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New standard-of-care in recurrent or metastatic, platinum refractory squamous head and neck carcinoma

In an article published on October 9th 2016 in "New England Journal of Medicine", Blumenschein et al. [1] reported results from randomized, open-label, phase 3 trial comparing nivolumab (at a dose of 3 mg/kg every 2 weeks) with a standard single-agent chemotherapy (investigator's choice of methotrexate, docetaxel or cetuximab) in patients with squamous-cell carcinoma of the head and neck, who progressed within 6 months after platinum-based therapy. Reported median overall survival reached 7.5 months in patients treated with nivolumab [95% confidence interval (CI), 5,5–9,1] and 5.1 months in patients treated with chemotherapy (95% CI 4.0–6.0), which translated into statistically significant improvement in overall survival (hazard ratio for death, 0.70; 97.73% CI 0.51–0.96; p = 0.01). The response rate was nearly two-fold higher in the nivolumab group (13.3% *vs* 5.8%), with 1-year survival rates higher by 19% (36.0% *vs* 16.6%). No difference regarding progression-free survival [2.0 months for nivolumab *vs* 2.3 months for standard therapy (hazard ratio for disease progression or death, 0.89; 95% CI 0.70–1.13; p = 0.32)]. Nivolumab treatment was also associated with lower risk of adverse events (all grades 58.9% *vs* 77.5%; grade 3 or 4 13.1% *vs* 35.1%) and better quality-of-life measures during therapy.

Presented data are first randomized phase 3 trial, which show superiority over standard chemotherapy in recurrent, platinum refractory squamous head and neck cancer, and determined Food and Drug Administration (FDA) to approve nivolumab for this setting. Up to now, possible therapies for patients with progression within 6 months after systemic platinum-based therapy in radical (neoadjuvant, adjuvant) or palliative setting typically included methotrexate, paclitaxel, docetaxel, cetuximab or 5-fluorouracil. However, no high-quality evidence proved positive impact of such chemotherapy on an overall survival. The results from accomplished phase 2 and 3 trials are disappointing, with reported median overall survival between 3 and 7 months. Even novel agents, such as afatinib, offers inconsiderable improvement in median progression free survival without unambiguous effect on overall survival. Nivolumab should be therefore considered as a new standard of care in this population. Similar effects of programmed cell death protein 1 (PD-1) modulation were shown for pembrolizumab in a phase 1b trial KEYNOTE-012 [2], which also led to FDA approval. Several ongoing trials with different immunotherapy drugs and their combinations, with or without chemotherapy, are ongoing and offers possible further advancements in systemic therapy of squamous head and neck carcinoma.

Immunotherapy in a 1st-line treatment of PD-L1 positive non-small cell lungs cancer (NSCLC)

Rapid development in the field of immuno-oncology led to establishing checkpoint inhibitors as a standard treatment for squamous and non-squamous NSCLC in a 2nd-line setting. Recently, in an article published on the 10th of November in New England Journal of Medicine, Reck et al. [3] presented results from phase 3 trial KEYNOTE-024 comparing pembrolizumab and platinum doublet-chemotherapy in patients with previously untreated advanced NSCLC exhibiting at least 50% expression of programmed death ligand-1 (PD-L1). Patients with both squamous and non-squamous tumor histology type, without mutations in the epidermal growth factor receptor (*EGFR*) gene or translocation of the anaplastic lymphoma kinase (*ALK*) gene, received pembrolizumab at a fixed dose of 200 mg per 3 weeks for up to 35 doses or investigator's choice of platinum-based doublet chemotherapy (cisplatin/carboplatin with pemetrexed, vinorelbine, gemcitabine or paclitaxel) for 4 to 6 cycles. Patients who progressed during or after chemotherapy were offered crossover to pembrolizumab, if eligible. The study was halted at the time of second interim analysis, due to significantly longer overall survival in the pembrolizumab group than in chemotherapy group (hazard ratio for death, 0.60; 95% CI 0.41–0.89; p = 0.005), with 6-monts survival rate of 80.2% with pembrolizumab *versus* 72.4%

with chemotherapy and response rates 44.8% *versus* 27.8%, respectively. Progression-free survival was also significantly prolonged in the pembrolizumab group — 10.3 months *versus* 6 months in the chemotherapy group (hazard ratio for disease progression or death, 0.50; 95% CI 0.37–0.68; $p < 0.001$). Grade 3, 4 and 5 treatment-related adverse events were less frequent in the pembrolizumab group (73.4% *versus* 90.0% for all grades and 26.6% *versus* 53.3% for grades 3, 4 and 5). Results were consistent both in squamous and non-squamous histological subtypes.

