REPORT ASCO 2020 VIRTUAL: RESPIRATORY ONCOLOGY

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1/ Early stage NSCLC - adjuvant targeted therapy

Current ESMO guidelines recommend adjuvant chemotherapy with a cisplatin-based doublet in resected stage II and IIIA NSCLC (and, when based on TNM 7th edition, consider it in stage IB disease if primary tumor >4 cm). The overall survival (OS) benefit with adjuvant chemotherapy is 5% at 5 years. Although the impact is higher with increasing stage, there is still room for improvement. The current ESMO guidelines do not recommend the use of targeted agents in the adjuvant setting in molecularly selected patients.

#LBA5 presented an interim analysis of the phase 3 ADAURA trial that assessed efficacy and safety of adjuvant ***osimertinib 80mg QD vs. placebo*** for 3 years in completely resected stage IB, II and IIIA (pTNM 7th) *EGFR*-mutation positive NSCLC. Standard of care adjuvant chemotherapy was allowed prior to randomization, while post-operative radiotherapy was not. The primary endpoint of disease-free survival (DFS) in stage II/IIIA patients was met, with median DFS not reached in the osimertinib arm vs. 20.4 months in the placebo arm after a median follow-up (FU) of at least 1 year in both treatment arms (hazard ratio (HR) 0.17, 95%CI 0.12-0.23, *P*=<0.001). Superior DFS was also present in stage IB patients (albeit less pronounced, HR 0.50), and was independent of prior adjuvant chemotherapy and other covariates. Importantly (since given for a total period of 3 years), adjuvant osimertinib was safe and well tolerated. This trial thus establishes osimertinib as the first targeted agent that may provide a clinically meaningful benefit in the adjuvant setting in resected *EGFR*-mutation positive NSCLC. Mature OS data are now awaited.

The question is now indeed whether the DFS benefit observed with adjuvant osimertinib will eventually be translated in an OS benefit (*i.e.* true increase in cure rates vs. only temporary control of remaining disease). For instance, the ADJUVANT trial previously showed a significant improvement in DFS with adjuvant gefitinib for 24 months vs. with standard cisplatin doublet in resected N1-N2 *EGFR*-mutation positive NSCLC (Zhong *et al.*, Lancet Oncol, 2018). **#9005** presented an update of DFS and the final (exploratory) OS analysis of this ADJUVANT trial after a median FU of 80 months. DFS benefit was confirmed with 30.8 vs. 19.8 months (HR 0.56, 95%CI 0.40-0.79). However, this DFS benefit was not translated in a significant OS difference (75.5 vs. 62.8 months, HR 0.92, 95%CI 0.62-1.36). Hence, based on current evidence, there is still no indication for the use of targeted agents in the adjuvant setting in molecularly selected patients, also taking into account the cost of 3 years osimertinib. Consequently, molecular tumor profiling is not (yet) indicated at the time of complete tumor resection.

2/ Advanced NSCLC – no oncogene addiction: 1L immunotherapy

Currently, there are several EMA-approved regimens reimbursed in Belgium: single agent pembrolizumab for NSCLC with PD-L1 ≥50% (Keynote-024); the combinations platinum-pemetrexed & pembrolizumab (Keynote-189) and carboplatin-paclitaxel-bevacizumab & atezolizumab (IMpower-150) for non-squamous NSCLC with any PD-L1 value; and the combination of carboplatin-paclitaxel & pembrolizumab for squamous NSCLC with any PD-L1 value (Keynote-407).

#9500 was an update on the previously reported CheckMate-227, where the co-primary endpoints for the comparison between ***nivolumab-ipilimumab (nivo-ipi) vs. doublet chemotherapy*** were progression-free (PFS) in TMB-high tumors and OS in PD-L1 positive (i.e. ≥1%) tumors. A mature 3-year OS analysis was now presented. For tumors with PD-L1 ≥1%, there was a continued OS benefit for nivo-ipi vs. chemotherapy: HR: 0.79, 95%CI 0.67–0.93). 3-year OS rates were 33% and 22%, respectively. For the exploratory endpoint of OS in PD-L1 <1%, findings were similar. In an exploratory landmark analysis according to response categories, the difference in survival was limited to responding patients; for those with stable disease or progression there

was no significant survival difference between the two arms. Grade 3-4 treatment-related adverse events (AEs) were observed in 33% of nivo-ipi and 36% of chemotherapy patients.

