REPORT ASCO 2019 CHICAGO: RESPIRATORY ONCOLOGY

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OUR 10 MESSAGE HIGHLIGHTS

1/ Early stage NSCLC: adjuvant chemotherapy

Current ESMO guidelines recommend adjuvant chemotherapy with a two-drug combination with cisplatin in resected stage II and IIIA NSCLC. The cisplatin-pemetrexed (cis-pem) regimen – superior in stage IV non-squamous NSCLC – until now had only been studied in the adjuvant phase 2 randomized TREAT trial (Kreuter *et al*, Ann Oncol 2013). It was better tolerated and achieved better dose delivery.

#8501 is a phase 3 randomized controlled trial (RCT) comparing ***cisplatin-pemetrexed versus cisplatin-vinorelbine*** in resected stage II-IIIA non-squamous NSCLC (JIPANG study, UMIN000006737). With 784 patients in the efficacy analysis and a median follow-up of 45 months, median relapse-free survival was similar: 38.9m for cis-pem and 37.3m for cis-vino (hazard ratio (HR) 0.98, *P*= 0.948). Overall survival (OS) rates at 3 years were comparable: 83.5% vs. 87.2%. Cis-pem was better tolerated (e.g. grade 3-4 febrile neutropenia 0.3% vs. 11.6%, *P*<0.001), and more patients could complete treatment with cis-pem (87.9% vs. 72.7%, *P*<0.001). This trial thus confirms the TREAT findings and adds phase 3 data that the efficacy of cis-pem is similar to cis-vino, so it is a possible regimen for non-squamous tumors.

Neoadjuvant immunotherapy (IO) in upfront resectable stage I-IIIA NSCLC recently gained a lot of attention based on a feasibility trial, in which all resectable patients could proceed to surgery, with a major pathological response (MPR) in 45% of the resection specimens (Forde *et al*, N Engl J Med 2018). Updates were presented on other trials with neoadjuvant IO. Of caution, in the atezolizumab trial (LCMC3, **#8503**), ***11/101 (11%) did not make it to surger***y (all stage III), and MPR was seen in 15/90 (17%) resected patients. In the trial with nivolumab ± ipilimumab (NEOSTAR, **#8504), *7/44 (16%) did not go to surgical resection*,** and MPR was seen in 24% of the ITT population.

2/ Locally advanced NSCLC: role of IO

Current ESMO guidelines recommend concurrent chemoradiotherapy (cCRT) for fit patients with unresectable stage III NSCLC. Not yet added to these guidelines is the substantial benefit in OS when one year of consolidation IO with durvalumab is added in patients without progression after cCRT (PACFIC trial). In this setting with curative intent, long-term OS benefits are crucial.

#8526 reported on mature 3-year OS data in this PACIFIC trial. After a median duration of follow-up of 33.3 months, updated OS curves remain clearly separated: HR 0.69 (95%CI 0.55-0.86), with ***3-year OS rates 57% vs. 43.5%.*** This long-term clinical benefit with durvalumab following cCRT reinforces the PACIFIC regimen as the standard of care in this population. Ongoing studies are investigating an earlier start of IO during the cCRT phase in unresectable stage III NSCLC. Feasibility of this approach is being revealed, however with a higher incidence of grade ≥2 pneumonitis than in PACIFIC **(#8511**, **#8512).**

In resectable stage IIIA (N2 or T4N0), **#8509** gave the final data of patients who underwent surgical resection in the Spanish phase 2 NADIM study with neoadjuvant chemo + IO (carboplatin-paclitaxel and nivolumab) 3 cycles, with nivolumab post-surgery for up to one year. 41 of the 46 included patients had R0 resection. 34/41 (83%) patients achieved MPR and ***24/41 (58%) had a complete pathologic response***. These major and complete pathologic response rates are unprecedented and promising for long-term outcomes. The results also show that neoadjuvant chemo + IO is probably a better research strategy than neoadjuvant IO alone, certainly in patients with node positive disease

3/ Advanced NSCLC: EGFR-TKI – anti-angiogenic drug combination for *EGFR*-mutated disease

