VIA MEDICA
CURRENT LITERATURE REVIEW

Maciej Kawecki

Department of Oncology and Radiotherapy, Maria Sklodowska-Curie Institute of Oncology, Warsaw

One more point for immunotherapy — a combination of atezolizumab and chemotherapy in the treatment of small-cell lung cancer

The therapeutic approach towards extensive-stage small-cell lung cancer (SCLC) has remained unchanged for the last 20 years. Benefit from the standard systemic treatment (platinum-based chemotherapy doublet) is limited despite high response rates. Numerous attempts of expanding treatment with the addition of other agents have failed to improve the outcomes. As novel immunotherapeutic drugs revolutionised treatment standards in several types of cancer, attempts were made to introduce this modality into the treatment of SCLC. Unfortunately, the results obtained from trials evaluating the combination of standard chemotherapy with CTLA-4 inhibitors and pembrolizumab maintenance after chemotherapy induction were negative. It is more than disappointing considering the high tumour mutational burden (TMB) often present in SCLC, which is proposed as a predictive marker for checkpoint inhibitors. Fortunately, recent data have proven that a PD-L1 inhibitor, atezolizumab, improves overall survival when combined with chemotherapy in the first-line treatment of extensive-stage SCLC.

Horn et al. [1] published the results of the IMpower 133 trial in the "New England Journal of Medicine" on 25th September 2018. The trial compared the combination of atezolizumab and chemotherapy (consisting of carboplatin AUC 5 on day 1 and etoposide 100 mg/m^2 given on days 1–3 of every 21-day cycle) with the same chemotherapy regimen plus placebo in patients with histologically or cytologically confirmed extensive-stage SCLC. After finishing four cycles of induction therapy, patients in both arms continued treatment with atezolizumab or placebo as a maintenance. No crossover after progression on placebo was planned. The primary endpoints were overall survival and investigator-assessed progression-free survival (PFS). The key secondary endpoints included response rate and duration of response. The trial enrolled 403 patients, randomised in a 1:1 ratio to both arms. After a median follow-up time of 13.9 months, the trial met its primary endpoint: median overall survival reached 12.3 months (95% confidence interval [CI] 10.8–15.9) in the patients receiving atezolizumab and 10.3 months (95% CI 9.3–11.3) in the patients receiving placebo, which resulted in the hazard ratio (HR) for death of 0.70 (95% CI 0.54–0.91; p = 0.007). The one-year overall survival was 51.7% in the atezolizumab arm and 38.2% in the placebo arm. Investigator-assessed PFS was also better in the experimental group: 5.2 months (95% CI 4.4–5.6) *versus* 4.3 months (95% CI 4.2–4.5) (HR of 0.77; 95% CI 0.62–0.96; p = 0.02). The achieved results were consistent among all analysed subgroups, but with a lower benefit from the addition of atezolizumab in patients with brain metastases and those below 65 years old. In contrast to previously available data, atezolizumab improved survival regardless of TMB status, without additional benefit in patients with the highest TMB. Responses were similar between both arm in terms of CR, PR, and SD, with a numerically higher rate of PD as the best response in patients receiving atezolizumab. Despite the prolongation of OS, median duration of response was similar in the experimental and control arms (4.2 and 3.9 months, respectively). Rates of adverse events were comparable between both groups, with identical rates of treatment-related deaths (1.5% in both arms). Immune-related adverse events occurred in 39.9% of patients in the atezolizumab arm and 24.5% in the placebo arm. Similar rates of patients in both groups received prophylaxis cranial irradiation after the induction part of the treatment.

The results of the IMpower 133 trial support new indications for immunotherapy — first-line treatment of extensive-stage SCLC. It is the first improvement in the field of SCLC within the last 20 years and has the potential to impact daily practice, especially in well-developed countries. However, the gain obtained with atezolizumab is only modest and cannot be considered a true breakthrough from a clinical point of view. The described data generate several issues, including questions about the role of tumour mutational burden in SCLC, regarding differences in the benefit from immunotherapy in different age groups and limited effectiveness in patients with brain metastases. As the rate of PD as the best response was numerically higher with the combination of atezolizumab and chemotherapy, it might be hypothesised that a subgroup of patients in the experimental arm were harmed by hyperprogression,

Oncology in Clinical Practice 2018, Vol. 14, No. 5: 290–294. DOI: 10.5603/OCP.2018.0038, copyright © 2018 Via Medica, ISSN 2450–1654

a phenomenon related to immune checkpoint therapy. Nevertheless, IMpower 133 is proof of the concept that patients with SCLC derive benefit from immunotherapy. Further research is undoubtedly needed, especially in the search for potential biomarkers that could improve patient selection, because combinational chemoimmunotherapy will generate a significant financial burden. The extension of overall survival, albeit limited, is the first improvement in SCLC in decades and brings expectations for further, hopefully more profound, progress.