#9501 was a first report of the CheckMate-9LA phase 3 trial comparing ***nivo-ipi plus two cycles of chemotherapy vs. doublet chemotherapy alone***. The hypothesis was that a limited number of initial chemotherapy cycles could provide rapid disease control and avoid the initial inferiority in OS with crossing of the survival curves as noted in CheckMate-227. One arm (N=361) received 360mg nivolumab q3w + 1mg/kg ipilimumab q6w + two doublet chemotherapy cycles, the other (N=358) 4 cycles of chemotherapy with optional pemetrexed maintenance if non-squamous histology. Immunotherapy was given until disease progression, unacceptable toxicity, or for a maximum of 2 years. Interim analysis of the primary endpoint of OS, with a minimum FU of 12.7 months, revealed that the experimental arm did better: median OS 15.6 vs. 10.9 months, HR 0.66, 95%CI 0.55-0.80; 1-year OS rates 63% vs. 47%. Clinical benefit was similar for both histologies and for PD-L1 subgroups. Grade 3-4 treatment-related AEs were reported in 47% of nivo-ipi-chemo vs. 38% of the chemotherapy alone patients.

A common aspect of these two trials is that their standard arm is no longer in line with current clinical practice, as most patients are now treated upfront with chemo-immunotherapy of pembrolizumab alone (PD-L1 ≥50%). The first trial will have little further consequences for Europe, as the authorization request was not accepted by EMA because of the numerous changes in study design during the course of the trial (both for biomarker guidance and primary endpoints). The second trial has a straightforward design and now a first interim analysis, suggesting that its study regimen may become another possible 1L therapy. Whether the current standard of chemotherapy plus single agent anti-PD(L)1 therapy will be challenged by this chemotherapy plus double checkpoint inhibition will become more clear once longer OS FU becomes available. Factors that may be of help in future treatment choices are smoking status, performance status, PD-L1 expression, aggressiveness of tumor growth, balances between efficacy and toxicity for a given patient, and hopefully more discriminative biomarkers.

#9502 was the first phase 3 trial comparing immunotherapy alone vs. chemo-immunotherapy. This Canadian Cooperative Group trial randomly assigned 301 patients to either ***durvalumab-tremelimumab (durva-treme) plus doublet chemotherapy vs. durva-treme alone*.** One group had 4 cycles of histology-based chemotherapy plus durva-treme followed by maintenance durva-treme, the other durva-treme until progression. Pemetrexed maintenance was allowed if non-squamous histology. There was no significant difference in OS: median 16.6 months for the combo, 14.1 months with durva-treme, HR 0.88, 90%CI 0.67-1.16. PFS was significantly improved with the combo (HR 0.67, 95%CI 0.52-0.88, median PFS 7.7 v. 3.2 months). There was more toxicity in the combo arm, with grade ≥3 AEs in 82% vs. 70%. While this trial addressed an important but hitherto unanswered question, its power is insufficient to draw final conclusions.

3/ Advanced NSCLC – no oncogene addiction: antibody-drug conjugates

While we recently witnessed remarkable progress in targeted therapies and immunotherapies for NSCLC, there has been a standstill in chemotherapy for more than a decade. Much hope now resides on 'targeted chemotherapy', consisting of a strong chemotherapeutic agent linked to a 'tumor-finding' monoclonal antibody: a so-called antibody-drug conjugate (ADC).

#9504 reported on ***trastuzumab-deruxtecan***, an ADC composed of an anti-HER2 antibody, cleavable tetrapeptide-based linker and a topoisomerase I inhibitor payload, studied in a phase 2 trial (DESTINY-LUNG01) in non-squamous NSCLC overexpressing HER2 or containing a *HER2*-activating mutation. Data on the *HER2*-mutated cohort, treated with 6.4mg/kg every 3 weeks, were shown. Most patients had prior chemotherapy and 55% had prior anti-PD(L)-1 treatment; 45% had central nervous system (CNS) metastases.

