New England Journal of Medicine

Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer

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New England Journal of Medicine. 2015;May 31,DOI: 10.1056/NEJMoa1504627

Background: For patients with advanced squamous-cell non–small-cell lung cancer (NSCLC) with progression during or after first-line chemotherapy, there are limited treatment options. This randomised, open-label, international phase 3 study evaluated the efficacy and safety of nivolumab, a human IgG4 programmed death 1 (PD-1) immune-checkpoint inhibitory antibody, compared with docetaxel.

Methods: We randomly assigned 272 patients to receive nivolumab at 3mg per kg body weight every two weeks, or docetaxel at 75mg per square meter of body-surface area every three weeks. The primary end-point was overall survival (OS).

Results: The median OS was 9.2 months (95% confidence interval [CI], 7.3 to 13.3) with nivolumab vs 6.0 months with docetaxel (95% CI, 5.1 to 7.3). The risk of death was 41% lower with nivolumab than docetaxel (hazard ratio, 0.59; 95% CI, 0.44 to 0.79; P<0.001). At one year, the OS was 42% (95% CI, 34 to 50) with nivolumab vs 24% with docetaxel (95% CI, 17 to 31). The response rate was 20% with nivolumab vs 9% with docetaxel (P=0.008). The median progression-free survival was 3.5 months with nivolumab vs 2.8 months with docetaxel (hazard ratio for death or disease progression, 0.62; 95% CI, 0.47 to 0.81; P<0.001). The expression of the PD-1 ligand (PD-L1) was neither prognostic nor predictive of benefit. Treatment-related adverse events of grade 3 or 4 were reported in 7% of the patients in the nivolumab group compared with 55% the docetaxel group.

Conclusion: Among patients with advanced previously treated squamous-cell NSCLC, OS, response rate and progression-free survival were significantly better with nivolumab than with docetaxel, regardless of PD-L1 expression level. (Funded by Bristol-Myers Squibb; CheckMate 017).

Reviewer's comments: We are at a cross-road on the management of non-small cell lung cancers due to developments in biological markers and targeted therapies. Encouraging results on the use of these agents with different mechanism of action and limited side effect concerns from currently on-going trials, even in previously treated relapsed non-small cell lung cancer, is encouraging. In 2015, targeted agents are valuable only for a selected group of lung cancer patients. Management with surgery, radiotherapy and conventional cytotoxic chemotherapy remains the backbone for majority. Docetaxel continues to be a universally accepted standard second-line systemic therapy, with limited benefits and high incidence of toxicities and an average median survival of ~9 months. Therefore, we need to explore new therapies to improve the outcome of most of patients suffering from advanced/metastatic non-small cell lung cancer. Like CheckMate 057 for non-squamous cell lung cancer, these results from CheckMate 017 with the use of nivolumab in squamous cell cancer are promising and represent a major step in right direction. However, one must not lose sight of the fact that these results are interim analyses and a relatively short follow-up. CheckMate 017 is a well-conceived and well-conducted trial with a large number of patients recruited, and has balanced characteristics within both arms. The results clearly show impressive and persistent improvement in PFS and OS with nivolumab. It is difficult to decide with any confidence whether nivolumab is more effective in squamous cell (HR 0.59, p=0.00025) that non-squamous cell cancer (HR 0.73, p=0.0015). Due to relatively smaller benefit with docetaxel, the overall incremental benefit seems to be greater with nivolumab in the squamous cell subtype. Therefore, for squamous cell histological subtype with which docetaxel does poorly, nivolumab could be the better option, except for the non-squamous subtype, and is now a new option. Further follow-up results could provide better estimates of its long-term survival gains.

The above results provide strong evidence that we could have a new class of drug for management of non-small cell lung cancer. Many other agents with different mechanism of actions are undergoing evaluation either on their own or in combination with docetaxel, for example anti-angiogenics, such as ramucirumab and nintedanib. These agents may be effective against non-small cell lung cancer. The outlook looks promising for a new option. Therefore, selection of the appropriate agent for the individual patient will be important. Its remains unclear whether anti PD-L1 or anti PD-1 will have the edge. The cost, the level of PD-L1 expression and toxicity may influence its wider use. The MHRA has already given approval to nivolumab in early access to medicine (EAMS) for the treatment of locally advanced or metastatic squamous cell lung cancer after prior chemotherapy in UK. – SU

Journal of Clinical Oncology

BEST: A Randomised Phase II Study of VEGF, RAF Kinase, and Mammalian Target of Rapamycin Combination Targeted Therapy with Bevacizumab, Sorafenib, and Temsirolimus in Advanced Renal Cell Carcinoma – A Trial of the ECOG-ACRIN Cancer Research Group (E2804)

Flaherty KT, Manola JB, Pins M et al. Journal of Clinical Oncology. 2015; Jul 20;33(21):2384-91.

