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ESMO 2018—personal highlights

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Summary This article intends to summarize personal highlights of the ESMO (European Society for Medical Oncology) 2018 meeting and does not aim to give a comprehensive overview. We will summarize the most recent presented data on the treatment of non-small cell lung establishing first-line combinational therapies (chemotherapy backbone with immunotherapy) as standard of care. Furthermore highly practice relevant data on the treatment of recurrent or metastatic head and neck squamous cell carcinoma were presented. Next the treatment landscape of metastatic prostate cancer is changing rapidly and some new aspects in metastatic disease are reported.

Keywords European Society for Medical Oncology meeting · Head and neck squamous cell carcinoma · Non-small cell lung cancer · Prostate cancer · Review

Introduction

The ESMO (European Society for Medical Oncology) 2018 meeting took place in October in Munich with approximately 28,000 international speakers and attendees. The congress was held under the tagline "securing access to optimal cancer care" and intended to bridge basic research and clinical oncological therapy. Recent advances in characterization of the tumor microenvironment gave the basics for the development of combinational strategies and first clinical data were presented at this year's meeting. It is becoming apparent that primary or secondary resistance against therapies can be most likely overcome via rationale combinational therapies.

Advanced stage non-small cell lung cancer (NSCLC)

Personal highlights of NSCLC therapy were the presentations of the IMpower 130 and 132 studies, both phase III investigating the combination of immunotherapy (atezolizumab) plus chemotherapy versus chemotherapy alone in the 1st line therapy of advanced stage non-squamous NSCLC [1, 2]. Importantly, among IMpower 132 and 130 the chemotherapy backbone and maintenance strategy varies: IMpower 132 included in analogy to the KEYNOTE-189 [3] study the combination of platinum/pemetrexed combined with atezolizumab versus platinum/pemetrexed alone and in the maintenance setting atezolizumab and pemetrexed were continued until disease progression versus pemetrexed alone maintenance. In contrast, IMpower 130 investigates the use of carboplatin/nab–paclitaxel plus atezolizumab (experimental arm) versus carboplatin/nab–paclitaxel alone and in the maintenance setting atezolizumab versus possible switch maintenance. Both studies showed a significant prolongation of progression-free survival (PFS; IMpower 132: PFS = 7.6 in combination chemotherapy/atezolizumab versus 5.2 months in chemotherapy alone; hazard ratio [HR] = 0.60, 95% confidence interval [CI]: 0.49–0.72; $p < 0.0001$; IMpower 130: PFS = 7.0 in combination chemotherapy/

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atezolizumab versus 5.5 months in chemotherapy alone; hazard ratio [HR] = 0.64, 95% CI: 0.54–0.77; $p < 0.0001$). Furthermore the PFS benefit observed in IMpower 130 study translated to a significant prolongation of overall survival (OS; median OS was 18.6 months for the combinational arm compared with 13.9 months for the chemotherapy alone arm HR = 0.79; 95% CI, 0.64–0.98, $p = 0.033$). While in the IMpower 132 only a numerical improvement of 4.5 months OS was observed, at this interim analysis statistical significance has not yet been met (median OS 18.1 versus 13.6 months; HR = 0.81, 95% CI: 0.64–1.03; $p = 0.0797$). Updated OS data for the IMpower 132 will be presented in 2019.

In conclusion both studies highlighted that combinational therapy of chemotherapy and immunotherapy is the new standard of care in advanced stage NSCLC without driver alterations and these therapies were already incorporated into the most recent ESMO guidelines [4]. The optimal therapeutic combination and predictive biomarker has not yet been identified; however PD-L1 expression crystallizes as the best biomarker at the moment. Furthermore in our opinion the maintenance strategy is an important issue in light of the IMpower 130 showing an OS benefit including a switch maintenance strategy to pemetrexed and in the experimental arm the continuation of atezolizumab. Therefore I think that however highly speculative also continuation with PD-1/PD-L1 maintenance monotherapy could be effective and opens the question if combinational maintenance therapy is necessary and hopefully these open questions will be answered at the next meetings this year.

