REPORT ASCO 2018 CHICAGO: RESPIRATORY ONCOLOGY

Johan Vansteenkiste / Christophe Dooms, Univ. Hospital KU Leuven and Leuven Lung Cancer Group

OUR 10 MESSAGE HIGHLIGHTS

1/ Advanced NSCLC 1st line: IO versus chemotherapy

#LBA4 on the KEYNOTE-042 study was presented in the plenary session. In this RCT, 1274 untreated patients with NSCLC without targetable drivers and a PD-L1 score ≥1% were randomized to:
"*pembrolizumab 200 mg q3w*" vs. "*platinum-based chemotherapy*".
Chemotherapy was either carboplatin-pemetrexed with optimal maintenance pemetrexed for non-squamous histologies, or carboplatin-paclitaxel. The primary endpoints, OS in PD-L1 ≥50%, ≥20%, and ≥1%, are represented in the table. Grade 3-5 drug-related AEs were less frequent with pembrolizumab (17.8% vs. 41.0%).

	PD-L1 ≥50%		PD-L1 ≥20%		PD-L1 ≥1%	
	pembro (n=299)	chemo (n=300)	pembro (n=413)	chemo (n=405)	pembro (n=637)	chemo (n=637)
Median OS [95%CI]	20.0m [15.4-24.9]	12.2m [10.4-14.2]	17.7m [15.3-22.1]	13.0m [11.6-15.3]	16.7m [13.9-19.7]	12.1m [11.3-13.3]
HR [95%CI]	0.69 [0.56-0.85]		0.77 [0.64-0.92]		0.81 [0.71-0.93]	
P	*P*=0.0003		*P*=0.0020		*P*=0.0018	

2/ Advanced NSCLC 1st line: chemotherapy + IO versus chemotherapy (histology oriented)

#LBA9000 brought the results from IMPower 131. This is the first report available from a randomized trial in this setting focusing on squamous NSCLC. Patients were randomly assigned to:
"*A: atezolizumab 1200 mg q3w + carboplatin-paclitaxel*"; "*B: atezolizumab 1200 mg q3w + carboplatin-nab-paclitaxel*"; and "*C: carboplatin-nab-paclitaxel*".
The primary analysis of investigator-assessed PFS for arm B (343 patients) vs. arm C (340 patients) was presented. Median PFS was 6.3m in arm B vs 5.6m in arm C (HR 0.72; 1-year PFS 24.7 vs. 12%; *P*=0.0001). PFS benefit was present in all PD-L1 positive subgroups, most pronounced in TC3 or IC3. Grade 3-4 treatment-related AEs were 68.0% in arm B and 56.9% in arm C. Preliminary OS data showed no difference in mOS (14 m in both arms), but curves tended to separate after 15m with a currently immature 2-year OS of 32 vs. 24%.

#105 reported the 2nd interim analysis of the KEYNOTE-407 study. 560 untreated patient with squamous NSCLC were randomly assigned to:
"*pembrolizumab 200 mg q3w + carboplatin-(nab)paclitaxel*" vs. "*placebo + carboplatin-(nab)paclitaxel*".
The primary endpoint OS was significantly in favor of the combined therapy with a HR of 0.64 (median OS 15.9 vs. 11.3m; P=0.0008). As for biomarkers, HR was 0.64 for PD-L1 ≥50%, 0.57 for PD-L1 1-49%, and 0.61 for PD-L1<1%. PFS was also in favor of pembrolizumab (HR 0.56; P<0.0001). Grade 3-4 AEs were similar across arms (69%), but twice as much patients interrupted therapy for AEs in the combined arm (13 vs. 6%).
Both of these trials are of interest for the 1L therapy of squamous NSCLC, although the chemotherapy is not the standard used in Europe. Data with platinum-gemcitabine are eagerly awaited.

