Maciej Kawecki

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

New opportunities in the treatment of patients with *BRAF V600E* mutated colorectal cancer

The introduction of multidrug schedules incorporating targeted agents has significantly improved the prognosis of patients with metastatic colorectal cancer, with a median overall survival (OS) surpassing three years in several clinical trials. This improvement of prognosis in the general population unveiled a poor prognosis associated with the presence *of BRAF V600E* mutation, with a median OS of only 12 months. Based on the success of BRAF inhibitors in *BRAF V600E* mutated melanoma, several attempts to utilise those drugs in patients with *BRAF V600E* mutated colorectal cancer were undertaken, but the activity of monotherapy with anti-BRAF agents was disappointing. However, the improvement in understanding the molecular effects of *V600E* mutations and mechanisms behind secondary resistance to BRAF inhibitors through MEK signalling pathway enabled the utilisation of BRAF V600E as a molecular target even in patients with metastatic colorectal cancer. The results of the BEACON study, which evaluated multiagent BRAF V600E inhibition in colorectal cancer, suggest a major shift in treatment strategy: introduction of the first multidrug schedule without classic cytotoxic drugs in colorectal cancer.

The BEACON study, published on 20th September 2019 in the "New England Journal" of Medicine by Kopetz et al. [1], was a randomised, open-label, phase III trial that compared the combination of encorafenib (BRAF inhibitor) and cetuximab (anti-EGFR antibody) with or without addition of binimetinib (MEK inhibitor), with a standard second-line chemotherapy: FOLFIRI with the addition of cetuximab. The study included patients with *BRAF V600E* mutated colorectal cancer, who failed one or two lines of therapy. The trial's primary endpoint was overall survival in patients receiving triplet-therapy as compared to standard therapy, with an additional primary endpoint that compared the response rates (RR). Major secondary endpoints included a comparison of OS in patients receiving doublet therapy compared to a standard arm, and a comparison of progression-free survival (PFS) between arms. From 1677 screened patients, 665 patients underwent randomisation in 1:1:1 ratio to all arms of the trial. After a median follow-up time of 7.8 months, the trial met its primary endpoint. Median OS in patients receiving encorafenib, binimetinib, and cetuximab was 9.0 months (95% confidence interval [CI] 8.0–11.4) as compared to only 5.4 months (95% CI 4.8–6.6) in patients receiving standard therapy, with a hazard ratio (HR) of 0.52 (95% CI 0.39–0.70; $p < 0.001$). The second primary endpoint — RR — was also significantly improved in patients receiving triplet therapy (26%; 95% CI 18–35) in comparison with the control arm (2%; 95% 0–7) ($p < 0.001$). The achieved results were consistent among most analysed subgroups, with a reduced benefit from triplet therapy in the North America region. Survival was also improved in patients receiving encorafenib with cetuximab, with a median OS of 8.4 months (95% CI 7.5–11.0) and HR of 0.60 (95% CI 0.45–0.79; $p < 0.001$), when compared to the control arm. A comparison of triplet therapy with doublet therapy, although not prefigured in the protocol, showed a trend for OS improvement with triplet therapy (HR 0.79; 95% CI 0.59–1.06). Analysis of PFS also demonstrated benefit of both triplet (4.3 months; 95% CI 4.1–5.2) and doublet (4.2 months; 95% CI 3.7–5.4) therapy versus the standard arm (1.5 months; 95% CI 1.5–1.7). As expected, the toxicity profile differed significantly between study arms, with a moderate increase of skin and gastrointestinal toxicities with triplet therapy. The rate of grade 3 or higher adverse events was 58% in patients receiving triplet therapy, 50% in patients receiving doublet therapy, and 61% in patients receiving standard chemotherapy. The rate of adverse events that led to treatment discontinuation was, respectively, 7%, 8%, and 11%. Additionally, no difference in the rate of adverse events that led to death was seen.

Significant OS benefit achieved in the BEACON study with both triplet and doublet targeted therapy can be considered as a major breakthrough in the treatment of patients with *BRAF V600E* mutated colorectal cancer. This is the first trial dedicated to patients with colorectal cancer that showed significant clinical benefit associated with combining molecularly targeted agents with acceptable toxicity profile. Based on these results, a combination of encorafenib with cetuximab with the addition of binimetinib should be considered the new standard of care in the second-line

treatment of patients with *BRAF V600E* mutated colorectal cancer. Nevertheless, attention should be paid to the significant patient selection, because the trial included fewer than 40% of screened patients, which mirrors the exceptionally poor prognosis among this group of patients. Traditionally, as is the case of most modern targeted therapies or immunotherapeutic agents, the single most important factor limiting wide implementation of this strategy is the cost of a therapy that utilises not just two, but three molecularly targeted agents. Cost-effectiveness assessment of triplet therapy may lead to disappointing conclusions, especially when including the only slightly inferior results achieved with doublet therapy.

