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Durvalumab as a maintenance therapy after a definitive chemoradiotherapy for a stage III non-small cell lung cancer — an interim analysis of the PACIFIC trial

The introduction of checkpoint inhibitor-based immunotherapy changed the therapeutic landscape for several types of solid cancers, including non-small cell lung cancer (NSCLC). The benefit from immunotherapy includes not only an improvement of overall survival in a metastatic setting, but also when applied as an adjuvant treatment. Initially, this was seen with ipilimumab after a resection of melanoma, but currently more evidence support the role of other checkpoint inhibitors in this setting. As for NSCLC, checkpoint inhibitors proved their role in the first-line treatment of a specific patient subgroup (this includes both monotherapy and combination with chemotherapy) and, as the standard-of-care, in the second-line treatment after failure of platinum-based chemotherapy. Furthermore, novel data regarding durvalumab as a maintenance therapy after chemoradiotherapy of stage III NSCLC support the growing role of the immunotherapy in an earlier settings than previously recognised.

On 8th September 2017 Antonia et al. [1] published in the "New England Journal of Medicine" the initial results from the PACIFIC trial. This phase III, randomised, placebo-controlled trial evaluated durvalumab, a monoclonal antibody aimed at PD-L1, as a maintenance therapy after a definitive chemoradiotherapy for stage III NSCLC not eligible for a radical resection. The chemoradiotherapy consisted of at least two cycles of platinum-based chemotherapy (as per local standards), concurrently with a radical radiation therapy of 54 to 66 Gy. Within 1 to 42 days after completing chemoradiotherapy, a total of 709 patients were randomised in a 2:1 ratio to either 10 mg per kilogram of durvalumab every two weeks for 12 months or a placebo in the same schedule. The study design included two co-primary endpoints: progression-free survival and overall survival. At the interim analysis performed after a median follow-up of 14.5 months, the study met one of the primary end-points — median progression-free survival reached 16.8 months [95% confidence interval (CI) 13.0–18.1] in durvalumab group *vs.* 5.6 months (95% CI 4.6–7.8) in placebo group, with a stratified hazard ratio (HR) for disease progression or death of 0.52 (95% CI 0.42–0.65; two-sided $p < 0.001$). Additionally, durvalumab improved also both the 12-month progression-free survival (55.9% in the durvalumab arm versus 35.3% in the placebo arm) and the 18-month progression-free survival (44.2% in the durvalumab arm *vs.* 27.0% in the placebo arm). The benefit in progression-free survival associated with durvalumab remained consistent in all subgroups analysed and was present irrespectively of the PD-L1 expression and the smoking status. Because overall survival analysis was not pre-planned into this interim analysis, no relevant conclusions regarding overall survival can be made. A secondary end-point of median time to death or distant metastasis was also improved in patients receiving durvalumab [23.2 months (95% CI 23.2 to not reached) *vs.* 14.6 months (95% CI 10.6–18.6), with HR 0.52 (95% CI 0.39–0.69; $p < 0.001$)]. Additionally, durvalumab treatment resulted in the lower rates of distant metastases (20.4% and 32.1% for, respectively, durvalumab group and placebo group) and specifically brain metastases (5.5% and 11.0%, respectively). The rates of all adverse events and grade 3 or 4 adverse events were similar between both arms, with slightly higher rates of pneumonitis and radiation pneumonitis in patients receiving durvalumab. Discontinuation due to adverse events occurred more frequently in the durvalumab group compared to the placebo group, but no difference in adverse events leading to death between both arms was seen.

The presented study brings a major change to the standard-of-care in unresectable stage III NSCLC. Despite the lack of evidence for a positive effect on overall survival, the significant improvement in progression-free survival justifies wide application of durvalumab as a maintenance therapy after finishing concurrent radiochemotherapy. Of the uttermost interest, immune checkpoint inhibitor treatment results in only a minor rise in adverse events, which were generally manageable. As with the other potential applications of immune checkpoint inhibitors, major concerns arise over the costs of the treatment, with the financial burden of novel immunotherapeutic agents having a great impact on healthcare systems, even in the well-developed countries.