Expanding armamentarium for systemic treatment of hepatocellular carcinoma beyond first line

Hepatocellular carcinoma (HCC) emerges as an important oncological challenge, mostly due to its rising incidence, even in Western countries. Localised HCC is best treated with either surgery or locoregional treatment modalities with curative intent. In the case of HCC refractory to locoregional therapy or in the case of metastatic disease, systemic treatment remains the basic modality. Classically, HCC was considered a chemotherapy-resistant tumour, with a limited activity of cytotoxic drugs such as doxorubicin. Advancements in understanding the molecular background of HCC, especially the role of vascular endothelial growth factor in tumour angiogenesis, led to the introduction of targeted therapies. This includes the first VEGF tyrosine kinase inhibitor (TKI) registered for advanced HCC: sorafenib. However, the benefit from TKI is limited only to a subset of patients with HCC and is temporary, with an almost inevitable development of secondary resistance. This need led to a vast search for agents active in second and latter lines of systemic treatment, with immunomodulating drugs and novel TKI being the most promising options. Cabozantinib, a representative of a novel generation of TKIs, inhibits not only kinases associated with VEGF, but also kinases associated with AXL and MET, which are responsible for a TKI resistance in pre-clinical models. Recently, several new systemic therapies for HCC became available, with the latest addition of cabozantinib in the second line.

The data from a phase 3 randomised trial evaluating activity of cabozantinib in previously treated patients with hepatocellular carcinoma were published on 5th July 2018 in the "New England Journal of Medicine" by Abou-Alfa et al. [2]. The trial included patients with a prior exposure to sorafenib, who received no more than two lines of systemic therapy and had Child-Pugh class A liver function. Patients were randomised in a 2:1 ratio to either cabozantinib at a dose of 60 mg daily orally or matched placebo. The primary endpoint was overall survival, with the secondary endpoints of progression-free survival and objective response rate. The trial included 773 patients, 707 of whom constituted the intention-to-treat population evaluated in the aforementioned article. The primary endpoint was met, with a median OS of 10.2 months (95% CI 9.1–12.0) in the cabozantinib arm and 8.0 months (95% CI 6.8–9.4) in the placebo arm, with an HR of 0.76 (95% CI 0.63–0.92; p = 0.005). The median PFS was also significantly longer in patients receiving cabozantinib (5.2 months; 95% CI 4.0–5.5) compared to patients receiving placebo (1.9 months; 95% CI 1.9–1.9), with an HR of 0.44 (95% CI 0.36–0.52; p < 0.001). Objective response rate and disease control rate were also higher in the cabozantinib arm. Improvement in PFS was consistent in all analysed subgroups, but the benefit in OS seemed to be limited in patients from the Asian region, without extrahepatic metastases, and in those with HCV as an aetiological factor of HCC. On the other hand, patients treated previously with only sorafenib had better numerical benefit from cabozantinib (median OS 11.3 *vs*. 7.2 months, with HR 0.70; 95% CI 0.55–0.88). In safety analysis, patients receiving cabozantinib had higher rates of any grade adverse events (99% *vs*. 92%), grade 3 and 4 events (68% *vs.* 36%) and serious adverse events (50% *vs*. 37%). The most common grade 3 and 4 toxicities associated with cabozantinib were palmar-plantar erythrodysesthesia, hypertension, increased aspartate aminotransferase levels, fatigue, and diarrhoea, a profile similar to previously described in patients treated with cabozantinib. Adverse events leading death occurred in six patients receiving cabozantinib and in one patient receiving placebo. Results of quality-of-life evaluation were not reported in the article.

