REPORT ASCO 2021 VIRTUAL: RESPIRATORY ONCOLOGY

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1/ Early stage NSCLC – local treatment modalities

All randomized controlled trials (RCTs) comparing surgical resection with stereotactic ablative radiotherapy (SABR) in this setting failed to bring reliable results because of poor accrual.

#8506 reported long-term results with SABR in operable stage IA NSCLC.
The *STARS* trial (NCT02357992) was originally designed as RCT, but suffered from the same accrual problem and thus was continued as a single-arm trial with risk-factor matched comparison with historical VATS results (n=229). The aim was demonstration of non-inferiority of SABR, defined as a 3-year overall survival (OS) not lower by more than 12%. Inclusion criteria were stage IA NSCLC (≤3 cm, N0, M0) staged by PET/CT and EBUS, and deemed operable by a multidisciplinary team. SABR used 54 Gy in 3 fractions for peripheral or 50 Gy in 4 fractions for more central lesions. The 5-year cumulative incidence rate of any relapse in the 80 SABR patients was 17.6% (6.3% local, 12.5% regional, 8.8% distant). The OS and disease-free survival (DFS) were 91% and 80% at 3 years, and 87% and 77% at 5 years, respectively. The propensity score matched comparison of SABR vs VATS revealed no significant differences in DFS (*P*=0.063), lung cancer-specific survival (*P*=0.075), or cumulative incidence rates of relapse. The SABR arm was associated with significantly higher OS (91% vs. 82% at 3 years and 87% vs. 72% at 5 years; *P*=0.012).
Comment: remarkably good results in a very dedicated trial with a limited number of patients in a very dedicated center. These data do not challenge the standard of surgical resection, but can be useful for often difficult decisions at multidisciplinary tumor boards. Moreover, it reinforces the critical need for a RCT in this setting.

In **#8504,** the final results of the *VIOLET* study (ISRCTN13472721) were presented, a randomized **comparison of VATS (n=247) vs. open lobectomy (OPEN, n=256)** in early stage lung cancer. At a previous WCLC, it was already shown that VATS resulted in less pain despite less analgesic consumption, less complications during hospitalization, and less pain and better physical function after hospitalization. Median hospital stay was one day shorter in the VATS arm (4 vs. 5 days), and there were less readmissions (29.0% vs. 35.9%). Now oncological outcomes up to one year were presented. Recurrence rate was similar: 7.7% for VATS vs. 8.1% for OPEN. DFS (hazard ratio (HR) 0.74, 95%CI 0.43-1.27; *P*=0.27) and OS (HR 0.67, 0.32-1.40; *P*=0.282) were not significantly different.
Comment: reinforces the already known advances of VATS over open approaches for early-stage lung cancer.

2/ Early-stage NSCLC – (neo)adjuvant targeted therapy

The classical role of adjuvant therapy in patients with resected NSCLC is improvement of cure rates, often measured by 5-year OS. Therefore, current ESMO guidelines recommend adjuvant chemotherapy with a cisplatin-based doublet in resected stage II and IIIA NSCLC.
In 2020, the interim results of the *ADAURA* study, with 3 years of adjuvant osimertinib in completely resected EGFR mutated stage IB-IIIA NSCLC, were presented at ASCO and ESMO. An early analysis of DFS (maturity 33%) showed an impressive difference for osimertinib vs. placebo in stage II/IIIA (HR 0.17), and with even less maturity (7%), a similar HR of 0.18 for central nervous system (CNS) DFS. This generated a global debate whether an early DFS benefit without OS data should change standard clinical practice or not. Two more trials in this setting with mature OS data were reported at ASCO 2021.

#8501 is the Japanese phase 3 RCT of **2 years of adjuvant gefitinib (n=116) vs. 4 cycles of cisplatin-vinorelbine (n=116)** in completely resected, *EGFR* mutated (exon 19 deletion or L858R), stage II-III NSCLC (*IMPACT*, WJOG6410L, UMIN000006252). The primary endpoint DFS was numerically longer with gefitinib arm (36 vs.