The open role of chemotherapy and targeted therapy combination in platinum-refractory urothelial carcinoma — a primary analysis of the RANGE trial

Despite the revolution in second-line treatment of urothelial carcinoma that came with the introduction of a modern immuno-oncology, the prognosis for the most patients remains poor. The benefit from novel checkpoint inhibitors is mostly limited to the responding patients, who unfortunately represent only about 10–20% of the population. Alternatives, usually a single-agent chemotherapy, have limited activity and further advancements are required. The available results from trials evaluating targeted therapies in the treatment of urothelial carcinoma are mostly disappointing, with little to no benefit. However, recent results from the RANGE trial open the field for a new possibility — a combination of docetaxel and ramucirumab, a monoclonal antibody targeting VEGFR-2.

In "The Lancet" from 18th November 2017, Petrylak et al. [2] published results from a randomised, double-blind, phase III RANGE trial that compared docetaxel with ramucirumab or placebo in the patients with a platinum-refractory urothelial carcinoma. The patients were required to progress during or within 14 months after completion of a platinum-based chemotherapy. Additionally, patients were permitted to receive prior a checkpoint inhibitor therapy if they progressed within 24 months of preliminary platinum-based treatment. Docetaxel was administered in a standard dose of 75 mg/kg (60 mg/kg in the Asian population) given every 3 weeks with the addition of 10 mg/kg ramucirumab or placebo. The primary endpoint was an investigator-assessed progression-free survival, with an overall survival as a secondary endpoint not included in the primary analysis. The study involved 530 patients in the intention-to-treat (ITT) population, randomised in a 1:1 ratio to either ramucirumab or placebo. After the median follow-up time of 5.0 months [interquartile range (IQR) 2.3–8.9], the study met its primary endpoint with median progression-free survival of 4.07 months [95% CI 2.96–4.47) in the ramucirumab arm *vs.* 2.76 (95% CI 2.60–2.96) in the placebo arm, with a stratified hazard ratio (HR) of 0.757 (95% CI 0.607–0.943; p = 0.0118). Similar results were obtained in a blinded, independent, central analysis [4.04 months for ramucirumab *vs.* 2.46 months for placebo; HR 0.672 (95% CI 0.536–0.842; p = 0.0005)]. The objective responses in the ramucirumab arm were reported in 24.5% (95% CI 18.8–30.3) and 22.2% (95% CI 16.7–27.8) of patients by, respectively, the investigators and the blinded, independent, central analysis. In the placebo arm the objective responses were reported, respectively, in 14.0% (95% CI 9.4–18.6) and 12.7% (95% CI 8.3–17.1) of patients. Of the 14 patients with a prior immune checkpoint inhibitor exposure in the ramucirumab arm, five responded to the treatment (36%). The median duration of response was numerically longer in the patients receiving ramucirumab than placebo (5.65 months *vs.* 4.17 months). The results of a quality of life assessment were similar between both arms, without a difference in time to sustained deterioration (non-stratified HR 0.931; 95% CI 0.701–1.235; p = 0.61). No significant difference was seen between the ramucirumab and placebo group in the rates of grade 3 or worse adverse events. Ramucirumab treatment resulted in a minor increase of grade 1–2 epistaxis (14% *vs.* 5%), hypertension (11% *vs.* 5%), haematuria (10% *vs.* 6%), and proteinuria (9% *vs.* 3%). Serious adverse events related to the study treatment occurred in the 24% of patients receiving ramucirumab and in the 20% of patients receiving placebo. However, adverse events leading to treatment discontinuation were reported more often in the ramucirumab than in the placebo arm (15% *vs.* 7%). Due to the immaturity of the data and the nature of primary analysis, the overall survival has not yet been assessed.