Nivolumab and ipilimumab as a first-line treatment of patients with non-small cell lung cancer

The introduction of immune check-point inhibitors (CPSs) is probably the single greatest achievement of the last decade in the systemic treatment of solid tumours. We must be aware that modern immunotherapy is not a universal solution in all solid tumours, but it has significantly revolutionised the treatment of several cancer types, including melanoma, renal cell carcinoma, and lung cancer. The benefit of CPIs in the treatment of patients with lung cancer, although numerically lower when compared to gains in melanoma or renal cell carcinoma, has its greatest impact on modern oncology practice due to the higher prevalence of lung cancer. Considering the actual guidelines, it seems that all patients with non-small cell lung cancer, excluding patients with present activating mutations (*EGFR*/*ROS*/*ALK*/*BRAF*), should receive CPIs in the first-line treatment — either as a monotherapy (in cases with PD-L1 > 50%) or as a combination with chemotherapy (in cases with PD--L1 < 50%). The number of phase III trials assessing CPIS with initial or complete data, which were published within the last two years might be intimidating, and we can even assume that the current standard will become at least partially obsolete in the near future. The role of platinum-based chemotherapy doublets, the long-time standard of care in the first-line treatment of non-small cell lung cancer, is now limited and may even become marginalised. This scenario is becoming a reality with the recent publication of a trial assessing the combination of nivolumab with ipilimumab in the first-line treatment of non-small cell lung cancer, which expands the chemotherapy-free approach also into the population with PD-L1 expression below 50%.

The results of the aforementioned trial were published on 28th September 2019 in the "New England Journal of Medicine" by Hellmann et al. [2]. The CheckMate 227 trial was a randomised, open-label, phase III trial that compared nivolumab alone or in combination with either ipilimumab or chemotherapy with a standard platinum-doublet chemotherapy. Patients recruited into the trial had non-small cell lung cancer, either squamous carcinoma or adenocarcinoma, without activating mutations in the *EGFR* gene or the presence of *ALK* gene fusions. Depending on the central assessment of PD-L1 status (either > 1% or < 1%), patients were randomised in 1:1:1 ratio to a combination of nivolumab with ipilimumab, nivolumab alone, or standard chemotherapy (if PD-L1 expression was > 1%) or to a combination of nivolumab with ipilimumab, a combination of nivolumab with chemotherapy, or standard chemotherapy (if PD-L1 expression was < 1%). The primary endpoint was overall survival in patients with PD-L1 expression > 1% compared between a combination of nivolumab and ipilimumab and standard chemotherapy (results of the second primary endpoint — a comparison of PFS in patients with tumour mutational burden [TMB] equal to or higher than 10 mutations per MB were published previously [3]). Patients assigned to the combination of nivolumab and ipilimumab received nivolumab at a dose of 3 mg/kg body weight every two weeks along with ipilimumab 1 mg/kg body weight every six weeks. Patients assigned to the nivolumab monotherapy received nivolumab at a fixed dose of 240 mg biweekly, and patients assigned to the combination of nivolumab with chemotherapy received nivolumab at a fixed-dose of 360 mg every three weeks along with standard platinum-based doublet chemotherapy every three weeks (up to four cycles of chemotherapy). The control arm for both PD-L1 > 1% and < 1% received standard treatment of platinum-based chemotherapy (patients with adenocarcinoma: up to four cycles of cisplatin or carboplatin with pemetrexed with an option of continuing maintenance pemetrexed; patients with squamous carcinoma: up to four cycles of cisplatin or carboplatin with gemcitabine). The trial included 1189 patients with a confirmed PD-L1 expression of > 1% and 550 patients with PD-L1 expression of < 1%. After a median follow-up time of 29.3 months, the trial met its primary endpoint in patients with PD-L1 expression > 1%: median OS in patients receiving nivolumab and ipilimumab reached 17.1 months (95% CI 15.0–20.1) as compared to 14.9 months (95% CI 12.7–16.7) in patients receiving chemotherapy (p = 0.007). HR for death was 0.79 (97.2% CI 0.65–0.96) with a commentary that this should be interpreted along with analysis of