The presented results establish cabozantinib, along with regorafenib, as a standard of care in sorafenib-resistant HCC. An immune checkpoint inhibitor, nivolumab, was registered in this setting by the Food and Drug Administration (FDA) based on a phase 1/2 trial, in contrast to the phase 3 trials of cabozantinib and regorafenib, and therefore should be considered only as an option. Within a few years, the armamentarium for treatment of HCC expanded significantly. First-line treatment now includes lenvatinib, a novel TKI inhibitor that proved non-inferior to sorafenib. Additionally, in HCC non-amendable for curative local treatment radioembolisation offered only marginally worse results than sorafenib. Second-line treatment, previously non-existent or limited to cytotoxic chemotherapy, was improved by the addition of regorafenib, cabozantinib, and nivolumab. We await results from late-phase trials of immunotherapy, both in the salvage setting and in first-line treatment, because this modality offers hope for significantly improved long-term survival.

Non-metastatic castration-resistant prostate cancer — a challenging disease with novel treatment options

As with most types of cancer, recent years brought significant improvement in the treatment of prostate cancer. The introduction of novel drugs modulating hormonal signalling, abiraterone and enzalutamide, revolutionised the treatment of metastatic castration-resistant prostate cancer. The addition of docetaxel or abiraterone to hormonal treatment in metastatic castration-sensitive prostate cancer resulted in a tremendous gain in overall survival. Prostate cancer became a truly chronic disease, with median overall survival reaching 50 months in some populations. Despite the advance, some clinical situations remain a significant challenge. With a broader availability of PSA testing and increasingly aggressive management of locally advanced prostate cancer, non-metastatic castration-resistant prostate cancer became more common. Lack of good quality evidence and difficulties in defining aims of therapy provided additional difficulties. Fortunately, two recently published trials provided data regarding management of patients in this setting.

The first trial data are from the SPARTAN trial, published by Smith et al. [3] in the "New England Journal of Medicine" on 12th April 2018. This double-blinded, randomised, phase 3 clinical trial compared apalutamide, a nonsteroidal antiandrogen that acts by a direct blockade of androgen receptor, with placebo in non-metastatic castration-resistant prostate cancer, which had a PSA-doubling time of 10 months or less. Apalutamide was given at a daily dose of 240 mg per day. Androgen-deprivation therapy (either by a bilateral orchidectomy or with gonadotropin-releasing hormone analogue agonist or antagonist) was required during the trial. The primary endpoint was metastasis-free survival and secondary end points included: time to metastasis, progression-free survival, time to symptomatic progression, and overall survival. The trial accrued 1207 patients, randomised in a 2:1 ratio to either apalutamide or placebo. After a median follow-up time of 20.3 months, the primary endpoint was met. Median metastasis-free survival reached 40.5 months in patients receiving apalutamide and 16.2 months in patients receiving placebo, with an HR for metastasis or death of 0.28 (95% CI 0.23–0.35; $p < 0.001$). Results were consistent in all analysed subgroups. This result led to the recommendation of the monitoring committee to unblind the trial and offer apalutamide treatment to patients receiving placebo. Secondary endpoints of time to metastasis, progression-free survival, and time to symptomatic progression were significantly better in the apalutamide arm compared to the placebo arm ($p < 0.001$ for all). Due to the data immaturity, the difference in OS have not reached significance, but a trend toward improvement in OS was seen with apalutamide ($p = 0.07$). In safety analysis, grade 3 and 4 adverse events were more commonly observed in the apalutamide arm than in the placebo arm (45.1% *vs.* 34.2%, respectively), but the rate of serious adverse events (24.8% *vs*. 23.1%, respectively) and adverse events leading to treatment discontinuation (10.6% *vs*. 7.0%, respectively) were similar between both arms. The most common adverse events attributed to apalutamide were fatigue (30.4% *vs*. 21.1%), rash (23.8% *vs*. 5.5%), falls (15.6% *vs*. 9.0%), fractures (11.7% *vs*. 6.5%), and hypothyroidism (8.1% *vs*. 2%). Adverse events leading to death were observed in six patients receiving apalutamide and in one patient receiving placebo.

