Maciej Kawecki

Department of Oncology, Military Institute of Medicine, Warsaw

Another active checkpoint inhibitor in the treatment of NSCLC — results from phase 3 OAK trial comparing atezolizumab and docetaksel in 2nd and 3rd line setting

Last two years brought tremendous changes to the therapeutic landscape of non-small-cell lung cancer. Novel group of compounds, known as checkpoint inhibitors, have settled as an effective modality in 1st, 2nd and subsequent lines of treatment. These agents influence the interaction of tumor cells, microenviroment and T limphocytes unblocking immunological response against cancer. Significant evidence from phase 3 trials established programmed cell death protein 1 (PD-1) inhibitors as an standard of care in the 1st line treatment of NSCLC patients with at least 50% expression of programmed cell death protein 1 ligand (PD-L1) in case of pembrolizumab and in 2nd line for both patients with expression of PD-L1 for both pembrolizumab and nivolumab as well as without PD-L1 expression (only nivolumab). Few ongoing phase 3 trials evaluate different checkpoint inhibitors and their combinations in NSCLC setting.

Atezolizumab, in contrast to nivolumab and pembrolizumab, acts by inhibiting PD-L1 (expressed on tumors cells and tumor-infiltrating immune cells, mostly on macrophages and dendritic cells). PD-L1 blockade results not only in attenuation of PD-1 and PD-L1 interactions, but also prevents PD-L1 from blocking B7.1 signalling, which is responsible for a costimulatory signal necessary for T-cell activation. Rittmeyer et al. [1] reported in „The Lancet" (January 21th 2017) the outcomes from phase 3 trial comparing docetaxel and atezolizumab in the 2nd and 3rd line of NSCLC treatment (OAK trial). The study recruited 1225 patients, who were randomized in 1:1 ratio to both of the arms. Patients were stratified by PD-L1 expression (evaluated separately on tumors cells and on infiltrating immune cells), number of previous treatment lines (1 or 2) and histology (squamous or non-squamous). Primary endpoint were overall survival in the intention-to-treat (ITT) population and in PD-L1 positive population. After median follow-up of 21 months, both primary endpoints were met. Median overall survival (mOS) in ITT population was 13.8 months (95% CI 11.8–15.7) for atezolizumab and 9.6 months (95% CI 8.6–11.2) for docetaxel, with HR of 0.73 (95% CI 0.62–0.87; p = 0.0003). The difference was numerically even more significant in PD-L1 positive population, in which mOS for atezolizumab achieved 15.7 months (95% CI 12.6–18) *vs*. 10.3 months for docetaxel (95% CI 8.8–12), with HR 0.74 (95% CI 0.58–0.93; p = 0.102). In the subgroup without PD-L1 expression, superiority of atezolizumab was also seen [12.6 months *vs.* 8.9 months, HR 0.75 (95% CI 0.59–0.96; p = 0.0215)]. Despite the difference in mOS, no improvement in median progression free survival (mPFS) in atezolizumab group was seen, with numerically better mPFS achieved with docetaxel [2.8 months in atezolizumab arm *vs*. 4 months in docetaxel arm, HR 0.95 (95% CI 0.82–1.1)]. Treatment with atezolizumab was also superior in safety analysis, with grade 3–4 adverse events rates of 37% in atezolizumab arm *vs*. 54% in docetaxel arm and grade 3–4 treatment related adverse events 15% *vs.* 43%, respectively. Rates of adverse events leading to treatment discontinuation were 8% in patients receiving atezolizumab and 19% in patients receiving docetaxel. No unexpected toxicities, including immune-mediated, were seen with atezolizumab.

Presented study validated PD-L1 as a new therapeutic target and reassured the important role of immunotherapy in NSCLC treatment. Currently at least 3 checkpoint inhibitors can be used for patients with NSCLC (either in 1st or in 2nd line treatment). Ongoing trials could bring even more active molecules or their combinations to further extend therapeutic options. However, several important aspects of lung cancer immunotherapy, such as standardisation of PD-1/PD-L1 expression measurement as a predictive factor for effectiveness of checkpoint inhibitors, remains unclear and await further studies.