The focus of upcoming treatment strategies for *EGFR*-mutated advanced NSCLC is on delaying and overcoming resistance to EGFR TKIs. A synergistic role for dual EGFR and tumor angiogenesis blockade has been suggested for a longer time. The recently published interim analysis of the Japanese ph3 NEJ026 trial (Saito *et al.*, Lancet 2019) showed a significant improvement in progression-free survival (PFS) with the upfront combination of the 1st generation EGFR TKI erlotinib and the VEGF-A blocking monoclonal antibody bevacizumab (16.9m vs. 13.3m, HR=0.60). Toxicity was substantial in the experimental arm, leading to discontinuation of bevacizumab in 30% of cases. Improvement in OS still has to be confirmed.

#9000 presented a double-blinded placebo-controlled ph3 trial (RELAY, n=449) that evaluated the superiority of **"*1L erlotinib + ramucirumab vs. 1L erlotinib + placebo*"** in a mainly Asian population (77%)**.** Patients with central nervous system (CNS) involvement were excluded. The addition of ramucirumab, a monoclonal antibody blocking VEGFR2, significantly prolonged investigator-assessed PFS: 19.4m versus 12.4m (HR 0.59, p<0.0001). This was not driven by a difference in objective response rate (ORR), but by a significantly longer duration of response. As expected, the improved outcome was at the cost of increased toxicity: grade ≥3 AEs in 72% vs. 53%, leading to a discontinuation rate of 33% for ramucirumab. OS data are not yet mature. Incidence of the T790M resistance mutation was similar in both treatment arms (42% vs. 47%), as was the frequency of patients that received second-line osimertinib (28% vs. 30%).

Although the improvement in PFS with the upfront combination of erlotinib and ramucirumab is clinically relevant, erlotinib can no longer be regarded as an appropriate comparator in first-line setting given the FLAURA data (Soria *et al*., NEJM 2018). Indeed, the FLAURA trial established the 3rd generation EGFR TKI osimertinib as the current standard of care upfront treatment. Superiority of osimertinib is not only based on the significantly longer PFS compared with 1st generation TKIs (18.9m vs. 10.2m, HR=0.46) - an improvement that is actually in the same range as that observed with erlotinib and ramucirumab - but also on the very favorable toxicity profile, good CNS activity and better quality of life (QoL). OS data for upfront osimertinib are now eagerly awaited. Meanwhile, **#9086** reported a ph2 trial (n=49) on the safety and efficacy of combining osimertinib and bevacizumab in first-line. PFS at one year (primary endpoint) was 76%. All patients with measurable CNS disease had a partial response (5/5). Treatment was largely well tolerated, with expected toxicity. In total, 18% of patients had to discontinue bevacizumab and 24% needed a dose reduction of osimertinib. A randomized study of osimertinib compared to osimertinib and bevacizumab as initial treatment is planned.

4/ Advanced NSCLC: EGFR TKI – chemotherapy combination for *EGFR*-mutated disease

All previously published ph3 RCTs comparing a 1st/2nd generation EGFR-TKI to chemotherapy could not demonstrate an OS benefit for the TKI, which was attributed to crossover in subsequent treatment line. At ASCO 2018, two ph3 trials (NEJ009 and ARCHER1050) demonstrated an OS benefit of the experimental regimen over the 1st generation TKI gefitinib. In particular, the NEJ009 trial showed a clear OS benefit with the upfront combination of gefitinib and chemotherapy vs. gefitinib followed by chemotherapy at progression (52.2m vs. 38.3m). An early effect of chemotherapy on 'TKI tolerant' cells was hypothesized to drive the OS benefit.

