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ESMO 2016 Congress: Three of the most important studies in the field of immuno-oncology

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ABSTRACT

The 2016 European Society for Medical Oncology (ESMO) annual congress highlighted the latest discoveries in different types of cancer research. Advances in cancer immunotherapy in recent years have caused a paradigm shift in cancer management. Numerous clinical trials results with immunotherapeutic agents (e.g., anti-CTLA-4, anti-PD-1) were presented at the annual ESMO meeting, which will change the treatment approach, especially for patients with melanoma, lung cancer, and head and neck cancer. In this paper three selected studies dedicated to the immuno-oncology field, which were presented during the meeting, will be discussed.

Key words: ESMO congress, immuno-oncology, ipilimumab, pembrolizumab, nivolumab

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Introduction

Immunotherapy was the main star at the European Society for Medical Oncology (ESMO) 2016 Congress in Copenhagen, the leading oncology meeting in Europe [1]. The immuno-oncology field is rapidly evolving. Immunotherapy can provide long-term cancer control and is usually characterised by lower incidence of acute toxicity to normal tissue compared to chemotherapy. In the era of multiple known and ongoing clinical trials dedicated to immunotherapy, and a number of already approved immune checkpoint inhibitors (e.g., anti-CTLA-4, anti-PD-1, anti-PD-L1), finding appropriate biomarkers is mandatory for medical and economical reasons. During the Congress there was also a debate on this subject [1]. And the usefulness of the most promising PD-L1 protein expression is still uncertain [1]. It was difficult to choose only three studies in the immuno-oncology field. Finally, after short consideration, data which will certainly have a meaningful influence on clinical practice are presented below.

Melanoma (ipilimumab) — adjuvant treatment

Ipilimumab is a human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody approved by the U.S. Food and Drug Administration (FDA) for treatment of unresectable or metastatic melanoma (in 2011) and adjuvant treatment of patients with cutaneous melanoma with 'pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy' (in 2015) [2]. Moreover, nivolumab and pembrolizumab as monotherapy and nivolumab in combination with ipilimumab are now approved treatments for advanced melanoma.

Patients with stage III (IIIA–IIIC) melanoma, who underwent lymphadenectomy within 12 weeks before randomisation were included in a randomised, double-blind, phase 3 trial [3, 4]. Patients received ipilimumab (10 mg/kg) or placebo every three weeks for four doses, then every three months for up to three years or shorter if, for example, recurrence of the disease (28.7% and 59.5%, ipilimumab and placebo group,

respectively) or unacceptable toxicity (53.3% and 4.6%, ipilimumab and placebo group, respectively) was noted [3, 4]. No previous systemic therapy for melanoma was allowed. At least one maintenance dose was received by 42% and 70% of patients in the ipilimumab and placebo group, respectively [3, 4]. Finally, 13.4% of patients in the ipilimumab group completed the three-year treatment period [3]. At a median of 5.3 years' follow-up the rate of recurrence-free survival and distant metastasis-free survival at five years was approximately 10.5% higher in the anti-CTLA-4 group [3, 4]. The rate of overall survival at five years was 11% higher in the immunotherapy arm (HR 0.72; 95.1% CI, 0.58–0.88; P = 0.001) [3, 4]. The trial supported the approval for ipilimumab in this setting.

Almost everyone who received anti-CTLA-4 had toxicity of any grade. Grade 3/4 adverse events (AEs) were seen in 54.1% of patients in the ipilimumab group, including 41.6% that were immune-related with the most common being gastrointestinal, followed by hepatic and endocrine [3, 4]. Five deaths before the start of maintenance therapy with ipilimumab were noted from colitis, myocarditis, and multiorgan failure [3, 4].

Also, interferon alpha is approved for the adjuvant treatment of melanoma patients [5–7].

Head and neck (nivolumab) — new hope

Nivolumab is a human IgG4 anti-PD-1 monoclonal antibody. It is indicated for the treatment of patients with unresectable or metastatic melanoma in monotherapy or in combination with ipilimumab, advanced renal cell carcinoma, who have received prior anti-angiogenic therapy, classical Hodgkin lymphoma that has relapsed or progressed after autologous haematopoietic stem cell transplantation (HSCT), and post-transplantation brentuximab vedotin, and finally metastatic non-small cell lung cancer and progression on or after platinum-based chemotherapy [8]. Patients with epidermal growth factor receptor gene (EGFR) or translocation of the anaplastic lymphoma kinase gene (ALK) genomic tumour aberrations should have disease progression on dedicated targeted therapy prior to receiving nivolumab [8]. Moreover, in September 2016 the FDA modified the dosage regimen for nivolumab for renal cell carcinoma, metastatic melanoma, and non-small cell lung cancer (240 mg intravenously every two weeks) [5]. In combination with ipilimumab for melanoma the dose remains the same, followed by nivolumab with a dose of 240 mg every two weeks [5].

For patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-based chemotherapy, pembrolizumab was approved in August 2016 by the FDA [5].

During the annual ESMO Congress the results of the Harrington et al. CheckMate 141 study using nivolumab for patients with head and neck cancer were presented [9]. The results were published in "The New England Journal of Medicine" [10]. It is a randomised, open-label phase 3 trial in which 361 patients with platinum-refractory, recurrent/metastatic squamous-cell carcinoma of the head and neck received treatment with nivolumab (3 mg/kg every two weeks) or a standard therapy (methotrexate, docetaxel, or cetuximab) [9, 10]. Cetuximab was administered in 13 cases [10]. Patients received radiotherapy (91.4%) and at least two lines of systemic treatment (54.5%) before randomisation [10]. Less than 30% of patients in each group had positive p16 status [10].