survival curves: initially favouring chemotherapy, then crossing and subsequentially favouring nivolumab and ipilimumab. Benefit from double immune blockade was confirmed in most subgroups, with the exception of patients with liver metastases and those without history of smoking. The response rate was 35.9% in patients receiving nivolumab and ipilimumab and 30% in patients receiving chemotherapy, with a median duration of response of, respectively, 23.2 months (95% CI 15.2–32.2) and 6.2 months (95% CI 5.6–7.4). Benefit from a combination of nivolumab with ipilimumab was also observed in the population with PD-L1 expression < 1% (pre-planned descriptive analysis): median OS was 17.2 months (95% CI 12.7–22.0) in patients receiving immunotherapy combination as compared to 12.2 months (95% CI 9.2–14.3) in patients receiving chemotherapy, with an HR of 0.62 (95% CI 0.48–0.78). Similar results were seen in combined analysis of PD-L1 > 1% and PD-L1 < 1% populations: median OS was 17.2 months (95% CI 15.2–19.9) and 13.9 months (95% 12.2–15.1), respectively. Comparison of nivolumab and ipilimumab with nivolumab monotherapy showed numerically better results achieved with the combination in terms of two-year survival rate and median duration of response, both in PD-L1 > 1% and PD-L1 > 50% populations. Better results in terms of two-year survival rate and median duration of response were seen also with immunotherapy combination as compared to combination of nivolumab and chemotherapy in the population with PD-L1 expression < 1%. In a detailed analysis neither PD-L1 expression, TMB status, nor their combination allowed selection of patients who could derive greater benefit from a combination of nivolumab and ipilimumab. Despite the previously shown correlation between TMB and median PFS [3], this has not translated into OS benefit. In terms of safety, the rate of grade 3 or greater adverse events was similar between the nivolumab-ipilimumab arm and the chemotherapy arm (32.8% and 36.0%, respectively). However, both severe adverse events (24.5% *vs.* 13.9%) and adverse events that led to treatment discontinuation (18.1% *vs.* 9.1%) were more common in patients receiving nivolumab with ipilimumab. No significant difference in rates of adverse events leading to death was seen (1.4% in the combination immunotherapy group *versus* 1.1% in the chemotherapy group). The published results did not include data regarding quality of life.

The results of CheckMate 227 have a meaningful impact on the role of immunotherapy in the first-line treatment of patients with non-small cell lung cancer and justify skipping chemotherapy in the majority of patients. However, it seems that the benefit from combined immunotherapy might be reduced in patients with PD-L1 expression 1–49%. The benefit seen in the whole population with PD-L1 expression > 1% is mostly driven by exceptional results obtained in patients with expression > 50%. Similar effects have also been reported in immunotherapy trials in different types of cancer. In practice, the patients with PD-L1 expression within 1–49% might be the best candidates for the combination of immunotherapy and chemotherapy. Other factors limiting the benefit from combined immunotherapy are the presence of liver metastases and lack of smoking history, which may provide guidance regarding treatment individualisation. Additionally, CheckMate 227 provided important, albeit negative, results assessing TMB as a predictive marker for immunotherapy. The idea that a higher number of genetic mutations increases the variety of presented neoantigens, promoting induction of immune response, does not translate into OS benefit. Unfortunately, none of the biomarkers reported in CheckMate 227 allow selection of a population with greater benefit from combined immunotherapy. Considering the remarkably high costs of such treatment, the lack of an adequate biomarker undermines wide implementation of combination immunotherapy into clinical practice. The growing potential of immunotherapy in the first-line treatment of patients with non-small cell lung cancer is revolutionising both patient treatment and the functioning of health care systems. The greatest challenge in the upcoming years, especially in chronically underfinanced systems, will be optimisation of treatment to achieve the best results with an acceptable immunotherapy-associated financial burden.

The next PARP inhibitors proved to be effective in the treatment of patients with ovarian cancer

Treatment of patients with ovarian cancer is a significant clinical challenge, despite its relative sensitivity to platinum-based chemotherapy, which can induce long-lasting responses. Unfortunately, the majority of patients achieving partial or complete response will eventually relapse with a reduced probability of re-inducing response. One of the strategies evaluated in this setting is inhibition of PARP, the enzyme responsible for the repair of single-strain DNA breaks. Inhibition of PARP activity leads to the accumulation of single-strain DNA breaks, which subsequently generates double-strain DNA breaks leading to cancer cell death. PARP inhibitors exhibit particular activity in the presence of other DNA repair dysfunctions, such as *BRCA1/2* mutations or the presence of other mechanism of homologous repair deficiency (HDR). PARP inhibi-

tion, initially developed as a salvage treatment, is useful also as a maintenance treatment after first-line therapy. Several different PARP inhibitors have proved effective as a salvage treatment (olaparib, rucaparib, veliparib), but until recently only olaparib has proved its role in the maintenance strategy. Now the situation is changing because the next two phase III trials evaluating PARP either as part of induction and maintenance treatment or just as maintenance treatment have been published.