Confirmed objective response rate (ORR) among 42 patients was 61.9%. Estimated median PFS was 14.0 months (95%CI 6.4-14.0). Hence, there is promising clinical activity. Grade ≥3 treatment-related AEs were seen in 52.4%. Since HER2 is expressed in normal lung tissue, interstitial lung disease (ILD) is an AE of special interest. In this trial, 5 cases (11.9%, all grade 2) of drug-related ILD occurred, warranting further monitoring and investigation.

#9505 looked at the ***CEACAM5 targeted ADC SAR408701*** in non-squamous NSCLC expressing carcino-embryonic antigen-related cell adhesion molecule 5 (CEACAM5). In the expansion part of the first-in-human study (heavily pretreated, median of 3 prior treatments), CEACAM5 expression was assessed by immunohistochemistry on archived tumor samples. SAR408701 was administered at 100mg/m2 i.v. every 2 weeks. ORR was 7.1% in the 28 moderate expressers (≥2+ intensity in 1-50% of tumor cells) and 20.3% in the 64 high expressers (≥2+ intensity in >50% of tumor cells). ORR was 17.8% in 45 patients with prior anti-PD(L)1. Grade ≥3 treatment-related AEs occurred in 15.2%, especially keratopathy/keratitis (all grades 38%) warrants special attention. A phase 3 trial evaluating SAR408701 vs. docetaxel in CEACAM5 expressing relapsed adenocarcinoma is ongoing (NCT04154956).

4/ Advanced NSCLC – oncogene addiction: EGFR-TKI combinations

A focus of 1L trials in the setting of *EGFR*-mutated advanced NSCLC is to maximize the benefit of established EGFR TKIs by delaying resistance.

#9506 presented the final OS analysis of Japanese phase 3 NEJ026 trial. A synergistic role for ***dual EGFR and tumor angiogenesis blockade*** has been suggested for a long time. The previously published interim analysis of NEJ026 (Saito *et al.*, Lancet 2019) showed a significant improvement in PFS with the upfront combination of the 1st generation EGFR-TKI erlotinib and the VEGF-A blocking monoclonal antibody bevacizumab (16.9 vs. 13.3 months, HR 0.60). Toxicity was substantial in the experimental arm and led to discontinuation of bevacizumab in 30% of cases. As reported now, the PFS benefit did not translate in OS benefit (50.7 vs. 46.2 months, HR 1.01, 95%CI 0.68-1.49). Subgroup analysis also failed to identify a subgroup with greater likelihood of benefit from the combination. Besides, erlotinib can no longer be regarded as an appropriate comparator in 1L setting, as based on the FLAURA trial that established osimertinib as the current standard of care upfront treatment for advanced *EGFR*-positive NSCLC (Ramalingam *et al.*, NEJM 2020).

#9507 assessed the tolerability and feasibility of the upfront ***combination of osimertinib and the 1st generation EGFR TKI gefitinib***. Preclinical data show a deferred development of acquired *EGFR* resistance mutations, such as C797S that occurs in up to 20% of osimertinib treated patients, with the combination. In 24 patients, the combination appeared tolerable with a comparable frequency of grade ≥3 AEs of any cause (48%) as with either TKI alone in the FLAURA trial (42% with osimertinib alone). The primary endpoint of feasibility was met, but the 30% discontinuation rate of gefitinib due to toxicity has to be noted. Moreover, ORRs were comparable as with osimertinib alone in FLAURA (89% vs. 80%). Mature PFS and OS data are now awaited to answer the question whether the combination is truly better than osimertinib alone.

5/ Advanced NSCLC – oncogene addiction: targeting *MET* alterations

MET exon 14 skipping mutations (*METex14*) and *MET* amplifications are targetable primary oncogenic drivers in advanced NSCLC. Several MET-specific TKIs are emerging. The MET-TKI capmatinib (Tabrecta®) has recently received FDA approval for first or later-line treatment of *METex14* advanced NSCLC. Approval is based on data of the phase 2 GEOMETRY mono-1 study, showing ORRs of 68% and 41%, respectively in treatment-naïve (cohort 5b) and pretreated (cohort 4) patients. Median OS was 9.7 vs. 5.4 months, respectively. Clinical

activity is combined with a favorable safety profile (mainly low-grade peripheral edema and gastro-intestinal side effects). EMA approval is awaited.