Purpose: From evidence that resistance to vascular endothelial growth factor (VEGF) receptor inhibition is caused by hypoxia-driven residual VEGF and other

proangiogenic factors, combinations of agents from these classes might improve treatment outcomes relative to VEGF pathway blockade with single-agents.

Patients and Methods: A total of 361 patients with metastatic clear cell renal cell carcinoma were randomly assigned equally to arm A (bevacizumab monotherapy 10mg/kg intravenously [IV] every two weeks), B (bevacizumab 10mg/kg IV every two weeks and temsirolimus 25mg IV every week), C (bevacizumab 5mg/kg IV every two weeks and sorafenib 200mg orally twice daily on days 1 to 5, 8 to 12, 15 to 19, and 22 to 26), or D (sorafenib 200mg twice daily and temsirolimus 25mg IV weekly). Progression-free survival was the primary end-point.

Results: Among 331 eligible treated patients, median PFS was 7.5 months for bevacizumab alone (90% CI, 5.8 to 10.8 months), 7.6 months for bevacizumab plus temsirolimus (90% CI, 6.7 to 9.2 months), 9.2 months for bevacizumab plus sorafenib (90% CI, 7.5 to 11.4 months), and 7.4 months for sorafenib plus temsirolimus (90% CI, 5.6 to 7.9 months). Hazard ratios from stratified Cox proportional hazards models were 1.01, 0.89, and 1.07 (with respective P values of 0.95, 0.49, and 0.68) for the three combinations, respectively, compared with bevacizumab alone. Adverse events did not differ significantly among treatment arms.

Conclusion: The activity of sorafenib, temsirolimus, and bevacizumab administered in double combinations did not significantly improve median progression-free survival in comparison with bevacizumab monotherapy.

Reviewer's opinion: The treatment of metastatic renal cell carcinoma (RCC), particularly the clear cell subtype, has been transformed in recent years by the introduction of both a monoclonal antibody and small-molecule tyrosine kinase inhibitors targeted against tumour angiogenesis (bevacizumab, sunitinib, sorafenib, pazopanib, axitinib). The rationale for anti-angiogenic treatment is that clear-cell RCC typically harbours deleterious somatic mutations in the VHL gene that lead to upregulation of HIF-1a and pro-angiogenic factors, such as VEGF and PDGFR. Drugs (e.g. temsirolimus and everolimus) interfering with the mTOR/MEK/PI3K/ERK pathway are also involved in advanced RCC. In clinical practice, these drugs are used sequentially as single-agent therapy (everolimus or axitinib typically as second-line therapy). This study explored the feasibility, safety and efficacy of combinations of anti-angiogenic and mTOR targeted therapies. The study population was restricted to clear-cell histology, patients who had only received one prior line of immunotherapy (not anti-angiogenic therapy). Approximately three-quarters of the patients were in the MSKCC good or intermediate risk categories, half of patients had extensive skeletal or hepatic metastases, and nearly one-third of patients had irresectable but non-metastatic disease. Combinational therapy had no benefit in terms of efficacy (% patients with stable disease at six months, median PFS and OS). Of some interest, the median overall survival approached 2.5 years with single-agent bevacizumab, although this is difficult to interpret without information on patients' subsequent therapies. There was evidence of additional benefit in terms of objective response rate when either temsirolimus or sorafenib was added to bevacizumab. However, the clinical importance of this remains uncertain in the absence of data on symptomatic improvement in these patients. Dose intensities of sorafenib and temsirolimus were suboptimal, particularly early in treatment, with doses lower than those administered in the pivotal Phase III single-agent trials. The amount of severe or life-threatening toxicity was 30-40% higher with combination therapy. This study showed no synergy between these anti-angiogenic and anti-mTOR therapies, or any delayed development of resistance with intolerably high rates of toxicity. The standard of care remains as sequential single-agent treatment, although we have to see whether the new generation of immunotherapeutic strategies, such as immune-checkpoint blockade (e.g. anti PD-1), would do better combined with anti-angiogenic therapy. This combination is particularly intriguing in view of the immune-stimulating effects of sunitinib, such as reduction in circulating myeloid-derived-suppressor-cells. – AR