25.2 m), but this did not reach statistical significance HR 0.92 (95%CI 0.67-1.28; *P*=0.63). OS was not significantly different either. Exploratory subset analysis showed a benefit in patients ≥70 years old. Adjuvant gefitinib thus appeared to prevent early relapse, but not to significantly prolong DFS or OS.

#8502 is the final OS analysis of the Chinese phase 2 RCT of **neoadjuvant erlotinib for 42 days (n=37) vs. 2 cycles of cisplatin-gemcitabine (n=35)** in patients with stage IIIA-N2 NSCLC with *EGFR* mutations in exon 19 or 21. In the erlotinib arm, therapy continued postoperatively up to 12 m (*CTONG1103*, NCT01407822). Previously, it was shown that erlotinib treatment significantly improved DFS. The now mature median OS was 42.2 m for erlotinib, 36.9 m for cisplatin-gemcitabine (HR 0.83, 95%CI 0.47-1.47, *P*=0.513). The 5-year OS rates were 40.8% and 27.6%, respectively.

Comment: With these two presentations, together with the published OS data of the Chinese *ADJUVANT* trial, a comparison of 2 years of adjuvant gefitinib vs. 4 cycles of cisplatin-vinorelbine (*CTONG1104*, J Clin Oncol 2021), we now have 3 RCTs on (neo)adjuvant use of EGFR-TKIs with mature OS data. In all three, a *first-generation* EGFR-TKI was administered for up to 2 years *instead of* up to 4 cycles of cisplatin-based chemotherapy. Each of these trials has a similar pattern: an initial DFS advantage that disappeared about 2 years after the end of TKI administration, not resulting in an OS benefit. The TKI seems to delay recurrence, not avoid it, and is thus not resulting in improved cure rates.
Further follow-up is needed to determine if 3 years of osimertinib as in ADAURA will improve cure rates. Several elements give hope that it may be: the clear superiority of osimertinib compared to first-generation EGFR-TKI in EGFR blockade and CNS control in the advanced setting, the longer duration of TKI in ADAURA (3 instead of 2 years), and the much more prominent effect on early DFS than in the trials with first-generation EGFR-TKIs. Until then, the decision to administer adjuvant osimertinib depends on the weight of benefit given to delay of recurrence and better CNS control vs. the clinical and financial toxicity of 3 years of osimertinib.

3/ Early-stage NSCLC – (neo)adjuvant immunotherapy

Current ESMO guidelines recommend adjuvant chemotherapy with a cisplatin-based doublet in resected stage II and IIIA NSCLC. Neo-adjuvant delivery of therapy may have several advantages (*e.g.*, earlier action on micro-metastases, better tolerability and early surrogate endpoints including pathological response). However, at least for chemotherapy, meta-analyses showed similar clinical outcomes in adjuvant and neo-adjuvant studies. Given the survival benefits in stage III and IV NSCLC, the potential of immunotherapy using immune checkpoint inhibition (ICI) to improve cure rates in early-stage NSCLC is actively being assessed in many trials. This year, first data from two phase 3 trials were presented.

#8500 reported the *IMpower010* trial that assessed efficacy and safety of **adjuvant atezolizumab *vs.* best supportive care** (BSC) for one year after complete resection – and adjuvant chemotherapy as clinically indicated – in stage IB-IIIA (pTNM 7th) NSCLC. The primary endpoint – DFS in the PD-L1 positive (≥1%) stage II-IIIA population – was met, with median DFS not reached in the experimental arm vs. 35.3 m in the BSC arm (HR 0.66, 95%CI 0.50-0.88, *P*=0.004). Superior DFS was also present in the entire stage II-IIIA population, however less pronounced (HR 0.79, *P*=0.02) but not in the PD-L1 negative subgroup. *EGFR*- and *ALK*-positive subgroups also did not seem to benefit from adjuvant ICI. DFS did not (yet) cross the significance threshold in the ITT population (*i.e.*, also including stage IB) in this interim analysis. The safety profile of adjuvant atezolizumab was as expected, with 10.7% grade 3-4 treatment-related adverse events (TRAEs) and 7.9% grade 3-4 immune-mediated AEs.
Comment: while longer (OS) follow-up is needed, the observed DFS benefit may establish atezolizumab as the first ICI with a clinically meaningful benefit in the adjuvant setting in completely resected PD-L1 positive stage II-IIIA NSCLC after adjuvant chemotherapy.