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Emerging changes in adjuvant treatment of locally advanced clear-cell renal-cell carcinoma — are we there yet?

Despite recent advancement in the field of renal-cell carcinoma (RCC), surgical resection remains only curative option in most patients. Nearly 60% of patients with locoregional disease, usually defined as a T3–4 primary tumor and/or involvement of regional lymph nodes (N1) — which mostly corresponds with stage III and locally advanced cases of stage IV in TNM classification — can be cured be the use of surgery. Remaining 40% of patients usually relapse within a few years and require palliative therapy. Several attempts to improve prognosis in this group were undertaken, such as adjuvant cytokine therapy, without clinically relevant effect. Introduction of tyrosine kinase inhibitors (TKIs) in the treatment of metastatic RCC brought attention to a possibility of utilizing TKIs in adjuvant setting. However, results from the first phase 3 study evaluating this hypothesis (ASSURE trial; E2805) [2], comparing sorafenib vs. sunitinib *vs.* placebo, were disappointing. No difference in the disease-free survival (DFS) was seen between both active compounds and placebo. When it seemed that we should give up using TKIs in the adjuvant setting, new data emerged.

In the issue of „New England Journal of Medicine" from 10th of October 2016, Ravaud et al. [3] reported results from S-TRAC trial, evaluating one-year adjuvant sunitinib therapy in patients with resected locoregional clear-cell RCC at high risk for relapse. The study randomized patients 615 patients in a 1:1 ratio to receive sunitinib 50 mg or placebo on 4-weeks-on/2-weeks-off schedule for 1 year. The primary end point was DFS. The results were reported after median duration of follow-up of 5.4 years. Full treatment was completed in 55.6% of patients in sunitinib arm and 69.4% of patients in placebo arm. The primary end point, disease-free survival, was 6.8 years (95% CI 5.8 to not reached) in sunitinib arm and 5.6 years (95% CI 3.8–6.6) in placebo arm, a difference that was statistically significant (HR 0.76; 95% CI 0.59–0.98; p = 0.03). Rates of DFS at 5 years were 59.3% and 51.3%, respectively for sunitinib and placebo. At the time of analysis, data regarding overall survival were immature with mOS not reached in both of arms (HR 1.01; 95% CI 0.72–1.44; p = 0.94). Rates of adverse events related to the treatment were 98.4% in patients receiving sunitinib and 75.7% in patients receiving placebo. Grade 3 or higher adverse events were noted in 63.4% of patients in sunitinib arm and 21.7% of patients in placebo arm. The treatment was discontinued due to adverse events in 28.1% of patients in sunitinib group and 5.6% of patients in placebo group. In the quality-of-life analysis, patients receiving sunitinib reported inferior scores than placebo ones, despite the fact that differences did not reached prespecified margin of importance.

The study is the first one to report significant improvement in a course of renal cell carcinoma with a usage of adjuvant treatment. However, available data are conflicting. S-TRAC trial and ASSURE trial, both evaluating TKIs in a adjuvant setting, presented different outcomes. The difference might be — at least in part — attributed to higher sunitinib doses and better adherence to treatment schedule in S-TRAC trial as well as to some differences in defining recurrence risk required from patients to participate in trials. Another important question is whether we will see any difference in overall survival as the data matures. With available data form S-TRAC, it is questionable that the difference in DFS of about 1,2 years translates into significant improvement of overall survival. When we consider a paradigm of TKIs acting mostly through inhibition of angiogenesis, which requires from metastases to be more than a single cancer cell, it is hard to exclude the possibility that for some of patients in S-TRAC trial adjuvant sunitinib treatment was a type of early first line treatment. This problem might be solved with the identification of clinically relevant biological or molecular predictive factors that may lead to more precise and more personalized treatment. Especially, if we consider fact that a whole new class of immunomodulating drugs — checkpoints inhibitors — awaits to be evaluated as an adjuvant therapy for RCC.