#9001 reported on a ph3 trial that randomly assigned 350 untreated *EGFR*-mutant advanced NSCLC patients (including 21% of PS2 patients) to ***"1L gefitinib in combination with carboplatin-pemetrexed vs. gefitinib alone"***. Patients with stable brain metastasis were included (17% vs. 19%, the majority received prior whole brain RT, 13% vs. 18%). ORRs and depth of response were increased in the combination arm, leading to a significantly longer investigator-assessed median PFS (16m vs. 8m, HR 0.51, p<0.0001). OS was improved (median NR vs. 17m, HR 0.45, p<0.0001) was confirmed, hereby corroborating the findings of NEJ009. Of note in the current trial is that few patients received second-line therapy: only 24% received

platinum-doublet chemotherapy in the gefitinib arm! 11% vs. 15% received osimertinib. As expected, toxicity was significantly increased with the combination (grade ≥3 AEs in 51% vs. 25%).

As mentioned above, osimertinib is now considered as the standard of care first-line treatment in EGFR-mutated advanced NSCLC based on the best mix of PFS improvement, mild toxicity profile, CNS control, QoL and practicality**.** However, chemotherapy still plays a role in the treatment of EGFR-mutated patients. Currently, platinum-doublet chemotherapy is the standard second-line treatment after osimertinib resistance. **#9083** reported retrospectively on the addition of chemotherapy to osimertinib (used in ≥2L) at osimertinib resistance. The combination appeared tolerable, with need of treatment discontinuation in only 3/35 patients (8%). Prospective data of this approach are needed to confirm safety and efficacy in front-line setting.

At ESMO 2018 (Ramalingam *et al.*), resistance mechanisms to upfront osimertinib identified in ctDNA of FLAURA patients were presented, including both on-target (e.g. *EGFR* C797S) and off-target genetic events (e.g. *MET* amplification). These data are now stimulating the development of more targeted strategies to overcome acquired osimertinib resistance. **#TPS9119** introduced the upcoming ph2 trial evaluating the combination of osimertinib and savolitinib (MET inhibitor) in *MET*-amplified patients, a combination that resulted in a partial response (PR) of 25% in the prior ph1b TATTON trial. Very early data (ph1) on two monoclonal antibodies after progression on osimertinib were also presented: **#9009** revealed a PR of 28% with an EGFR- and cMET-bispecific antibody (JNJ-372), and **#9010** revealed a PR of 31% with a HER3 antibody drug conjugate (U3-1402). More data on targeted strategies to overcome osimertinib resistance are expected in the nearby future.

5/ Advanced NSCLC: activity and resistance to MET TKIs

MET exon 14 (*MET*ex14) skipping mutations are present in 3-4% of cases with stage IV non-squamous NSCLC and are mutually exclusive with other established driver mutations. Although doubted for quite some time, they by now have been established as primary oncogenes that can effectively be targeted in advanced NSCLC. At the 2018 ESMO meeting, data of the GEOMETRY mono-1 trial showed high response rates to capmatinib, an oral highly selective MET inhibitor (Wolf *et al*, #LBA52).

#9004 now presented results on duration of response (DOR) and PFS, as well as updated results for ORRs of GEOMETRY mono-1 in previously treated (cohort 4, n=69) and untreated (cohort 5b, n=28) patients. Although immature at the time of data analysis, data on DOR and PFS by independent review committee (IRC) are promising. In cohort 4, ORR, median DoR, and median PFS were 40.6%, 9.7m, and 5.4m respectively. For cohort 5b, this was 67.9%, 11.1m and 9.7m.

ORR in both cohorts were confirmed. In the subgroup of patients with brain metastasis at inclusion (n=13), intracranial responses were confirmed by IRC in 54%. The safety profile remained favorable. These data establish **capmatinib** as a promising treatment option for patients with *MET* exon 14-mutated stage IV NSCLC, for which it was granted Breakthrough Therapy Designation by the FDA.

#9005 reported on a ph2 study of **tepotinib**, another highly selective MET inhibitor (VISION trial). In this study, *MET*ex14 skipping mutations could have been identified in a liquid (DNA-based assay) or a tissue biopsy (RNA-based assay). Overall ORR by IRC was 50% in patients with the driver mutation detected in a liquid biopsy (with highest ORRs in first-line setting), and 45.1% in those selected based on a tissue biopsy. Median PFS by IRC was 9.5m and 10.8m in the liquid and tissue biopsy group, respectively. No data on intracranial responses were provided. Grade 3 treatment-related adverse events occurred in 19.5% of cases.