The second study, the PROSPER trial, was published by Hussain et al. [4] in the "New England Journal of Medicine" on 28th June 2018. The PROSPER trial was a phase 3, double-blinded, placebo-controlled clinical trial evaluating enzalutamide, an antiandrogen directly blocking androgen receptor, in patients with non-metastatic castration-resistant prostate cancer with a PSA doubling time of less than 10 months and PSA level of at least 2 ng/ml. The primary endpoint of the trial was metastasis-free survival, and secondary endpoints included time to PSA progression, PSA response rate, time to the subsequent therapy initiation, quality-of-life (FACT-P score), overall survival, and safety. The PROSPER trial enrolled 1401 patients, randomised in a 2:1 ratio to either enzalutamide (given at a standard dose of 160 mg daily) or matched placebo. The primary endpoint was met, with the median metastasis-free survival reaching 36.6 months in the enzalutamide arm and 14.7 months in the placebo arm (after a median follow-up time of 18.5 months and 15.1 months, respectively). This resulted in an HR for radiographic progression or death of 0.29 (95% CI 0.24–0.35; $p < 0.001$). Achieved effects were comparable in all subgroups analysed. From the secondary endpoints, the time to PSA progression and the time to subsequent therapy initiation were significantly better in the enzalutamide arm ($p < 0.001$ for both). Median overall survival was not been reached in either arm, without significant differences between arms (HR for death of 0.8; 95% CI 0.58–1.09; $p = 0.15$). Results of quality-of-life assessment were comparable between both arms, including similar time to score degradation. Rate of grade 3 or worse adverse events and rate of serious adverse events were numerically higher in patients receiving enzalutamide (31% and 24%, respectively) when compared to patients receiving placebo (23% and 18%, respectively). More fatigue, hypertension, major cardiovascular events, and mental impairment disorders were observed in the experimental

arm. Adverse events leading to death occurred more often in the enzalutamide group (3% *vs.* 1%; 32 events and 3 events).

Both trials, SPARTAN and PROSPER, provide good quality data supporting treatment of non-metastatic castration-resistant prostate cancer with novel antiandrogens. Apalutamide and enzalutamide were proved to prolong metastasis-free survival, showed activity in this setting, and can be considered an option of care. However, because both trials have not yet provided evidence of OS prolongation and both drugs are associated with an increased risk of adverse events, every decision regarding their implementation should be carefully deliberated. Fortunately, the results of the SPARTANT trial suggest a trend towards improvement of OS, and further data might provide more arguments for the usage of novel antiandrogens in the non-metastatic castration-resistant prostate cancer setting.

Hunting down breast cancer harbouring mutated *BRCA1/2* genes

Breast cancer associated with *BRCA1/2* gene mutations is a significant burden in modern oncology, mostly due to the hereditary nature of this disease. Additionally, the presence of *BRCA1/2* mutations in cancer cells often corelates with aggressive triple-negative immunophenotype, with a worse prognosis even at early stages. Generally, it is estimated that about 5–10% of breast cancers harbour mutated *BRCA1/2* genes, with prevalence varying deeply between different populations. Beside germinal mutations, about 3% of all breast cancer patients harbour somatic *BRCA1/2* mutations and are not hereditary. Since their identification, *BRCA1/2* genes are considered a promising therapeutic target. Poly(adenosine diphosphate-ribose) polymerase inhibitors (PARPi), initially registered for the treatment of germline *BRCA* mutated ovarian cancer, are active in the treatment of metastatic breast cancer harbouring germline *BRCA* mutations. This was confirmed in a phase 3 trial comparing olaparib with the physicians' choice of chemotherapy. Now, another PARPi showed superiority over cytotoxic chemotherapy in patients with metastatic germline *BRCA1/2* mutated breast cancer.