Small step forward in the management of pancreatic cancer — results from ESPAC-4 trial comparing adjuvant gemcitabine and capecitabine *versus* gemcitabine alone

With rising incidence and extremely poor prognosis, management of pancreatic cancer emerges as an important area in modern oncology. For metastatic pancreatic cancer, several novel therapeutic options have been developed, including combination chemotherapies such as FOLFIRINOX or nab-paclitaxel combined with gemcitabine in the 1st line treatment and FOLFIRI with liposomal irinotecan in 2nd line, slightly improving patients' prognosis. Results from ESPAC-3 trial [4] established gemcitabine monotherapy as a standard option for adjuvant therapy after resection of pancreatic cancer, improving 5-year survival from about 10% to around 16–21%. However, most of patients experience recurrent disease within months after completion of adjuvant therapy. Various approaches are under evaluation in this setting, with a combination of gemcitabine and capecitabine being one of them.

Neoptolemos et al. [5] presented in 24th January 2017 issue of „The Lancet" results from phase 3 trial ESPAC-4, which compared 24 weeks of adjuvant therapy with gemcitabine plus capecitabine with gemcitabine alone. The primary end point was overall survival, secondary end points were survival at 2 and 5 years and relapse-free survival (RFS). The study randomly assigned 732 patients in 1:1 ratio to both of the arms with the median follow-up of 43.2 months (95% CI 39.7–45.5). The mOS with gemcitabine plus capecitabine was 28.0 months (95% CI 23.5–31.5) *vs*. 25.5 months (95% CI 22.7–27.9) with gemcitabine alone, which resulted in HR of 0.82 (95% CI 0.68–0.98; p = 0.032). Rates of overall survival at 2 and 5 years were 53.8% (95% CI 48.4–58.8) and 28.8% (95% CI 22.9–35.2) — respectively — for gemcitabine plus capecitabine group and 52.1% (95% CI 46.7–57.2) and 16.3% (95% CI 10.2–23.7) — respectively — for gemcitabine alone. Improved overall survival was seen in most of presented clinical subgroups, most noticeably in patients with negative resection margins (HR 0.68 in favor of combined treatment; 95% CI 0.49–0.93), with maximum tumor size of less than 30 mm (HR 0.67; 95% CI 0.50–0.92) and without local invasion (HR 0.72; 95% CI 0.54–0.91). The median RFS was 13.1 months (95% CI 11.6–15.3) in gemcitabine arm and 13.9 months (95% CI 12.1–16.6) in gemcitabine plus capecitabine arm, with HR of 0.86 (95% CI 0.73–1.02; p = 0.082). Grade 3–4 adverse events occurred in 62.9% patients treated with combination therapy and 53.5% patients treated with monotherapy. Quality of life assessment showed no significant difference in longitudinal estimate of quality of life between compared arms (HR –0.10; 95% CI –0.29–0.09; p = 0.3).

Results from this study should establish combination therapy of gemcitabine and capecitabine as a standard adjuvant treatment after microscopically radical resection of pancreatic cancer. Improvement of overall survival, albeit limited in number, present important and immediate advancement in the care of patients with pancreatic cancer. Several currently ongoing studies, evaluating different combinations of adjuvant chemotherapy such as FOLFIRINOX and nab-paclitaxel plus gemcitabine, give hope for further ameliorations in this difficult field.

Combination of chemotherapy and radiotherapy in glioblastoma should not be limited by age — results from randomized phase 3 trial of radiochemotherapy *versus* radiotherapy alone in older patients

Even though incidence of glioblastoma increases with age, patients older than 70 year old are usually underrepresented in clinical trials. Current standard of care for general population, radiotherapy of 60 Gy over 6 weeks combined with temozolomide for 6 months during and after radiotherapy, is based on the study by Stupp et al. [6], which excluded patients older than 70 year old. Also, post hoc analyses from this study regarding group aged from 65 to 70 years, showed no improvement with radiochemotherapy compared to radiotherapy alone. Standard of care for older patients, short-course of radiotherapy of 40 Gy in 15 fractions alone or temozolomide chemotherapy alone, was established on the results of study by Malmström et al. [7], which compared 3 arms: short-course radiotherapy, chemotherapy with temozolomide and standard radiotherapy of 60 Gy over 6 weeks. Outcomes regarding overall survival were worse with standard radiotherapy when compared to other arms. Many older patients with glioblastoma presents features of frailty syndrome, significant comorbidities and higher susceptibility for adverse events, which limits possible therapeutic approaches. Despite available options, prognosis of older patients with glioblastoma remains poor.