#9556 presented an update of the MET-TKI ***tepotinib 500mg QD*** in advanced *METex14* NSCLC, either identified in liquid and/or tissue biopsy (VISION trial). Overall ORR by independent review committee (IRC) was 46.5%, median PFS was 8.5 months. ORR in the 11 patients with asymptomatic brain metastases at baseline was 55%. Grade 3 treatment-related AEs occurred in 27.6% of cases, with 11.2% treatment discontinuations.

#9519 reported on the safety and activity of ***savolitinib 600mg QD*** in a phase 2 trial of *METex14* NSCLC. ORR by IRC in 61 patients was 49.2%, median PFS was 13.8 months in pretreated patients and 5.6 months in treatment-naïve patients. The lower PFS in treatment-naïve patients (in contrast with other MET-TKI trials) was attributed to a 50% proportion of pulmonary sarcomatoid tumors (known for their more aggressive behavior) in this subgroup. Savolitinib showed acceptable tolerability with grade 3 treatment-related AEs in 41.4% of cases, with 14.3% treatment discontinuations.

#9509 reported on the activity of ***capmatinib 400mg BID*** in high-level *MET* amplified (gene copy number/GCN ≥10) advanced NSCLC (GEOMETRY mono-1 trial). ORRs by IRC were 29% in 69 pretreated patients (2L/3L, cohort 1a) and higher (40%) in 15 treatment-naïve patients (cohort 5a). Median PFS was about 4 months in both cohorts, and median OS about 10 months. The safety profile was favorable and consistent with previous reports. The activity of capmatinib is thus lower in the setting of *MET* amplification (compared with *METex14*).

Overall, based on upcoming treatments, screening for *MET* alterations should become part of standard of care molecular testing at diagnosis.

6/ Advanced NSCLC – oncogene addiction: *RET*, new kid on the block

RET fusions are present in up to 2% of advanced NSCLC cases. Two potent RET-selective TKIs are emerging. Selpercatinib (LOXO-292) recently received FDA approval for the treatment of *RET*-fusion positive advanced NSCLC based on positive data of the phase 1/2 LIBRETT0-001 trial. A second RET inhibitor is pralsetinib (BLUE-667), which is undergoing FDA review.

#3584 reported an update on the efficacy and safety of ***selpercatinib 160mg BID*** in LIBRETT0-001. In heavily pretreated patients (N=105), ORR was 64% and median PFS 17 months (median FU of 14 months). In treatment-naïve patients (N=39), ORR was 85% and PFS not reached (median FU of 9 months). Selpercatinib is very well tolerated, with only 2% of patients discontinuing treatment because of toxicity.

#9516 confirmed intracranial activity in a prespecified subgroup analysis of LIBRETTO-001 in patients with baseline CNS metastases. In 22 efficacy-evaluable patients, an impressive intracranial ORR of 82% was observed by IRC, including 5 complete responses (23%). The median duration of CNS response (DoR) was 9.4 months.

#9515 showed updated results of ***pralsetinib 400mg QD*** in the phase 1/2 ARROW trial. In line with data on selpercatinib, ORRs were high (65%), and higher in treatment-naïve vs. pretreated patients (73 vs. 61%). CNS activity was confirmed, with 56% intracranial ORRs (although in only 9 patients). FU is still short to show relevant survival data. Safety profile is again good, with only 4% of patients discontinuing treatment because of treatment-related AEs.

A randomized phase 3 trial in 1L setting comparing selpercatinib to platinum-doublet chemotherapy +/- pembrolizumab is currently ongoing (NCT04194944). Inclusion of patients with asymptomatic brain metastases is, as expected, allowed. If intracranial activity of the drug is confirmed, then the need of local therapy will have to be questioned also in case of symptomatic CNS metastases. For pralsetinib, the phase 3 AcceleRET trial will compare pralsetinib vs. SoC in 1L (NCT04222972). Hence, two potent and CNS-active RET inhibitors are approaching use in clinical practice. Especially data in the treatment-naive setting are compelling, justifying the routine screening for *RET*-fusions in newly diagnosed stage IV non-squamous NSCLC.

7/ Advanced NSCLC – oncogene addiction: the search for *EGFR exon 20* mutant selective drugs

EGFR exon 20 insertions are present in about 6% of *EGFR*-mutated advanced NSCLC patients. However, currently approved EGFR TKI regimens are largely ineffective in this patient group and prognosis is poor.