Litton et al. [5] published on 23rd August 2018 in the "New England Journal of Medicine" the results of a phase 3 trial comparing talazoparib, a PARPi, with standard single-agent chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine) in patients with breast cancer harbouring germline *BRCA* mutations. Talazoparib was administered orally at 1 mg daily in a continuous manner. The primary endpoint was progression-free survival, assessed by an independent central review. The secondary endpoint included: overall survival, objective response rate, clinical benefit rate at 24 weeks, and duration of response. The trial included quality-of-life analysis through EORTC QLQ-C30 and QLQ-BR23 questionnaires. The trial accrued 431 patients, randomised in 2:1 ratio to either the experimental arm with talazoparib or the standard arm with chemotherapy. After a median follow-up of 11.2 months, the trial met its primary endpoint, with an improvement of median PFS to 8.6 months (95% CI 7.2–9.3) in the talazoparib arm from 5.6 months (95% CI 4.2–6.7) in the standard arm, with the HR for disease progression or death of 0.54 (95% CI 0.41–0.71; $p < 0.001$). The effect was consistent across all analysed subgroups, with slightly less benefit seen in patients previously treated with platinum compounds. At described interim analysis, the difference in overall survival between both arms did not achieve statistical significance (22.3 months [95% CI 18.1–26.2] in patients receiving talazoparib *vs*. 19.5 months [95% CI 16.3–22.4] in patients receiving standard chemotherapy) (HR 0.76; 95% CI 0.55–1.06; $p = 0.11$), which might be due to the immaturity of the data. The talazoparib group achieved better results in response rate (62.6% *vs*. 27.2%), clinical benefit at 24 weeks (68.6% *vs.* 36.1%), and duration of response (5.4 months *vs*. 3.1 months). The rate of serious adverse events (31.8% in patients receiving talazoparib and 29.4% in patients receiving chemotherapy) and rate of grade 3 and 4 serious adverse events (25.5% and 25.4%, respectively) were similar between both arms. More haematological grade 3 and 4 adverse events were observed with talazoparib (55% *vs.* 38%), with opposing results regarding non-haematological grade 3 and 4 adverse events (32% *vs.* 38%). Adverse events led to treatment discontinuation in 5.9% of patients receiving talazoparib and in 8.7% of patients receiving chemotherapy. Significantly better results regarding quality of life were seen in the talazoparib arm with both QLQ-C30 questionnaire (increase of 3.0 points [95% CI 1.2–4.8] *vs.* –5.4 points [95% CI –8.8 to –2.0; $p < 0.001$]) and QLQ-BR23 (decrease of symptoms of –5.1 points [95% CI –6.7 to –3.5] *vs.* –0.1 points [95% CI –2.9–2.6; $p = 0.002$]).

As a result of the trial, talazoparib joins olaparib as a treatment option for patients with metastatic cancer harbouring germline *BRCA1/2* mutations, providing further proof for PARPi activity in this setting. Benefit of talazoparib is limited not only to progression-free

survival, but comes also with a significant improvement in the quality-of-life scores. Additionally, numerical improvement in median OS was seen, although this requires confirmation as the data mature. Several questions remain unanswered, especially considering comparison of PARPi and platinum derivatives, because cancers with present *BRCA1/2* mutations might be more sensitive to both PARPi and platinum compounds. Other questions concern activity of PARPi in breast cancers with somatic *BRCA1/2* mutations and activity of PARPi in *BRCA1/2* mutated cancers other than breast cancer. Hopefully, further studies will expand the indication for PARPi, and more patients will be able to benefit from a more personalised therapeutic approach.

References

1. Horn L, Mansfield AS, Szczęsna A, et al. IMpower133 Study Group. First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer. N Engl J Med. 2018 [Epub ahead of print], doi: 10.1056/NEJMoa1809064, indexed in Pubmed: 30280641.
2. Abou-Alfa GK, Meyer T, Cheng AL, et al. Cabozantinib in Patients with Advanced and Progressing Hepatocellular Carcinoma. N Engl J Med. 2018; 379(1): 54–63, doi: 10.1056/NEJMoa1717002, indexed in Pubmed: 29972759.
3. Smith M, Saad F, Chowdhury S, et al. Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer. New England Journal of Medicine. 2018; 378(15): 1408–1418, doi: 10.1056/nejmoa1715546.
4. Hussain M, Fizazi K, Saad F, et al. Enzalutamide in Men with Nonmetastatic, Castration-Resistant Prostate Cancer. N Engl J Med. 2018; 378(26): 2465–2474, doi: 10.1056/NEJMoa1800536, indexed in Pubmed: 29949494.
5. Litton JK, Rugo HS, Ettl J, et al. Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation. N Engl J Med. 2018; 379(8): 753–763, doi: 10.1056/NEJMoa1802905, indexed in Pubmed: 30110579.