The consistently higher ORRs to MET-directed therapy in the first-line setting support the routine testing of *MET* exon 14 skipping mutations at diagnosis. Testing is preferably performed as part of a broader DNA sequencing panel. However, as exemplified by **#9005,** RNA-based approaches are now being assessed to

more comprehensively capture *MET* exon 14 skipping events, given the various genomic locations of exon 14 skipping alterations.

#9006 was an early report on resistance mechanisms to MET TKIs in *MET*ex14-mutated disease, mainly (91%) with crizotinib, a non-specific MET inhibitor with ORR of 32%. Primary resistance appeared to correlate with MET protein expression: ORR 0% in the absence of MET expression vs. 54% with MET expression in the tumor. Acquired resistance was analyzed by use of 14 paired pre- and post-treatment biopsies, and revealed on-target or off-target resistance mechanisms in 50% of cases. Data on resistance mechanisms to the newer more specific MET TKIs are needed to further guide MET-directed therapy.

6/ Advanced NSCLC: known targets, new drugs

- *EGFR* exon 20 insertions: are present in about 6% of *EGFR*-mutated advanced NSCLC patients, however, currently approved EGFR TKIs are largely ineffective in these patients. **#9007** presented an update on a ph1/2 trial exploring the safety and efficacy of the selective TAK-788 in 28 pretreated patients. Overall ORR was 43% and was higher in patients without vs. with brain metastasis at baseline: 56% vs. 25%. Median PFS was 7.3m, and longer in patients with no CNS involvement at baseline (8.1m vs. 3.7m). Grade 3 or higher treatment-related AEs occurred in 40% of cases, mainly diarrhea.

- *RET* fusions: few responses to multikinase inhibitors have been observed. At ASCO 2018 (#102) ph1 data on the selective RET inhibitor LOXO-292 showed an ORR of 77%. This year, **#9008** presented a ph2 trial with the selective RET inhibitor BLU-667 (ARROW trial). Overall ORR was 58%: 71% in treatment-naïve patients and 60% in patients previously treated with platinum-based chemotherapy. Responses were seen regardless of the presence of CNS metastases. The drug was well tolerated with mainly low grade treatment-related AEs. The FDA granted Breakthrough Therapy Designation to BLUE-667 for RET-driven NSCLC with progression after platinum-based chemotherapy.

- *KRAS* G12C mutations: KRAS mutations are prevalent in advanced NSCLC, however, not yet effectively targeted by a drug. KRAS G12C mutations are present in 13% of cases, and are selectively and irreversibly inhibited by AMG510. **#3003** reported on the ph1 first-in-human study with AMG 510. Responses were promising and confirmed in 5/10 NSCLC patients that were previously treated with standard therapy. The drug was generally well tolerated; there were no serious drug-related AEs. The ph2 part of the study will soon start enrollment.

- *ROS1* fusions: crizotinib is currently approved for ROS1-mutated NSCLC, with an ORR of 72% and median PFS of 19.3m. Repotrectinib is developed specifically to overcome the most common resistance mutation G2032R. **#9011** reported preliminary results of the TRIDENT-1 trial with repotrectinib. Confirmed ORR was 82% in treatment-naïve patients and 55% in pretreated patients (ORR influenced by the dose). Activity against G2032R was confirmed: ORR of 40%. Promising CNS activity was present in 100% of untreated patients and 75% of pretreated patients. Overall, the drug was well tolerated. Outcome data are awaited, as is the recommended ph2 dose.