#8503 presented the surgical outcomes in the *CheckMate 816* trial, previously reported at the AACR meeting (#CT003). In this trial, 3 cycles of a **neoadjuvant combination of nivolumab and chemotherapy *vs.* chemotherapy alone** were given to stage IB-IIIA (pTNM 7th) NSCLC patients eligible for surgery. The primary endpoint – pathological complete response (pCR, *i.e.* 0% residual viable tumor cells in primary tumor and lymph nodes) – was significantly better with the combination: pCR 24% vs. 2.2% (OR 13.9, *P*<0.0001). The benefit was consistent across disease stages and PD-L1 levels. Importantly, safety profiles were similar across both treatment arms. Details on surgical findings at this ASCO meeting showed no delay in surgery (21% *vs.* 18%), no impairment of surgery (16% vs. 21% cancelled), no reduction in completeness of resection (83% vs. 78%) and no increase in 90-day surgical toxicity (41% vs. 47%), respectively with the combination *vs.* with chemotherapy alone.
Comment: these data indicate that the neoadjuvant incorporation of nivolumab does not comprise feasibility and safety of surgery. Although an association between the surrogate endpoint pCR and OS has been described, more mature event-free and eventually OS data are needed for CM816 to become practice changing for resectable early-stage NSCLC.

4/ Unresectable stage III NSCLC – increased cure rates with immunotherapy

Based on the placebo-controlled phase 3 *PACIFIC* trial in patients with unresectable stage III NSCLC and concurrent chemoradiotherapy (cCRT), 1 year of durvalumab consolidation became standard of care.

#8511 brought the 5-year mature OS analysis of this *PACIFIC* trial. The updated HR for OS was 0.72 (95%CI 0.59-0.89), and OS at 5 years was 42.9% for durvalumab and 33.4% with placebo. By this, PACIFIC is the first trial that meets improvement in cure rate, as measured by 5-year OS in an immunotherapy trial in non-metastatic NSCLC. Future trials will define if immunotherapy concurrent to RT will be a further step forward.

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

Currently, there are several EMA-approved regimens for NSCLC reimbursed in Belgium: single agent pembrolizumab (PD-L1 ≥50%, Keynote-024) or atezolizumab (high PD-L1 expression ≥50% of tumor cells or ≥10% tumor-infiltrating cells, IMpower-110); combinations of 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). EMA-approval for nivolumab plus ipilimumab (nivo-ipi) with two initial cycles of chemotherapy (CheckMate-9LA) has been obtained in November 2020, and reimbursement in Belgium is awaited. An unanswered question is whether we can reduce chemotherapy in this setting.

#9000 reported an update (follow-up ≥24 m) of *CheckMate-9LA* comparing **nivo-ipi plus two cycles of chemotherapy vs. doublet chemotherapy alone**. The experimental arm received 360 mg nivo q3w + 1 mg/kg ipi q6w (for a max. of 2 years) plus two initial doublet chemotherapy cycles, versus the standard arm 4 cycles of chemotherapy (with optional pemetrexed maintenance if non-squamous histology). The experimental arm did better with median OS of 15.8 vs. 11.0 m, HR 0.72, 95%CI 0.61-0.86, and a durable 2-year OS rate of 38% vs. 26%. This clinically meaningful benefit was maintained across key subgroups, including PD-L1 expression (<1% and ≥1%) and histology (squamous and non-squamous). Grade 3-4 TRAEs were reported in 47% of nivo-ipi & chemo vs. 38% in chemotherapy alone. TRAEs leading to discontinuation of all components was observed in 17% vs. 6%, respectively. The updated results of CheckMate-9LA confirm nivo-ipi & two initial cycles of chemotherapy as an efficacious 1L treatment option for advanced stage NSCLC. They support the idea that we can reduce the number of initial chemotherapy cycles in NSCLC.

