Letter to the Editor

Dear Sir,

Presentations at this year's European Society for Medical Oncology congress (ESMO 2017), held in Madrid from 8–12 September, highlighted that it was clearly a very good year of exciting results in oncology and, in particular, immunotherapy. There were at least three important studies which will change clinical practice, but there were also important results in targeted therapy in lung cancer, which will lead to a new standard-of-care (SoC) for first-line therapy for patients with epidermal growth factor receptor mutant (EGFRm) advanced non-small cell lung cancer (NSCLC).

As announced in *The Daily Reporter* newspaper of the ESMO meeting, "consolidation immunotherapy offers new hope for patients with stage-III locally advanced NSCLC". Dr. Luis Paz-Are from Madrid presented results from the phase-III PACIFIC study of consolidation immunotherapy with durvalumab (PD-L1 targeting) for patients with stage-III locally advanced unresectable NSCLC who had not progressed following platinum-based doublet chemotherapy concomitant with radiotherapy [1]. 709 patients were randomized 2:1 to receive either durvalumab 10 mg/kg every 2 weeks up to 12 months or placebo. With a median follow-up of 14.5 months, median progression-free survival (PFS) was 16.8 months with durvalumab *versus* 5.6 months with placebo with a hazard ratio (HR) of 0.52 ($p<0.0001$). Severe adverse events (SAEs) were comparable in both arms [2].

Another important presentation, the FLAURA study, has defined a new SoC for first-line therapy for patients with EGFRm advanced NSCLC [3]. Osimertinib (80 mg p.o. once daily), a third-generation central nervous system (CNS) active EGFR tyrosine kinase inhibitor (EGFR-TKI) that inhibits both EGFRm and T790M resistance mutations, was superior to SoC gefitinib or erlotinib with a median PFS of 18.9 months over 10.2 months in the SoC arm [4]; HR 0.46 (95% confidence interval [CI] 0.37-0.57; $p<0.0001$). Interim overall survival (OS) results showed promising survival favoring osimertinib and the safety profiles were the same, with a lower discontinuation rate and a lower rate of AEs grades ≥3 with osimertinib. An interesting question was raised about the post-resection follow-up of localized lung cancers. Should we move away from computed tomography (CT) scans? There is no statistical difference in OS after 9 years of follow-up in patients who received minimal follow-up (clinical examination and chest X-ray) *versus* maximal follow-up (plus CT scan). A CT scan every 6 months is not useful during the first 2 years, but a yearly chest CT scan after 2 years to detect secondary primary tumors is important [5].

An important Presidential Symposium presentation was the first report of a randomized study comparing 3 cycles of neoadjuvant chemotherapy plus surgery (NACT-surgery) *versus* standard chemoradiotherapy (CRT) for locally advanced (stage IB2 to IIB) squamous cell cervical cancer [6]. This study from India randomized 633 patients (against 730 planned) during 12 years. The majority of patients had advanced disease, and radiotherapy or CRT was performed in arm A in the case of no response to chemotherapy, no surgery and bad prognostic factors post-operation. Surgery was performed in 71.8% of patients after 3 cycles and then 44.6% of patients finally received radiotherapy. Finally, CRT resulted in significantly higher 5-year disease-free survival compared with NACT-surgery

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(primary endpoint; 76.7% *vs* 69.3% of patients; HR 1.38; p=0.038) and there was no significant difference in 5-year OS between the two treatment arms. Also, the PFS results are clearly better with CRT for stage IIB disease; for stage IB2 and IIA disease, PFS is quite similar. NACT-surgery is not superior to standard CRT for locally advanced cervical cancer, and CRT is still the standard of treatment. A surgery approach could be proposed in some cases for stage IB2 or IIA.

Year follows year at ESMO, and so it was this year for melanoma! Last year was the year of the first report of immunotherapy in an adjuvant setting with ipilimumab [7]; this year, two major advances were presented, and one of them has already made the results of last year obsolete. The first tested targeted therapy (a bi-therapy BRAF/MEK inhibitor) in the adjuvant setting for patients with stage-III BRAF V600 mutated tumors. A randomized phase-3 trial study evaluated safety and efficacy of dabrafenib plus trametinib over double placebo for 12 months for patients with completely resected stage-III melanoma [8]. After a median follow-up of 2.8 years and 870 patients included, the study had met its primary endpoint, finding a significantly lower risk of recurrence with no new toxic effects. The estimated 3-year recurrence-free survival is 39% in the placebo group and 58% in the combination-therapy group (HR 0.47).

The second study compared two types of immunotherapy; CheckMate 238 is a randomized 1:1, phase 3, double-blind study evaluating the safety and efficacy of nivolumab over ipilimumab for patients with completely resected stage-IIIB-IV melanoma [9]. 906 patients were treated for up to 1 year or until disease recurrence. The results are encouraging, with a better recurrence-free survival of 66% in the nivolumab group *versus* 53% in the ipilimumab group at 18 months (HR 0.65; p<0.0001) with a significantly better tolerance profile. We can today argue that adjuvant interferon and ipilimumab therapy for melanoma is already in the past! The problem is the choice of the best adjuvant therapy for patients with BRAF V600 mutated tumor. Two key results were reported the same day in the *New England Journal of Medicine* [10, 11].

For metastatic renal cell carcinoma (mRCC), the CheckMate 214 study asked the question of the combination of a PD-L1 inhibitor (nivolumab) and a CTLA4 inhibitor (ipilimumab) over the SoC (sunitinib) in first-line therapy [12]. This study showed a higher overall response rate (ORR) and longer PFS for nivolumab + ipilimumab in intermediate/poor risk mRCC (n=847; ORR 42% *vs* 27%, median PFS 11.6 *vs* 8.4 months; HR 0.82), particularly in patients with tumor PD-L1 expression ≥1% (n=214; ORR 58% *vs* 22%, median PFS 22.8 *vs* 5.9 months; HR 0.48) with a manageable safety profile. The findings confirmed the results of the recently published CheckMate 016 study [13]. These results support the use of nivolumab + ipilimumab as a potential first-line treatment.

In urothelial tumors, the antiangiogenic agent ramucirumab enhanced the action of docetaxel (DOC) in metastatic urothelial tumors. The phase-III RANGE study confirms the results of the randomized phase-II with a significant if small improvement of PFS (2.8 to 4.1 months) [14].

The MONARCH 2 trial evaluated patients with hormone receptor-positive, HER2-negative breast cancer whose disease progressed while receiving endocrine therapy [15]. Adding the CDK4/6 inhibitor abemaciclib plus fulvestrant resulted in a 7.2-month extension in median PFS compared with the placebo arm (HR 0.553; 95% CI 0.449-0.681; p<0.001) [15]. The international, double-blind phase-III MONARCH 3 trial randomized 493 post-menopausal patients with advanced breast cancer to frontline abemaciclib 150 mg or placebo twice daily combined with a non-steroidal aromatase inhibitor (NSAI), either anastrozole or

letrozole, once daily as initial treatment until disease progression or unacceptable toxicity [16]. The primary endpoint was PFS. AEs were similar to those in previous studies of abemaciclib. Abemaciclib plus NSAI improved PFS (median not reached *vs* 14.7 months, HR 0.543) and ORR (59.2% *vs* 43.8% in patients with measurable disease). The exploratory subgroup analysis suggests that patients with indicators of poor prognosis had substantial benefit from the addition of abemaciclib, while in patients with a long treatment-free interval and bone metastases only, single agent endocrine therapy may be an appropriate initial therapy. This study confirms the role of CDK4/6 inhibitors in advanced breast cancer; the optimal sequence of treatment has yet to be defined.

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