7/ Advanced NSCLC: outcome after combined chemo-IO in first-line

KEYNOTE-189 (platinum-pemetrexed plus pembrolizumab) has revolutionized the approach to stage IV non-squamous NSCLC. Abstract **#9013** gave updated OS data and the first data on post-study therapy and ***PFS2 (progression after the Keynote-189 therapy and the next line of therapy).*** With a median follow-up of 18.7-m, OS remained strongly in favor of the triplet: HR 0.56 (95CI 0.45-0.70, *P*<0.00001, median 22.0 vs. 10.7 m). Second-line therapy was received by 45% in the chemo/pembro arm and 59% (54% IO) in the chemo arm. Even with 54% crossover to 2L IO, PFS2 was longer for 1L chemo/pembro: HR 0.49, 95%CI 0.40-0.59, *P*<0.00001; median 17.0 vs. 9.0 m), and this in all PD-L1 cohorts.

8/ Advanced NSCLC: response prediction with IO

While PD-L1 expression on tumor cells now is universally recognized as an enrichment biomarker of single agent anti-PD-(L)1 IO, further refinement of response prediction is a high need.

In a science symposium, **#102** reported on how NGS may help with the identification of genomic predictors of IO response. It has already been reported that *STK11/LKB1* gene alterations predict resistance to single agent IO, this abstract now reported the findings for response to platinum-pemetrexed + pembrolizumab.

STK11/LKB1 genomic alterations were present in 102/377 patients treated with platinum-pemetrexed + pembrolizumab, and were associated with significantly shorter PFS (median 4.8 vs. 7.2 m, P=0.0063) and OS (median 10.6 vs. 16.7 m, P=0.0083). Importantly, this was not only prognostic, but predictive as well: ***in patients with STK11/LKB1-mutant NSCLC, addition of pembrolizumab to platinum-pemetrexed did not improve PFS or OS*** (median 4.8 vs. 4.3 m, P=0.75, and median 10.6 vs. 10.3 m, P=0.79, respectively). This information also reinforces the evidence that broad NGS profiling is to be preferred for molecular analysis of NSCLC, rather than single gene PCR tests.

9/ Advanced NSCLC: IO in patients with autoimmune disorders

Patients with active autoimmune disorders (AD), or even those with a history of AD, have in general been excluded from clinical trials with IO in lung cancer. Nevertheless, in clinical practice, they are estimated to represent about 13.5% of patients with lung cancer (Khan *et al*, Lung Cancer 2018).

#110 is a retrospective real-world study of IO in NSCLC patients with AD. Among 2425 patients, AD was present in 22% (N=538). There was no association between AD status and outcomes: median OS in all patients was 12.4 m (95%CI 11.3-13.5). Time-to-treatment-discontinuation (3.68 vs. 4.24 m, *P*=0.10) and ***OS (11.5 vs. 12.8 m, P=0.20) did not differ*** between the two cohorts. There was no overall increased incidence of AEs in the AD group, but sub-analysis in patients with ***active AD showed higher rates of select AEs including endocrine, GI and blood disorders***.

10/ SCLC: new agents

Over the last decades, the only progress in systemic therapy for metastatic SCLC was the addition of atezolizumab to carboplatin-etoposide, resulting in a (modest) improvement in survival (Horn *et al*, N Engl J Med 2018).

#8506 reported on the relapsed SCLC cohort of a multicenter phase 2 basket trial with lurbinectedin (n=105). Lurbinectedin is a novel anti-cancer drug that inhibits activated transcription and induces DNA double-strand breaks, leading to apoptosis. Response rate was 35%: 21% in platinum-resistant relapse (<90 days), 47% in platinum-sensitive relapse (≥90 days). Median duration of response was 5.3 m: 4.7 m in resistant and 6.2 m in sensitive patients. Median OS was 10.8m: 5.1 m in resistant and 15.2 m in sensitive relapse. These data are comparable to slightly superior to Topotecan, but with a quite better tolerability profile (febrile neutropenia in 3.8%, treatment-related discontinuations in 3.8%). These promising data have been further explored in a phase 3 trial comparing doxorubicin + lurbinectedin vs. standard 2nd line chemotherapy. Data are awaited.

Full abstracts of this ASCO meeting can be found at: http://abstracts.asco.org/239/CatView_239_B.html

For your calendar:

Respiratory Oncology Update 2019: 19/102019 in La Hulpe. https://www.update-respiratoryonco.be/