by the FDA in September 2017. Nevertheless, it should be stressed that pembrolizumab cannot be considered as the standard of care in second and subsequent lines of treatment, but only as a potential option for selected patients (with PD-L1 CPS equal to or higher than 1). This is probably one of the reasons why the European Medicines Agency (EMA) have not yet registered pembrolizumab in this indication. As evidence of nivolumab activity cannot be translated to the European population, with limited benefit of pembrolizumab and marginal activity of avelumab, it seems that the concept of ICI monotherapy for advanced gastric cancer has failed. Despite promising ICI activity, monotherapy is not enough to induce significant clinical benefit. ICIs are currently under intensive evaluation, mostly in early treatment lines and in combinations. Combining ICIs with chemotherapy can prevent early treatment failure, allowing the patient to achieve long-term benefit from immunotherapy. Unfortunately, the question of whether this assumption is correct or not will remain unanswered for many months or years.

Adjuvant treatment for biliary tract and gallbladder cancers — one vote "yes", one vote "no"

Biliary tract cancers are relatively uncommon and responsible for only one per cent of all cancer cases. It is quite a heterogenic group, which includes typical biliary tract cancers (intrahepatic and extrahepatic cholangiocarcinoma and sometimes separated subtypes of perihilar and distal common bile duct cancers) and, traditionally included in this group, gallbladder cancer. Despite the anatomical proximity of all these cancers, they form few completely separate molecular subtypes, which impedes conduction of clinical trials. Unfortunately, most cases are inoperable at the point of diagnosis, with only 20% of cases amendable with surgery. Even with optimal surgical treatment, the prognosis remains poor, with five-year survival rates lower than 15%. As a result of lack of good quality data regarding adjuvant chemotherapy, many patients receive adjuvant treatment based on fluoropyrimidine compounds or gemcitabine. This may change because last year brought early results from randomised phase III trials that compared adjuvant chemotherapy with observation. Strikingly, the available results lead to completely different conclusions.

The most mature data came from PRODIGE 12-ACCORD 18-UNICANCER GI trial and were published in the Journal of Clinical Oncology on 1st February 2019 by Edeline et al. [5]. The ACCORD study was a randomised, non-blinded, phase III trial that compared six months of chemotherapy (gemcitabine and oxaliplatin) with sole observation. GEMOX chemotherapy consisted of gemcitabine administered at a dose of 1000 mg/m^2 on day 1 of each cycle and oxaliplatin at a dose of 85 mg/m^2 on day 2 of each cycle, with cycles repeated biweekly. Patients were recruited within three months after both microscopically radical (R0) and non-radical (R1) procedures. The primary end-point was relapse-free survival (RFS) and time to definitive deterioration (TDD) of health-related quality of life. OS was one of the secondary end-points. The trial included 196 patients, randomised in 1:1 ratio to both arms. After a median follow-up of 46.5 months, the study failed to meet its primary endpoints. Median RFS was 30.4 months (95% CI 15.4–43.0) in the GEMOX arm and 18.5 months (95% CI 12.6–38.2) in the observation arm, which resulted in an HR of 0.88 (95% CI 0.62–1.25; p = 0.48). The rate of distant relapses were similar in both arms (75% in the GEMOX group and 71% in the observation group). There was no significant difference in TDD of health-related quality of life (log-rank p = 0.39) or in OS (median OS was 75.8 months [95% CI 34.4 to not reached] in the GEMOX arm *vs.* 50.8 months [95% CI 38.0 to not reached] in the observation arm, with an HR of 1.08 (95% CI 0.70–1.66; p = 0.74)). Any analysed subgroup derived benefit from chemotherapy, with significantly better results with observation in patients with gallbladder cancer. Safety analysis showed significantly higher risk of adverse events in the chemotherapy arm (p < 0.001 for grade 3 and 4 adverse events), but no difference in mortality within the first six months was seen (three deaths in the GEMOX arm *vs.* two deaths in the observation arm).

Initial analysis of the BILCAP trial, available only as an abstract from 2017 Congress of American Society of Clinical Oncology published by Primrose et al. [6], can lead to different conclusions. The trial included 447 patients after R0 and R1 resection of biliary tract and gallbladder cancers, randomised in a 1:1 ratio to either six months of capecitabine (eight cycles of capecitabine 1250 mg/m^2 twice per day for 14 days of each 21-day cycle) or sole observation. Primary end-point was overall survival (OS). Initial results of intention-to-treat analysis failed to meet the primary end-point, with median OS in the capecitabine arm of 51 months (95% CI 35–59) compared to 36 months (95% CI 30–45) in the observation arm (HR 0.80; 95% CI 0.63–1.04; p = 0.097). However, per-protocol analysis showed statistically significant benefit from adjuvant chemotherapy (median OS 53 months in the capecitabine arm [95% CI 40 to not reached] *vs.* 36 months in the observation arm [95% CI 30–44], with HR of 0.75 [95% CI 0.58–0.97; p = 0.028]). Full results have not yet been published due to data immaturity.

Currently, we dispose one full report of the negative ACCORD trial and one primary report of the positive BILCAP trial. Strictly according to evidence-based medicine (EBM) methodology, we should recognise that no adjuvant chemotherapy should be used in biliary tract and gallbladder cancers until full data from the BILCAP trial are published. Simultaneously, from a purely practical perspective, it is difficult to resign from adjuvant treatment in all patients, considering their poor prognosis. The more contradictory the evidence, the more important is honest discussion with the patient – understandable description of treatment options, limited evidence in favour of chemotherapy and unfavourable prognosis. Patients' preferences are an additional, case-specific factor that can support or dismiss the idea of adjuvant chemotherapy and support decision-making.

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