#9016 reported mature 4-year OS results for *CheckMate-227*, comparison of **nivo-ipi up to 2 years vs. chemotherapy alone**. A durable long-term OS benefit was demonstrated, regardless of PD-L1 expression or histology: 4-year OS was 29% vs. 18% (PD-L1 ≥1%), 24% vs. 10% (PD-L1 <1%), 20% vs. 6% (squamous), and

32% vs. 23% (non-squamous), respectively. TRAEs leading to discontinuation of nivo-ipi were observed in 17%. In a post-hoc analysis, discontinuation of nivo-ipi due to TRAE had no negative impact on the long-term benefit seen at 4 years; approximately half of the responders who had TRAEs leading to discontinuation of all drugs maintained their response for ≥3 years after treatment discontinuation.

Comment: a common aspect of these two trials is that the standard arm is no longer in line with current clinical practice, as most patients nowadays are treated upfront with chemo-immunotherapy (any PD-L1) or pembrolizumab alone (PD-L1 ≥50%). Whether the current standard of chemotherapy plus single agent anti-PD(L)1 therapy will be challenged by the double checkpoint inhibition plus 2 initial cycles of chemotherapy will become clearer once longer OS follow-up becomes available. Factors that may be of help in treatment choices are smoking status, PD-L1 expression level, histology, and co-morbidities for a given patient.

#9002 reported a post-hoc exploratory **pooled analysis of immune-related adverse events (irAEs) and efficacy** from three phase 3 IMpower trials (IMpower 130, 132, and 150). Patients in the atezolizumab-containing arms who experienced irAEs showed a longer median OS of 25.7 m vs. 13.0 m for those without irAEs, both in time-dependent Cox model (HR 0.69, 95% CI 0.60-0.78) and adjusted for landmark analysis at 1 m (HR 0.85), at 3 m (HR 0.81), at 6 m (HR 0.82) and at 12 m (HR 0.75). Remarkably, patients in the atezolizumab-containing arm with grade 3-5 irAE had the shortest OS versus those with grade 1-2 or no irAE, potentially due to treatment interruption or discontinuation.

6/ Advanced NSCLC – oncogene addiction: *EGFR* & overcoming osimertinib resistance

Disease progression on 1L osimertinib is led by the development of a broad range of resistance mechanisms: commonly yet unknown (>50%), or known on-target (such as acquired C797X mutation, *EGFR* amplification, …) or bypass alterations (such as *MET* amplification, *PI3KCA* mutation, …).

#9006 reported on *CHRYSALIS*, a phase 1 trial of **amivantamab plus lazertinib** for the treatment of osimertinib-relapsed and chemotherapy naïve *EGFR*-mutant NSCLC. Avimantamab is a bispecific antibody that targets EGFR and MET, while lazertinib is a potent third generation EGFR-TKI. In 45 evaluable patients, an ORR of 36%, DCR of 64%, median DoR of 9.6 m, and median progression-free survival (PFS) of 4.9 m were observed. *EGFR*- or *MET*-based resistance (by NGS or IHC) was predictive for response; however, half of the confirmed responders were not identified as *EGFR*- or *MET*-based. A tolerable safety profile was reported, 16% of grade ≥3 TRAEs and 4% TRAEs leading to discontinuation.

#9007 reported extended follow-up data from a phase 1 trial of **patritumumab-deruxtecan (HER3-DXd)** in TKI-resistant and heavily pretreated (median of 4 lines) *EGFR*-mutant NSCLC. **HER3-DXd** is an antibody drug conjugate of a monoclonal Ab targeting HER3 (expressed in 83% of NSCLC) and deruxtecan. In 57 evaluable patients (median follow-up time of 10.2 m) treated with HER3-DXd (5.6 mg/kg) after failure to EGFR-TKI (86% osimertinib), an ORR of 39%, DCR of 72%, median DoR of 6.9 m, and median PFS of 8.2 m were observed. Responses were observed in patients across all HER3 expression levels and a spectrum of EGFR-TKI resistance mechanisms (including *EGFR* mutations C797S or Ex20ins, *EGFR* amplifications, and non-*EGFR* mutations and fusions). Safety profile was manageable with of note treatment-related interstitial lung disease (7%), grade ≥3 TRAE of 54% and a low rate of TRAEs leading to discontinuation (11%).