#9513 presented data on the safety and efficacy of ***osimertinib*** in a dose of ***160mg QD*** in a phase 2 trial including 15 response-evaluable pretreated patients. Clinical activity was observed, with an ORR of 24% and median PFS of 9.6m. The therapy was generally well tolerated. Osimertinib will be further studied in this setting.

#9514 reported on ***poziotinib 16mg QD***, a TKI of exon 20 mutant *EGFR* and *HER2*, in 115 pretreated patients (ZENITH20 study). The primary endpoint of ORR (14.8%) was not met. Median PFS was 4.2 months. In addition, toxicity is of concern with 65% of patients needing dose reductions.

EGFR exon 20 mutated NSCLC remains difficult to tackle. At last year ASCO, data of a phase 1/2 trial assessing TAK-788 in 28 pretreated patients were presented. An overall ORR of 43% and median PFS of 7.3m were shown; grade ≥3 treatment-related AEs occurred in 40% of cases. Updated results of this trial are awaited, as well as results of trials investigating EGFR exon 20 targeting antibodies (e.g. the EGFRex20-MET bispecific antibody amivantamab, **#9512**).

8/ Non-metastatic SCLC

Concurrent chemoradiotherapy is the standard treatment of localized SCLC; 45 Gy in 30 fractions BID is the most recommended RT schedule. **#9007** presented a randomized phase 2 trial comparing ***60 Gy BID vs. the standard 45 Gy*** in non-metastatic SCLC. Patients received 4 courses of platinum-etoposide and were randomly assigned to BID thoracic radiotherapy of 60 vs. 45 Gy. Responders had PCI of 25-30 Gy. Primary endpoint was a 25% improvement of 2-year OS from 53% to 66% with a one-sided α=0.10 and β= 0.802. In total, 160 patients completed RT per protocol (60 Gy: N=84, 45 Gy: N=76). Significantly more patients of the 60 Gy arm were alive after 2 years (60 Gy: 70% vs. 45 Gy: 46%, *P*=0.001), and they had a significantly longer median OS (42 vs. 23 months, HR 0.63, 95%CI 0.41-0.95, *P*=0.027). There were no significant differences in grade 3-4 esophagitis, pneumonitis, or other toxicities.

The result of a better 2-year OS together with similar toxicity is remarkable, but probably not yet practice changing as it concerns a phase 2 trial with a limited number of patients per arm, no baseline stratification for prognostic factors, and the analysis was not intent-to-treat. The data, however, call for further study of higher doses of thoracic RT in non-metastatic SCLC.

9/ Metastatic SCLC

Two recent RCTs established platinum-etoposide plus atezolizumab (IMpower-133 study) or durvalumab (CASPIAN study) as new standards of care for metastatic SCLC. A similarly significant improvement in both PFS and OS was noted in both trials. Two new trials and an update of CASPIAN were presented at ASCO 2020.

#9000 reported on the ECOG-ACRIN 5161 randomized phase 2 trial (N=160) of ***platinum-etoposide alone vs. in combination with nivolumab*** as 1L therapy. Nivolumab was given concurrent with 4 cycles of platinum-etoposide in a dose of 360mg every 3 weeks, and then in maintenance 240mg every 2 weeks until progression or up to 2 years. PCI was permitted at the investigator's discretion. The primary endpoint – PFS – was significantly improved with nivolumab: HR 0.65 (95%CI 0.46-0.91), median PFS 5.5 vs. 4.6 months. OS was also improved: HR 0.67 (95%CI 0.46-0.98), median OS 11.3 vs. 8.5 months. Grade 3-4 treatment-related AEs were 77% vs. 62%, AEs leading to discontinuation 6.2% vs. 2.1%.

#9001 was the report of the double-blind phase 3 Keynote-604 trial with ***platinum-etoposide plus either pembrolizumab (N=228) or placebo (N=225)*****.** Patients with untreated CNS metastases were not allowed. Patients received 4 cycles of platinum-etoposide concurrent with pembrolizumab 200mg q3w or placebo, and then maintenance pembrolizumab or placebo for up to 35 cycles. Responding patients could have PCI at investigator discretion. Co-primary endpoints were OS and PFS, and the protocol had two interim analyses and a final analysis. Pembrolizumab significantly improved PFS: HR 0.75 (95%CI 0.61-0.91, *P*=0.0023). OS was improved as well – HR 0.80, 95%CI 0.64-0.98, *P*= 0.0164 – but this did not reach formal statistical significance, as the boundary for OS significance was set at *P*=0.0128 due to the interim analyses. Grade 3-4 any-cause AEs were 77% vs. 75%, and led to discontinuation in 15% vs. 6%.