Last decade of research led only to limited changes in the 1st-line treatment of advanced NSCLC, with clear benefit limited mostly to a group of patients with *EGFR* gene mutations or *ALK* and *ROS1* genes rearrangements, that are found in only up to 15% of all patients. Presented results may change 1st line standard-of-care in another 20–30% of patients, with PD-L1 exhibited in at least 50% of tumor cells. In this group pembrolizumab resulted in improvement in overall survival, progression-free survival, response rate and lower rates of adverse events. Also, additional data from KEYNOTE-024 presented at the 17th World Conference on Lung Cancer in Vienna showed improvement in quality of life (QoL) and in the time to deterioration of symptoms in the pembrolizumab group compared to chemotherapy. Therefore, pembrolizumab can be considered treatment of choice for patients with advanced NSCLC with PD-L1 expressed in at least 50% of tumors cells. Other ongoing studies, evaluating role of dual immune checkpoint inhibitors or immunotherapy combined with chemotherapy, offers further possibilities for changes in the 1st-line treatment of NSCLC.

Longer-interval of zolendronic acid as effective as standard dosing

Despite common recognition of zolendronic acid as a basic therapy for prevention of skeletal-related adverse events and treatment of patients with bone metastases, currently use dosing intervals lacks evidence-based background. Several studies investigated less intensive dosing intervals, mostly reporting outcomes comparable to those of the standard dosing. Himelstein et al. [4] published in an 3rd January edition of "Journal of American Medical Association" results from non-inferiority trial comparing standard treatment every 4 weeks to alternative schedule of zolendronic acid every 12 weeks. The study included patients with bone metastases from breast cancer, prostate cancer and multiple myeloma. The primary end point was incidence of at least one skeletal-related event (clinical fracture, spinal cord compression, need of bone irradiation or surgical procedure). After the median follow-up of 1.2 years, 29.5% patients receiving zolendronic acid every 4 weeks and 28.6% patients receiving zolendronic acid every 12 weeks experienced at least 1 skeletal-related event. According to preplanned intention-to-treat (ITT) with a Cochran-Mantel-Haenszel test, zolendronic acid administered every 12 weeks was noninferior to standard dosing (risk difference, –0.3% [1-sided 95% CI −4% to ∞]; $p < 0.001$ for noninferiority). The effect was consistent in all neoplasms included in the study. No significant differences in mean pain scores were seen during the study ($p > 0.001$). However, there was a statistical trend for increased risk of osteonecrosis of the jaw (2% *vs* 1%, $p = 0.08$) and a statistically significant higher risk for developing increased creatinine level (when compared to baseline) (19.9% *vs* 15.5%; $p = 0.02$) among patients receiving zolendronic acid every 4 weeks compared to those receiving every 12 weeks.

The study results show, that 12-week interval of zolendronic acid administration should be considered as an option of skeletal-related event prevention for patients with bone metastases from multiple myeloma, breast cancer and prostate cancer. Considering universal usage of zolendronic acid, this could translate into relevant changes in practice, especially in resource-limited conditions and in palliative setting, when over-medication should be discouraged. Further analyses from the presented study, including cost-effectiveness analyses, should bring additional insight into optimal zolendronic acid dosing interval.

Increased survival with methylnaltrexon treatment in patients with advanced cancer and opioid-induced constipation

According to the World Health Organization (WHO) analgesic ladder, opioids are the basis of analgetic management of patients with medium and severe cancer-related pain. One of the most important opioid mechanism of action include agonizing effect on μ-opioid receptor (MOR). However, *in vitro* and *in vivo* data suggest that MOR antagonists might inhibit cancer progression. In an article published on the 29th August 2016 in "Annals of Oncology", Janku et al. [5] published results from pooled data analysis of overall survival from two randomized studies evaluating methylnaltrexone (MNTX), a peripheral MOR antagonist, in the treatment of opioid-induced constipation in advanced cancer patients. Both trials compared MNTX given subcutaneously and pla cebo, with a possible crossover to MNTX from placebo after initial double-blinded phase.

A statistically significant prolongation in median overall survival was seen in MNTX group when compared to placebo [76 days (95% CI 43–109) *vs* 56 days (95% CI 43–69; p = 0.033), respectively]. Even more noteworthy difference was seen in patients who responded to MNTX (which was defined as an effective laxation) compared to patients not responding [118 days (95% CI 59–177) *vs* 55 days (95% CI 40–70; p< 0.001)]. In a multivariable analyses response to therapy was independent prognostic factor for increased OS (hazard ratio 0.47; 95% CI 0.29–0.76; p = 0.002). No difference in overall survival between MNTX and placebo was seen in patients with diseases other than cancer, who were also treated in these studies (p = 0.88).

Presented data support existence of clinically important relationship between opioids, MOR and cancer progression. Several limitations, such as retrospective character or lack of survival endpoints in the design of original trials, restricts drawing strong conclusions. Available preclinical data about proangiogenic effects of morphine or possible epithelial-mesenchymal transition induced by MOR activation, as well as retrospective clinical data correlating opioid use with shorter progression-free survival in prostate cancer patients or with higher risk of cancer recurrence after resection of lung cancer, warrant the need for further studies. The role of MNTX as an adjuvant drug for opioid-induced constipation is indisputable, despite high costs of the therapy. However, application of MNTX as an anticancer therapy remains dubious and should be carefully evaluated in prospective trials.