The results from the RANGE trial were published at an unfortunate moment. If published over two years ago, they could have been considered ground-breaking. Now, due to the introduction of immune checkpoint inhibitor, they can be considered only interesting and somehow vague. Because only a small proportion of patients in the RANGE trial received prior PD-1/PD-L1 inhibitor, it is difficult to fully evaluate the potential of docetaxel and ramucirumab combination as a salvage therapy after an immune checkpoint inhibitor failure. The presented analysis of the RANGE trial, without results regarding the overall survival, cannot support ramucirumab and docetaxel as an alternative to the standard-of-care in the second-line setting — pembrolizumab [3]. Nevertheless, the combination of ramucirumab and docetaxel adds a new quality to the armamentarium of urothelial carcinoma treatment and should be preferred over classic single-agent salvage chemotherapy. Further results, such as the overall survival data from the RANGE trial, should shed more light on the role of ramucirumab in the treatment of urothelial carcinoma. Additionally, a strong rationale behind the combination of immunotherapeutic agents with VEGFR inhibition brings hope for a new quality in the area.

Sometimes less is more — the detrimental effects of continuing gefitinib with a chemotherapy after a progression on first-line gefitinib monotherapy

The introduction of tyrosine kinase inhibitors (TKIs) in the treatment of EGFR-mutated advanced non-small-cell lung carcinoma (NSCLC) provided a tremendous benefit in the terms of progression-free survival and overall survival, with an acceptable toxicity profile. Nevertheless, the responses seen with TKIs are usually temporary, and most of the patients inevitably progress. The development of third-generation EGFR inhibitors established a new standard of care in the presence of T790M mutation in the EGFR gene because osimertinib exhibited astonishing activity in this setting [4]. The question of whether a continuation of first-generation TKIs beyond progression provide an additional benefit, was evaluated in the IMPRESS trial, the final results of which were published recently.

The results were published by Mok et al. [5] in the „Journal of Clinical Oncology" on 20th December 2017. The IMPRESS trial was a randomised, phase III trial, which compared gefitinib 250 mg with a placebo in the patients with EGFR-mutant NSCLC receiving platinum-doublet after a progression on first-line TKIs. EGFR status was confirmed by a plasma-derived circulating tumour DNA test. The chemotherapy consisted of cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2 given intravenously every three weeks. The trial recruited 265 patients, randomised in a 1:1 ratio to either gefitinib or placebo, with a progression-free survival as a primary end-point and an overall survival as a secondary end-point. The primary end-point was not met, with the median progression-free survival of 5.4 months in both arms (HR 0.86; 95% CI 0.65–1.13; p = 0.27), as reported previously [6]. The recent report regarding the secondary-end point provided a surprising result: gefitinib continuation was associated with a significantly worse survival (median overall survival 13.4 *vs.* 19.5 months in the gefitinib and placebo arm, respectively, with HR 1.44; 95% CI 1.07–1.94; p = 0.016). The effect was consistent in all patient subgroups. The negative effect of gefitinib on overall survival was most pronounced in the T790M mutation-positive group (HR 1.49; 95% CI 1.02–2.21; p = 0.0432), with the detrimental effect not reaching a statistical significance in the T790M mutation-negative subgroup (HR 1.15; 95% CI 0.68–1.94; p = 0.6093). A trend toward improved progression-free survival was seen with gefitinib in patients without T790M mutation, without reaching a statistical significance (6.7 months with gefitinib *vs.* 5.4 months with placebo, with HR 0.67; 95% CI 0.43–1.03; p = 0.0745).

The IMPRESS trial, despite being a negative study, provided valuable insights into the biological mechanism behind an acquired resistance to EGFR inhibitors. Clearly worse results in an overall survival achieved with gefitinib continuation beyond primary progression debunked the idea of a constant EGFR inhibition as a necessity in the treatment of patients with EGFR-mutated NSCLC. Additionally, because the presented results strongly correlate the detrimental effect of continuous gefitinib exposure with the presence of the T790M mutation, it may seem that gefitinib endorses alternative signalling pathways related to the T790M mutation, which results in promotion of cancer cell proliferation and survival. Fortunately, we currently dispose osimertinib, which effectively inhibits the T790M mutation and should be considered the standard of care in NSCLC patients with T790M mutated EGFR gene.