7/ Advanced NSCLC – oncogene addiction: *KRAS(G12C)*

In lung adenocarcinoma, a somatic activating *KRAS* mutation is present in 30%. The most common variant is KRAS(G12C) accounting for 13% of all lung adenocarcinoma. Sotorasib is a small molecule inhibitor that irreversibly and selectively binds to the cysteine residue of the mutant KRAS protein.

#9003 reported an update including mature OS and exploratory subgroup analyses from the registrational phase 2 *CodeBreak 100* trial evaluating **sotorasib 960 mg QD orally** in pretreated *KRAS*(G12C)-mutant NSCLC. 93% of the included patients were current smokers, 81% received platinum-based chemotherapy and ICI. ORR was 37%, DCR 81%, median DoR 11.1 m, median PFS 6.8 m, and median OS 12.5 m. Sotorasib appeared to be less active in case of *KEAP1* co-mutations (19%), while the benefit was not hampered in case of *STK11* co-mutations & wild type *KEAP1* (21%). TRAEs were mostly low grade, grade 3 was observed in 20% (4% diarrhea; 12% liver function abnormalities) and grade 4 was observed in 1% (pneumonitis). TRAEs with dose modification occurred in 22%, and treatment discontinuation in 7%. A confirmatory phase 3 *CodeBreak 200* trial evaluating sotorasib vs. docetaxel in 2L/3L pretreated KRAS(G12C)-mutant NSCLC is ongoing.

8/ Advanced NSCLC – oncogene addiction: updated results on *EGFRex20ins/ HER2ex20/ MET/ RET*

a. *EGFR* exon 20 insertion

Present in about 4-6% of *EGFR*-mutant NSCLC and difficult to tackle target. Several targeted therapies are in clinical investigation. At WCLC 2020, a phase 2 trial of **poziotinib** *(ZENITH20*; n=115) reported an ORR 15%, median PFS 5.5 m, and grade ≥3 TRAE 30%. Also at WCLC 2020, the first results of **amivantamab** (CHRYSALIS phase 1; n=81) demonstrated an ORR 40%, median PFS 8.3 m, and grade ≥3 TRAE in 16%.
#9014 now presented updated phase 1//2 results on **mobocertinib** 160 mg QD in platinum-pretreated patients (n=114; median follow-up time 14 m): ORR 28%, DCR 78%, median DoR 17.5 m, median PFS 7.3 m, and grade ≥3 TRAEs in 47%, TRAE leading to treatment discontinuation in 17%.

b. *HER2* exon 20

#9015 presented phase 2 data on the triplet **trastuzumab+pertuzumab+docetaxel**, a combination of a taxane with two antibodies against HER2, in pretreated *HER2*ex20 NSCLC (n=46): ORR was 29%, DCR 85%, median DoR 11 m, median PFS 6.8 m. No treatment discontinuation due to toxicity. Grade ≥3 TRAEs were observed in 64% of patients, mostly neutropenia (33%), diarrhea (13%), and anemia (9%).

c. *MET* alterations (exon 14 skipping mutation or amplification)

#9020 Updated results on **capmatinib 400 mg BID** from *GEOMETRY mono-1* study showed an ORR of 67% in treatment-naïve cohorts (n=60) and 44% in pretreated cohorts (n=100), while median DoR were 12.6 m and 9.7 m, median PFS 10.8 m and 5.5 m, respectively. Favorable safety profile (mainly low-grade peripheral edema and gastro-intestinal side effects). Capmatinib has recently received FDA approval for first or later-line treatment of *MET exon 14* advanced NSCLC. EMA approval is awaited.
#9021 is the first report from the phase 2 *VISION* cohort B that evaluated **tepotinib 500 mg QD** in advanced NSCLC with MET amplification (n=24) defined as MET gene copy number ≥2.5 as detected by liquid biopsy: ORR 42%, median PFS 4.2 mo. Patients receiving tepotinib in 1L appeared to be more sensitive with an ORR 71%. Grade ≥3 TRAEs occurred in 29% of patients, without a need for treatment discontinuation.