Nivolumab improved median overall survival of 2.4 months (hazard ratio for death, 0.70; 97.73% CI, 0.51–0.96; P = 0.01), and it was 7.5 months [10]. The highest median OS was noted among patients with p16-positive tumours treated with nivolumab, and it was 9.1 months [10]. The median follow-up time was 5.1 months [10]. No significant difference was noted with regard to the median progression-free survival, which was approximately two months for both groups [10]. The rate of progression-free survival at six months was higher of 9.8% in the nivolumab group [10]. For the response, patients had to wait at least two months in each cohort [10].

Treatment-related grade 3/4 AEs were more then 2.5 times more frequent in the standard therapy arm [10]. In the anti-PD-1 group, the most common AEs of any grade were fatigue, nausea, rash, decreased appetite, and pruritus [10]. Those who received standard of care had worse quality of life [9]. The results suggest that study participants receiving immunotherapy had less pain, fatigue, and dyspnea compared with standard-therapy [9]. Treatment-related deaths were reported in two patients in the nivolumab group and in one in the standard-therapy group [10].

The early observations from this study suggest that patients with tumour PD-L1 expression (≥ 1%) or/and p16-positive tumours may achieve even better results with nivolumab treatment [10].

We still need to find biomarkers to identify the patients most likely to benefit from anti-PD-1 therapy to avoid unnecessary adverse events and costs, and to offer patients the best treatment possible.

Non-small cell lung cancer (pembrolizumab) — first line

In 2014, the FDA granted accelerated approval to the first anti-PD-1 drug, known as pembrolizumab, for the treatment of patients with unresectable or

metastatic melanoma and disease progression following ipilimumab, and those with *BRAF V600* mutation should have disease progression on BRAF inhibitor [5]. Pembrolizumab is also approved for patients with HNSCC in indications mentioned above and in the US and EU for previously treated, PD-L1-expressing advanced non-small cell lung cancer (NSCLC) [5].

KEYNOTE-024 (NCT02142738), an open-label, phase 3 study of pembrolizumab *vs.* platinum-doublet chemotherapy as first-line therapy for advanced NSCLC with PD-L1 expression on at least 50% of tumour cells, without treatable EGFR mutations or ALK translocations was presented at the ESMO 2016 Congress in Copenhagen [11–13].

Patients (n = 305) were randomised to pembrolizumab (200 mg every 3 weeks) or 4–6 cycles of carboplatin or cisplatin with pemetrexed, carboplatin, or cisplatin with gemcitabine, or carboplatin with paclitaxel, also with optional pemetrexed maintenance for nonsquamous NSCLC [12, 13]. The most common scheme of chemotherapy was carboplatin plus pemetrexed [13].

After a median follow-up of 11.2 months, 48.1% of patients remained on anti-PD-1, 10% remained on chemotherapy, and 43.7% crossed over to pembrolizumab after disease progression. A significant improvement in the median PFS in the pembrolizumab arm was noted as compared to chemotherapy schemes (HR 0.50, 95% CI 0.37–0.68, P < 0.001; median 10.3 *vs.* 6.0 months) [12]. The six-month rates of OS were 80.2% and 72.4% in the pembrolizumab and chemotherapy group, respectively (HR 0.60, 95% CI, 0.41–0.89, P = 0.005). Median overall survival was not reached [13]. Moreover, immunotherapy was also related with longer response duration and higher objective response rate, for which patients had to wait 2.2 months in both cohorts [12, 13]. Pembrolizumab was better tolerated, with lower incidence of AEs [12]. Twice as often Grade 3 to 5 treatment-related AEs in the chemotherapy group were noted (53.3%) [13]. And among them were diarrhoea and pneumonitis in the anti-PD-1 group and, for example, anaemia, neutropenia, and decreased platelet count in the chemotherapy cohort [13].

According to these findings, the potential use of immunotherapy in this setting should be based on the expression level of PD-L1. Based on mentioned study, pembrolizumab was approved in first-line treatment of metastatic NSCLC in October, 2016 by FDA [5].

It is worth mentioning that the results from a randomised, phase 2 cohort of the open-label KEYNOTE-021 study in which patients with chemotherapy-naïve, stage IIIB or IV, non-squamous NSCLC without oncogenic alterations were assigned to two groups: pembrolizumab plus chemotherapy (four cycles of pembrolizumab, pemetrexed, and carboplatin, followed by pembrolizumab for 24 months and optional indefinite pemetrexed maintenance therapy) and chemotherapy-alone (four cycles pemetrexed, carboplatin, followed by optional indefinite pemetrexed maintenance therapy) are available [14]. The findings from this study, which suggest that a combination of pembrolizumab plus chemotherapy could be an effective and tolerable first-line treatment option for patients with advanced non-squamous NSCLC, are currently under an ongoing phase 3 study investigation, and will not be discussed in this paper [14].

Moreover, at the time of preparing this article, the FDA approved atezolizumab for the treatment of patients with metastatic NSCLC, whose disease progressed during or following platinum-containing chemotherapy [5]. Atezolizumab is the first approved programmed death-ligand 1 (PD-L1) blocking antibody. Those with EGFR or ALK genomic tumour aberrations should have disease progression on dedicated targeted therapy [5]. The decision of approval was based on the results of the OAK and POPLAR study [5].

Conclusions

The ESMO 2016 Congress in Copenhagen brought new information across therapeutic areas, mostly in the immuno-oncology field. Advances in cancer immunotherapy had a huge influence on cancer management. Some results presented above confirmed earlier findings, and some of them are a prelude to obtaining a new treatment approach. Certainly, this is not the end of new breakthrough immunological therapies.

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