#9021 reported on HR-QoL data in the KEYNOTE-189 study. In this large double-blind, ph3 trial, 616 patients with non-squamous NSCLC were randomized to:
"*Pembrolizumab 200 mg q3w + platinum-pemetrexed*" vs. "*Placebo + platinum-pemetrexed*".
A quite impressive improvement with the combined arm of both OS (HR 0.49; 1-year OS 69 vs. 49%) and PFS (HR 0.52; 1-year PFS 34 vs. 17%) was reported recently. The current abstract reported on prespecified

patient-reported outcomes (PRO). The analyses were based on the EORTC QLQ-C30 and QLQ-LC13. Questionnaire compliance was high. It was shown that the combined therapy maintained or improved HR-QoL over chemotherapy alone, despite the higher grade 3-5 treatment-related AEs with the combination.

#9002 reported the interim OS findings in IMPower150. This was a RCT in 1202 patients with non-squamous NSCLC with 3 arms:

"*A: atezolizumab 1200 mg q3w + carboplatin-paclitaxel*"; "*B: atezolizumab 1200 mg q3w + carboplatin-paclitaxel-bevacizumab*"; and "*C: carboplatin-paclitaxel-bevacizumab*".

A benefit in PFS with arm B over arm C has been reported previously (HR 0.62; 1-year PFS 37 vs. 18%). Presented now was the interim OS analysis with 13.5m minimal follow-up. OS was improved in arm B vs. C (HR 0.78; *P*= 0.016; 1-year OS 67 vs. 61%). The median OS was 22.5 vs. 16.4m in PD-L1 positive patients, 17.1 vs. 14.1m in the PD-L1 negative patients. Benefits were also reported in patients with EGFR+/ALK+ NSCLC previously treated with TKI (N=104; OS HR 0.54) and those with liver metastases (N=94; HR 0.54). Remarkably, there was little OS difference between arm A and arm C (HR 0.88; *P*=0.204). Gr 3-4 treatment-related AEs occurred in 43%, 57%, and 49% of patients in arms A, B, and C, respectively.

3/ Advanced NSCLC 1st line: chemotherapy + IO versus chemotherapy (all histologies)

#9001 presented a next analysis from the very large (1739 randomized patients) but also very complex ph3 trial CHECKMATE-227. This study was designed with 3 arms in tumors ≥1% PD-L1 expression, and 3 arms in those with <1% PD-L1 expression. Quite late in the course of the trial – but with data still blinded – another biomarker was introduced, i.e. tumor mutation burden (TMB). Because of the secondary introduction of this biomarker, its results were available in only 57.7% of the samples. In that subgroup, another subgroup analysis in the 44.2% of tumors with high TMB (i.e. at least 10 mutations per megabase) was reported recently to be positive for PFS (299 patients; HR 0.58; P<0.001). At ASCO, a descriptive analysis of PFS in 363 patients with tumors with <1% PD-L1 expression was shown for:

"*Nivolumab 360 mg q3w + platinum doublet chemotherapy*" vs. "*doublet chemotherapy alone*".

PFS was improved with the combination (HR 0.74; 1-year PFS 26 vs. 14%), more pronounced in non-squamous (HR 0.68) than in squamous NSCNC (HR 0.92).

4/ Advanced NSCLC EGFR-TKIs

All previously published ph3 RCTs comparing a 1st/2nd generation EGFR-TKI to chemotherapy could not demonstrate an OS benefit for the EGFR-TKI, which was attributed to cross-over in subsequent treatment. At this ASCO two ph3 trials (NEJ009 and ARCHER1050) and one ph2R trial could demonstrate an OS benefit of the experimental regimen over the 1st generation TKI gefitinib.

#9005 is a Japanese ph3 trial (NEJ009)and randomly assigned 344 patients to:

"carboplatin-pemetrexed+gefitinib"* vs. *"gefitinib with platinum-based chemotherapy at progression".