The VELIA/GOG-3005 study, the results of which were published by Coleman et al. [4] on 28th September 2019 in the "New England Journal of Medicine", evaluated veliparib used as an addition to standard first-line induction chemotherapy (carboplatin and paclitaxel) and continued as a maintenance treatment. This randomised, double-blinded, phase III trial included chemotherapy-naive patients with stage III or IV (according to International Federation of Gynaecology and Obstetrics; FIGO) high-grade serous carcinoma of the ovary, fallopian tube, or peritoneum, irrespective of *BRCA1/2* and HDR status. Veliparib was used orally at a dose of 150 mg twice daily during chemotherapy and then 300 mg twice daily with a possible escalation to 400 mg twice daily as a maintenance treatment. Patients were randomised in a 1:1:1 ratio to either veliparib used during both induction and maintenance phases, veliparib used during induction phase and placebo during maintenance phase, or to placebo used both during induction and maintenance phases (control arm). The primary endpoint was the comparison of PFS between patients receiving veliparib in the induction and maintenance phase with the control arm, evaluated hierarchically first in patients with *BRCA* mutations, then in patients with confirmed HDR, and finally in the intention-to-treat (ITT) population. One of the key secondary endpoints was overall survival. Altogether, 1140 patients were recruited into the trial, among whom 298 (26%) had *BRCA* mutations (19% germinal mutations and 7% somatic tumour mutations) and 627 (55%) had confirmed HDR status. After a median follow-up of 28 months, the trial met its primary endpoint in all hierarchically analysed groups. In patients with *BRCA* mutations the median PFS reached 34.7 months in the veliparib arm compared to 22.0 months in the placebo arm (HR for progression or death 0.44; 95% 0.28–0.68; $p < 0.001$). In HDR patients the PFS reached, respectively, 31.9 months as compared to 20.5 months (HR 0.57; 95% CI 0.43–0.76; $p < 0.001$), and in ITT analysis 23.5 *vs.* 17.3 months (HR 0.68; 95% CI 0.56–0.83; $p < 0.001$). The achieved effect was seen in most of the analysed subgroups with the exception of patients with macroscopically non-radical cytoreduction — no benefit from veliparib was seen in this group. Patients without confirmed HDR also gained less benefit from veliparib when compared to patients with either HDR or *BRCA* mutations. Due to data immaturity, OS analysis was impossible. In the safety analysis a modest increase of adverse events was seen in patients receiving veliparib in the induction and maintenance phases (88% *vs.* 77% in the placebo arm), although this did not reduce the chemotherapy intensity. The most common veliparib-related adverse event was thrombocytopaenia. Among patients receiving veliparib one case of myelodysplastic syndrome and one case of acute myeloid leukaemia were seen, which is comparable to the risk described with other PARP inhibitors. Quality-of-life comparison showed no difference between study arms.

Results of the second trial were published by González-Martín et al. [5] also on 28th September 2019 in the "New England Journal of Medicine". The PRIMA/ENGOT-OV26/GOG-3012 trial was a randomised, double-blinded, phase III trial that compared niraparib, a novel PARP inhibitor, with placebo in patients with FIGO stadium III–IV ovarian, fallopian tube, or peritoneal cancers, who achieved response (CR or PR) after induction chemotherapy. Patients were randomised in a 2:1 ratio to either neratinib (administered at a dose of 300 mg once daily, although on-trial amendment allowed reduction of initial dose to 200 mg per day in patients under 77 kg body weight or with thrombocytopaenia below 150,000 platelets per cubic millimetre) within 12 weeks after finishing induction chemotherapy. The primary endpoint was PFS assessed hierarchically in the population with positive HDR status and then in the overall population. Key secondary endpoints included overall survival. The trial included 733 patients, and after a median follow-up time of 13.8 months it met its primary endpoint. In patients positive for HDR the median PFS reached 21.9 months in the niraparib group and 10.4 months in the placebo group (HR for progression or death 0.43; 95% CI 0.31–0.59; $p < 0.001$). In the overall population the difference was 13.8 months in the intervention arm as compared to 9.2 months in the control arm (HR 0.62; 95% CI 0.50–0.76; $p < 0.001$). This effect was maintained in all analysed subgroups. At the point of analysis OS data were immature (about 11% of events), but per-protocol OS analysis was undertaken. The rate of two-year survival was 84% in the niraparib arm and 77% in the placebo arm (HR 0.61; 95% CI 0.27–1.39; not statistically significant). The most common adverse events associated with niraparib were anaemia, thrombocytopaenia, and neutropaenia. The rate of grade 3 or worse adverse events was 70.5% in patients receiving niraparib and 18.9% in patients receiving placebo. Dose reductions were required in 70.9% of patients receiving niraparib and 8.2% of patients receiving placebo, with a discontinuation rate due to adverse events of, respectively, 12% and 2.5%. Quality-of-life comparison showed no difference between study arms.

The two presented trials broaden the availability of PARP inhibitors for patients with ovarian cancer, confirming the potential of PARP inhibition also at the early phase of treatment. The differences between specific compounds and in trial designs limits direct comparison, but also enables individualisation of treatment according to risk-factor profile, patient performance, and preferences. From this perspective, diversity is highly desirable.

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