#9002 was an updated report of the ***platinum-etoposide plus durvalumab-tremelimumab arm (N=268) from the CASPIAN trial*****.** In a previous report, platinum-etoposide plus durvalumab was reported to result in significantly better OS (HR 0.75, 95%CI 0.62-0.91, median OS 12.9 vs. 10.5 months) than chemotherapy alone. In the now reported arm, patients received 1L platinum-etoposide plus durvalumab 1500mg and tremelimumab 75mg q3w for 4 cycles, followed by maintenance durvalumab until disease progression. While chemotherapy plus durva-treme numerically improved OS over chemotherapy alone, this did not reach statistical significance: HR 0.82, 95%CI 0.68-1.00, *P*=0.0451, while the significance boundary was *P*≤0.0418. Median OS was 10.4 months.

There are four randomized datasets on platinum-etoposide plus single agent immunotherapy now: IMpower-133 with atezolizumab, CASPIAN with durvalumab, Keynote-604 with pembrolizumab, and the ECOG-ACRIN with nivolumab. They all show a very similar improvement in PFS and OS when immunotherapy is added to chemotherapy. This establishes the place of immunotherapy in stage IV SCLC in 1L use. The benefit is modest, however, and at present, no biomarker has been demonstrated to be useful in the selection of patients. Both atezolizumab and durvalumab will find their place in clinical practice. In the Keynote-604 trial, pembrolizumab did not yield statistically significant improvement of OS, probably because too much statistical power was given to the two preceding interim analyses. The nivolumab data are at present from a non-placebo-controlled phase 2 randomized trial.

An extra lesson from CASPIAN is that adding an anti-CTLA-4 component to chemo-immunotherapy for SCLC does not further improve outcome. The shape of the OS curve suggests this may be due to excessive toxicity. Indeed, grade 3-4 all-cause AEs were 70.3% (vs. 62.8% for chemotherapy alone), AEs leading to discontinuation were 21.4% (vs. 9.4%), and treatment-related AEs leading to death were 4.5% (vs. 0.8%).

10/ Mesothelioma

Also in mesothelioma, the focus of trials is now on moving immunotherapy to 1L to take advantage of the synergy with chemotherapy, exemplified by e.g. the recently started ETOP BEAT study with atezolizumab added to 1L therapy (NCT03762018).

#9003 reported on a phase 2 (N=55) study of ***durvalumab added to 1L cisplatin-pemetrexed*****.** Patients received up to 6 cycles of cisplatin-pemetrexed and durvalumab 1120mg q3w, followed by maintenance durvalumab up to 1 year. Primary endpoint was OS, for which a median of 20.4 months was noted and a 1-year OS of 70%. No dose-limiting toxicities were noted. PD-L1 expression and TMB were not associated with OS. The data are quite promising in comparison with historical ones, and this regimen will be taken forward in a phase 3 trial (DREAM3R study, NCT 04334759).

#9004 was a randomized phase 2 study of ***gemcitabine with or without ramucirumab*** (a monoclonal antibody blocking VEGFR2) as 2L treatment. Patients received gemcitabine 1000mg/m^2 i.v. on days 1 and 8 every 3 weeks, with ramucirumab 10mg/kg on day 1 every 3 weeks until intolerability or progressive disease (N=80) vs. placebo (N=81). The primary endpoint OS was significantly longer with ramucirumab: median 13.8 vs. 7.5 months, HR 0.71 (70%CI 0.59-0.85, *P*=0.057). No significant differences in grade 3-4 hematological toxicity or thromboembolic events were noted. The authors concluded that gemcitabine plus ramucirumab could be considered as 2L therapy for mesothelioma.

Full abstracts of this ASCO meeting can be found at:
https://meetinglibrary.asco.org/results?meetingView=2020%20ASCO%20Virtual%20Scientific%20Program

For your calendar:
Respiratory Oncology Update 2020: 14/11/2020 in La Hulpe. https://www.update-respiratoryonco.be/