Expanding armamentarium in the treatment of hepatocellular carcinoma — selective internal radiotherapy (SIRT) in patients not eligible for a curative therapy

Intermediate- and advanced-stage hepatocellular carcinoma (HCC) is usually associated with a poor prognosis. Despite the fact that transarterial chemoembolisation (TACE) provides a chance for cure in an intermediate-stage disease, most of the patients benefit only temporarily. Introduction of sorafenib, a tyrosine kinase inhibitor aimed primarily at VEGFR, PDGFR, and Raf family kinases, resulted in an improvement of prognosis in advanced-stage hepatocellular and is currently considered the standard-of-care in this setting, regardless of several novel competitors such as lenvatinib [7]. The progress in the treatment of HCC is slow and additional treatment modalities are desired. From this perspective, novel data comparing sorafenib *vs.* selective internal radiotherapy (SIRT) are very appealing.

In the December 2017 issue of "The Lancet Oncology", Vilgrain et al. [8] published the results of SARAH study — an open label, randomised, phase III trial comparing sorafenib with SIRT in patients with an intermediate-stage refractory to TACE or with a primarily advanced-stage HCC, without evidence of a distant metastases. The trial compared standard dose

of sorafenib (800 mg daily in two equal doses) with a two-step SIRT procedure involving an arterial administration of ^{90}Y-loades microspheres. The primary endpoint was overall survival, with several secondary endpoints including progression-free survival and times to progression within and outside of the liver. The study recruited 467 patients, randomised in a 1:1 ratio to both arms. In the SIRT arm, about 22% of patients did not receive the planned procedure, mostly due to an anatomical unsuitability, and about 37% of patients required more than one SIRT procedure. Median overall survival in the intention-to-treat analysis reached 8.0 months (95% CI 6.7–9.9) in the SIRT arm and 9.9 months (95% CI 8.7–11.4) in the sorafenib arm, which resulted in a hazard ratio (HR) of 1.15 (95% CI 0.94–1.41; p = 0.18). In the per-protocol analysis the median overall survival was similar in both arms (9.9 months in the SIRT group *vs.* 9.9 months in the sorafenib group; HR 0.99, 95% CI 0.79–1.24). The results were consistent among all analysed subgroups, both in the intention-to-treat and the per-protocol populations. Median progression-free survival was also similar between both arms in the intention-to-treat population, with 4.1 months (95% CI 3.8–4.6) in the SIRT arm and 3.7 months (95% CI 3.3–5.4) in the sorafenib arm (HR 1.03; 95% CI 0.85–1.25; p = 0.76). Additionally, SIRT therapy was associated with a lower cumulative incidence of progression within the liver as the first event (p = 0.0143) and a higher cumulative incidence of progression outside the liver as a first event (p = 0.0265). In the safety analysis, fewer treatment-related adverse events were described in the SIRT arm (all grade 77% in the SIRT arm *vs.* 94% in the sorafenib arm; grade 3 and worse 41% *vs.* 63%, respectively). However, the number of treatment-associated deaths was numerically higher in the SIRT than in the sorafenib arm (19 cases *vs.* 12 cases, respectively). The global health status subscore assessed in a quality-of-life analysis was significantly favourable in patients receiving SIRT (group effect p = 0.0048).

As a results of the SARAH trial, SIRT may be considered as a possible alternative to sorafenib in patients with HCC limited to the liver and not amendable to a curative approach or with a progression after TACE. Similar results obtained within Asian and Pacific patients additionally support the role of SIRT in the treatment of advanced HCC [9]. Unfortunately, SIRT is a complicated and expensive procedure, which requires vast experience and, at least initially, a regular supervision by an independent specialist. The need for this monitoring can be seen within the SARAH data — generally SIRT was associated with a lower rates of grade 3 and worse treatment-related adverse events, but the number of fatalities attributed to SIRT was substantially higher than the number attributed to sorafenib. Nevertheless, SIRT brings a valuable addition to HCC armamentarium and will hopefully contribute to a slow but steady increase in HCC treatment efficacy.

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