New data from phase 3 study assessing combination of short-course radiotherapy with temozolomide was published by Perry et al. [8] in March 16th issue of „New England Journal of Medicine". The trial randomized 562 patients older than 65 years in 1:1 ratio to receive either radiotherapy of 40 Gy for 3 weeks or the same schedule of radiotherapy with concurrent temozolomide administered for a total period of 12 months. The median age was 73 years (range from 65 to 90) and 70.6% were older than 70 years. The mOS was 9.3 months (95% CI 8.3–10.3) with combined arm and 7.6 months (95% CI 7.0–8.4) with radiotherapy only arm, with HR of 0.67 (95% CI 0.56–0.80; p < 0.001). The effect remained significant after adjustment for baseline factors in Cox regression, with the same HR value of 0.67 (95% CI 0.56–0.80; p < 0.001). The benefit of radiochemotherapy was higher in patients aged over 70 years, with patients age 65 to 70 years without clear evidence of improved survival (HR 0.93; 95% CI 0.68–1.27). Similar results were achieved regarding progression-free survival: median of 5.3 months with combined arm *versus* 3.9 months with radiotherapy alone and HR 0.50 (95% CI 0.41–0.60; p < 0.001). Improvement of overall survival was seen regardless of MGMT methylation status, yet patients with methylated MGMT promoter derived more significant benefit from addition of temozolomide, with HR of 0.53 (95% CI 0.38–0.73; p < 0.001). As predicted, addition of temozolomide was associated with higher rates of G3–4 hematologic adverse events. However, rates of serious adverse events leading to death were similar in both arms. In the quality of life assessment,

no significant differences were seen between compared groups and only nausea and constipation scores favored radiotherapy alone.

Presented results supports usage of combined radiotherapy and temozolomide in patients with glioblastoma older than 70 years. The most distinctive difference was seen in patients with methylated MGMT promoter and special emphasis should be given to exposing this patients to temozolomide. One of the most important aspects of the study is the fact of maintaining quality of life with the usage of more toxic treatment. It seems that radiochemotherapy, if properly given, can be sustainable and translate into viable clinical benefit for older patients with glioblastoma.

References

1. Rittmeyer A, Barlesi F, Waterkamp D et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicenter randomised controlled trial. The Lancet 2016; 389: 255–265.
2. Haas NB, Manola J, Uzzo RG et al. Adjuvant sunitinib or sorafenib for high-risk, non-metastatic renal-cell carcinoma (ECOG-ACRIN E2805): a double--blind, placebo-controlled, randomised, phase 3 trial. The Lancet 2016; 387: 2008–2016.
3. Ravaud A, Motzer RJ, Pandha HS et al. Adjuvant Sunitinib in High-Risk Renal-Cell Carcinoma after Nephrectomy. New England Journal of Medicine 2016; 375: 2246–2254.
4. Neoptolemos JP, Stocken DD, Bassi C et al. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: A randomized controlled trial. JAMA 2010; 304: 1073–1081.
5. Neoptolemos JP, Palmer DH, Ghaneh P et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. The Lancet 2017; 389: 1011–1024.
6. Stupp R, Mason WP, van den Bent MJ et al. Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma. New England Journal of Medicine 2005; 352: 987–996.
7. Malmström A, Grønberg BH, Marosi C et al. Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, phase 3 trial. The Lancet Oncology 2012; 13: 916–926.
8. Perry JR, Laperriere N, O'Callaghan CJ et al. Short-Course Radiation plus Temozolomide in Elderly Patients with Glioblastoma. New England Journal of Medicine 2017; 376: 1027–1037.