Head and neck squamous cell carcinoma (HNSCC)

"The use of immunotherapy in recurrent or metastatic head and neck squamous cell carcinoma is expanding" was the heading of the daily ESMO news on 23 October 2018 based on the results of the presented KEYNOTE-048 study. KEYNOTE-048 investigated whether pembrolizumab could prolong OS compared to standard treatment and included patients with HNSCC who had not received prior therapy for recurrent or metastatic disease [5]. Thereby, the study investigated two important research questions: (1) if immunotherapy monotherapy stratified by PD-L1 combined positive score (CPS, defined as PD-L1 expression on tumor cells as well as on surrounding cells) is more effective compared to standard therapy and (2) if the addition of immunotherapy to standard therapy increases efficacy. The study protocol randomly allocated patients in a 1:1:1 ratio to: (1) standard treatment with platinum-based chemotherapy (5-fluorouracil with cisplatin or carboplatin) and cetuximab (EXTREME control group); (2) pembrolizumab alone or (3) a novel combination of pembrolizumab and platinum-based chemotherapy. The study showed that in patients with CPS >20% OS was significantly longer with pembrolizumab (14.9 months) than standard treatment (10.7 months, HR 0.61, $p = 0.0007$). Also in the CPS >1% OS was prolonged (12.3 months versus 10.3 months, HR 0.78, $p = 0.0086$). Interestingly only some 23.3% responded to pembrolizumab and 36.1% responded to standard treatment (CPS >20%). Although pembrolizumab had a lower overall response rate, responses were substantially more durable (median response duration was longer with pembrolizumab (20.9 months) than standard therapy (4.5 months)).

Secondly the addition of pembrolizumab to chemotherapy compared to the standard EXTREME therapy showed that the OS was prolonged with the combination (13.0 months) versus standard care (10.7 months, HR 0.77, $p = 0.0034$). Response rates were 35.6% for the pembrolizumab combination and 36.3% for standard treatment. There was no difference in progression-free survival between groups (HR 0.92, 95% CI 0.77–1.10). Important to mention is that the side effects were as expected: pembrolizumab alone was less toxic than EXTREME and chemotherapy plus pembrolizumab was similar toxic as EXTREME.

Concluding, KEYNOTE-048 is the first study to show superior OS over the decade-old standard of care, platinum-based chemotherapy and cetuximab and will change treatment algorithm in HNSCC. Furthermore PD-L1 CPS score testing should be routinely measured in HNSCC.

Metastatic prostate cancer

Hormone-sensitive disease

According to the previously published LATITUDE trial abiraterone acetate improves OS for patients with high risk primary metastatic hormone sensitive prostate cancer (PCa) defined as Gleason score of 8 higher, three bone lesions or greater or the presence of measurable visceral metastasis (2/3 criteria have to be fulfilled) [6]. At the ESMO 2018 data on the Arm G of the STAMPEDE trial revealing the impact of abiraterone acetate + prednisone in 901 patients with both high-risk but also low-risk hormone sensitive primary metastatic PCa have been presented. In general, STAMPEDE is a multi-arm, multi-stage design trial, assessing various drugs and outcomes in patients starting on long-term ADT with M1 or high-risk M0 disease [7]. The primary endpoint of the study was to evaluate heterogeneity of abiraterone acetate + prednisone effect OS and failure-free survival (FFS). Of note, this study was a retrospective subgroups analysis. Nevertheless, data revealed that abiraterone acetate + prednisone treated patients had significant OS improvements in both high- (HR 0.54) and low-risk (HR 0.66) groups. Patients treated by abiraterone acetate + prednisone also benefited from prolonged FFS within both high- (HR 0.31) and low-

Fact box—take-home message

Chemotherapy and immunotherapy is standard of care in NSCLC:

- IMpower 132 study: platinum/pemetrexed combined with atezolizumab: PFS 7.6 vs. 5.2 months; OS 18.1 vs. 13.6 (n. s.; update pending)
- IMpower 130 study: carboplatin/nab-paclitaxel plus atezolizumab: PFS 7.0 vs. 5.5 months; OS 18.6 vs. 13.9 months*;

Chemotherapy and immunotherapy is standard of care in head and neck cancer:

- In patients with CPS ≥20% pembrolizumab monotherapy is a new standard of care.
- In CPS ≥1% the combination of pembrolizumab plus platinum chemotherapy should be used.