Superior progression-free survival achieved with cabozantinib in the 1st-line treatment of metastatic renal cell carcinoma

First decade of XXI century brought tremendous evolution into the treatment of metastatic renal cell carcinoma (mRCC). Better understanding of molecular biology led to the introduction of tyrosine kinase inhibitors (TKI), such as sunitinib or sorafenib, and inhibitors of mTOR signalling pathway (everolimus and temisirolimus). In few subsequent years additional TKIs (pazopanib, axitinib) established their role in the available armamentarium. Last two years brought important changes into the 2nd-line setting, with an introduction of immune check point inhibitors (nivolumab), novel TKIs (cabozantinib) and their combination with mTOR inhibitors (lenvatinib + everolimus). Recent data from CABOSUN study, published by Choueiri et al. [6] on the 13th October in "Annals of Oncology", are signs of changes that may also affect the 1st-line treatment of advanced renal cancer. CABOSUN, a randomised phase 2 trial, compared standard-of-therapy sunitinib 50 mg/daily with a novel TKI cabozantinib 60 mg/daily in 1st-line treatment of patients with mRCC and intermediate or poor prognosis according to the International Metastatic Renal Cell Carcinoma Database Consortium criteria (also known as Heng criteria).The primary end point of the study, progression free survival, was 8.2 months with cabozantinib (95% CI 6.2–8.8 months) and 5.6 months with sunitinib (95% CI 3.4–8.1 months), with translated into 34% reduction of disease progression rate (adjusted hazard risk for progression or death, 0.66; 95% CI 0.46–0.95; one-sided p = 0.012). Also, overall response rate was higher in cabozantinib group [46% (95% CI 34–57%) *vs* 18% (95% CI 10–28%)]. Reporter median overall survival reached 30.3 months (95% CI 14.6–35.0) in patients treated with cabozantinib and 21.8 months (95% CI 16.3–27.0) in patients treated with sunitinib, a difference that was statistically non-significant (adjusted hazard ratio, 0.80; 95% CI 0.50–1.26). Rates of adverse events were similar, with 99% patients experiencing any grade events in both groups. The incidence of grade 3 and 4 events were 67% in cabozantinib arm and 68% in sunitinib group. Characteristics of occurring toxicities were similar, with hypertension being most common grade 3 and 4 adverse event in both drugs.

Presented results, if confirmed in a randomized phase 3 trial, might be a game-changer in the 1st-line treatment of mRCC. TKI treatment, even if initially successful, nearly inevitably leads to the development of resistance, which lead to cancer progression. One of the possible TKI resistance mechanisms include bypassing VEGF inhibition via MET signaling pathway and AXL upregulation. Cabozantinib, with a spectrum of action covering not only VEGF, but also MET and AXL inhibition, has a potential to prevent or delay development of such TKI resistance. Other intensively studied possibilities of improving the 1st-line treatment of patients with mRCC include combination of currently used therapeutic options with immunotherapy (i.e. TKIs combined with immunotherapy) and double immune checkpoint inhibition (combination of PD-1 and CTLA-4 antagonists). Preliminary data regarding such solutions, with responses seen in up to 70% of patients and median overall survivals exceeding 30 months, are promising. In the most optimistic variant, we may see changes as deep and as profound as those seen with the introduction of TKIs.

References

1. Ferris RL, Blumenschein G, Fayette J et al. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. N Engl J Med 2016; 375: 1856–1867.
2. Laura QMC, Robert H, Shilpa G et al. Antitumor Activity of Pembrolizumab in Biomarker-Unselected Patients With Recurrent and/or Metastatic Head and Neck Squamous Cell Carcinoma: Results From the Phase Ib KEYNOTE-012 Expansion Cohort. J Clin Oncol 2016; 34: 3838–3845.
3. Reck M, Rodríguez-Abreu D, Robinson AG et al. Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer. N Engl J Med 2016; 375: 1823–1833.
4. Himelstein AL, Foster JC, Khatcheressian JL et al. Effect of Longer-Interval vs Standard Dosing of Zoledronic Acid on Skeletal Events in Patients With Bone Metastases: A Randomized Clinical Trial. JAMA 2017; 317: 48–58.
5. Janku F, Johnson LK, Karp DD, Atkins JT, Singleton PA, Moss J. Treatment with methylnaltrexone is associated with increased survival in patients with advanced cancer. Ann Oncol 2016; 27: 2032–2038.
6. Choueiri TK, Halabi S, Sanford B et al. CABOzantinib versus SUNitinib (CABOSUN) as initial targeted therapy for patients with metastatic renal cell carcinoma (mRCC) of poor and intermediate risk groups: Results from ALLIANCE A031203 trial. Ann Oncol 2016; 27 (suppl 6): LBA30_pr.