d. RET fusion

RET fusions are present in up to 2% of advanced NSCLC cases. Two potent RET-selective TKIs, selpercatinib and pralsetinib recently received FDA approval for the treatment of *RET*-fusion positive advanced NSCLC.
#9089 showed updated results (median follow-up 17.11 m) of **pralsetinib 400 mg QD** in the phase 1/2 *ARROW* trial, including 194 patients with RET fusion-positive NSCLC of whom 126 platinum-pretreated and 68 treatment-naïve. The ORR was 62% and 79%, DCR 91% and 93%, median DOR 22.3 m and NR, and median PFS 16.5 m and 13.0 m, respectively. Treatment discontinuation due to TRAEs occurred in 6%. RCTs in 1L setting comparing these potent selective RET-inhibitors to platinum-doublet chemotherapy +/- pembrolizumab are ongoing (NCT04194944 selpercatinib; NCT04222972 pralsetinib).

9/ Advanced NSCLC – oncogene addiction: NRG1, new kid on the block

#3003 *Neuregulin 1* (NRG1) is a ligand that binds to HER3, promoting activation of PI3K/AKT/mTOR signaling. *NRG1* rearrangements (detected by RNAseq) are oncogenic drivers in solid tumors (0.3% of all NSCLC; enriched in lung invasive mucinous adenocarcinoma). Efficacy and safety of zenocutuzumab, a bispecific antibody that docks on HER2 and blocks NRG1 interaction with HER3, is evaluated in an ongoing phase 1/2 open label multi-tumor trial. In 24 NSCLC patients, an ORR of 29% was observed, and zenocutuzumab was well tolerated with only 3% grade 3/4 TRAE.

10/ Non-metastatic SCLC

In the updated ESMO Clinical Practice Guidelines for SCLC (Ann Oncol 2021), limited stage (LS, stage I-III) SCLC patients, eligible for treatment of curative intent, should be given concurrent chemoradiotherapy, preferably consisting of 4 cycles of cisplatin-etoposide and 45 Gy twice daily (BID) thoracic radiotherapy (TRT) in 30 fractions over 3 weeks (starting at cycle 1 or 2), followed by prophylactic cranial irradiation in non-progressive (PS 0-1) patients.

#8505 The *CALGB 30610/RTOG 0538* phase 3 trial compared a **high-dose of 70 Gy (once daily, QD, in 7 weeks) to standard 45 Gy (BID) TRT** in LS-SCLC patients. A third randomization arm of 61.2Gy concomitant boost TRT over 6 weeks was prematurely closed. CALGB 30610, with its 70 Gy QD TRT arm was designed to test 'superiority' over the Intergroup 0096 (Turrisi, 1999) 45 Gy BID TRT trial results. In the Turrisi trial, the control arm had a lower QD TRT dose of 45 Gy. In total, between March 2008 and January 2019, 638 pts were randomized. After a median follow-up of 2.84 years, 70 Gy QD TRT compared to BID TRT did not result in superior OS (HR 0.94, *P*=0.9) or PFS (HR 0.96, *P*=0.94). Rates of most G3+ AEs, and, especially, 'any' esophageal toxicity, were similar between the 2 cohorts (18.6% QD arm; 16.7% BID arm). A higher grade G5 toxicity, observed in the 70 Gy QD arm, warrants further monitoring (cardiac dose?) and clarification. Protocol modifications (like variable starting time of TRT and substituting carbo- for cisplatin) were made to support accrual and may have influenced the results.
Comment: based on these phase 3 CALGB 30610 results, 70 Gy QD TRT does not significantly improve OS results compared to 45 Gy BID TRT, which continues to be standard of care.

Full abstracts of this ASCO meeting can be found at:
https://meetinglibrary.asco.org/results?meetingView=2021%20ASCO%20Annual%20Meeting

For your calendar:
Respiratory Oncology Update 2021: Saturday 16/10/2021, format according to pandemic, follow on https://www.update-respiratoryonco.be/