Prostate cancer:

- Abiraterone acetate + prednisone treated patients had significant OS improvements in both high- and low-risk groups.
- Prostate radiotherapy improved failure-free survival but not OS. Beneficial data of a subgroup analysis, however, support the concept of prostate radiation therapy + ADT in patients with less than 4 bone metastases and no visceral metastases.
- The simultaneous combination of abiraterone acetate and radium-223 should currently not administered.

risk groups (HR 0.238). In addition to OS and FFS skeletal-related events, PFS and PCa specific deaths were exmined.

According to the current guidelines of the European Society of Urology for men with newly diagnosed metastatic PCa systemic treatment with androgen deprivation therapy (ADT) and docetaxel-based chemotherapy or abiraterone acetate is recommended. At the ESMO 2018 Parker et al. presented a subanalysis of the STAMPEDE study investigating if radiotherapy (55 Gy) improves OS in men with newly diagnosed metastatic PCa. The study included 2061 patients (median age 68 years) newly diagnosed with metastatic PCa randomly allocated to standard treatment consisting of lifelong ADT + early docetaxel or ADT + radiotherapy to the prostate. Results showed that prostate radiotherapy improved failure-free survival (HR 0.68) but not OS (HR 0.92) in the whole group of patients [8].

However, interestingly subgroup analysis showed that radiotherapy improved OS in 32% of patients with a low burden of metastatic disease (HR = 0.68) defined as less than 4 bone metastases without visceral metastases.

Based on these data the authors of the study conclude that prostate radiotherapy in addition to ADT should now be a standard treatment option for men with oligometastatic disease.

Metastatic castrate resistant prostate cancer (mCRPC)

In past years the landscape of treatment options in patients with mCRPC has been extended. Beside chemotherapeutic options (docetaxel, cabazitaxel) next generations ADT like abiraterone acetate + prednisone or enzalutamide have proven clinical efficacy and are successfully used in daily routine [9]. Radium-223 is a targeted alpha-emitter, approved since 2013 for mCRPC with bone metastases [10]. Although the single substances are working effectively, one tries to combine these substances (or including new drugs) to further improve OS of mCRPC patients that currently ranges from 12 to 40 months after post hoc analysis of an international, early access, phase 3b open-label study suggested a survival benefit of radium-223 + abiraterone acetate/enzalutamide over radium-223 alone with no overlapping toxicity profiles [6].

In the ERA-223 study 806 specific asymptomatic or mildly symptomatic men with chemotherapy-naïve mCRPC and bone metastases (>2 bone metastases) in a 1:1 ratio of abiraterone acetate + prednisone plus radium-223 or abiraterone acetate + prednisone + placebo were enrolled [11]. The primary endpoint was symptomatic skeletal events-free survival (SSE-FS) defined as the need of external beam radiation therapy to relieve skeletal symptoms, new symptomatic pathologic fracture, spinal cord compression or surgical intervention. Concerning treatment outcomes, the primary endpoint was not met as median SSE-FS was 22.3 months with the combination therapy vs. 26.0 months in the abiraterone acetate monotherapy arm (HR 1.122). In addition, fractures occurred in 29% of patients in the combination group while only in 11% the monotherapy group although it is important to mention that many of the differences were actually not pathologic fractures, but rather related to osteoporosis. In contrast to the EAP program OS was not significantly different among the two treatment arms (HR 1.195).

To summarize, the simultaneous combination of abiraterone acetate and radium-223 should currently not be used; however, there is still a biologic rationale for the use of radium-223 once bone metastatic mCRPC patients progress on secondary androgen-deprivating substances.

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