The protocol was amended for multiple prespecified primary endpoints with hierarchical testing (PFS1 - PFS2 - OS). The combination achieved a superior PFS1 with a HR 0.49 (95%CI 0.39-0.63) and mPFS of 20.9 vs 11.2 m, resulting in a superior OS with a HR 0.70 (95% CI 0.52-0.93) and mOS of 52.2 vs 38.8 months. Hematological toxicities were more common in the combination arm although few patients (10%) discontinued due to toxicities in both arms. No difference was observed in PFS1 of the experimental arm vs. PFS2 of the standard arm (20.9 vs 21.1 m). The OS benefit of the experimental arm seems to be driven by the upfront combination therapy given the higher ORR (84 vs. 67%) – which might be responsible for reducing clonal diversity and targeting of tolerant cells augmenting the natural history of the disease – and by the fact that 26% of patients in the standard arm received no subsequent chemotherapy at progression. NEJ009 underscores the role of chemotherapy in EGFR-Mt NSCLC, and gefitinib combined with platinum-pemetrexed may be an effective option for 1L treatment of advanced EGFR-Mt NSCLC.

#9004 reported the OS analysis of the ph3 ARCHER 1050 trial with 2nd generation irreversible pan-HER TKI dacomitinib. 452 patients were randomly assigned to:

"dacomitinib 45 mg/d"* vs. *"gefitinib 250 mg/d".

Of note, patients with (asymptomatic) brain metastases were not allowed in the trial. The primary endpoint of PFS was met with a mPFS of 14.7 vs 9.2 months; HR 0.59 (95%CI 0.47-0.74), *P*<0.0001. Dacomitinib also demonstrated a significant improvement in the prespecified secondary OS endpoint with mOS of 34.1 vs 26.8 months, HR 0.76 (95%CI 0.58-0.99), *P*=0.044. There was no difference in subsequent treatment between both arms. Dacomitinib caused significantly more grade 2 and 3 side-effects vs. gefitinib: rash 33 vs. 9%; stomatitis 21 vs. 3%; diarrhea 37 vs. 10%.

#9013 was a small Latin American ph2R trial of 116 patients evaluating the addition of metformin to a 1st or 2nd generation EGFR-TKI. There was an improvement in both PFS (mPFS 14 vs. 10 m) and OS (mOS 31.7 vs. 17.5 m; HR 0.67 (95%CI 0.01-0.54), *P*=0.02).

Since the publication of FLAURA (Soria *et al*. NEJM 2018;378:113-25), osimertimib could be considered the new standard of care 1st line treatment for patients with EGFR-mutant lung cancer. Median PFS was significantly longer with osimertinib than with standard 1st generation EGFR-TKI with a mPFS 18.9 vs 10.2 months, HR 0.46 (95%CI 0.37-0.57), and an early separation of the curves at 6 weeks of treatment. Mature OS data are still pending and eagerly awaited as these, combined with the very favorable toxicity profile, could tailor the optimal choice of first line EGFR-TKI regimen to the individual patient preference.

5/ Advanced NSCLC EGFR-TKIs and anti-angiogenesis

A synergistic anti-tumor activity of dual VEGFR and EGFR inhibition overcoming T790M resistance was suggested in the past. A European ph2 single arm 1L study with erlotinib-bevacizumab (BELIEF; n=109) demonstrated a mPFS of 13 months in ITT and 16 months in T790M positive tumors.

#9007 reported the OS analysis of a smaller Japanese ph2 RCT (J025567; n=154) initially presented at ASCO 2014, with a significantly longer PFS for erlotinib-bevacizumab vs. erlotinib (mPFS 16 vs 9.7 months; HR 0.54). The trial was not truly powered to assess OS, but at this ASCO, a lack of OS difference between the two arms was reported. However, recently the published AURA and FLAURA trials with osimertinib, a third generation EGFR-TKI surpassing T790M resistance, make erlotinib as the control arm obsolete.

#9006 is a Japanese ph3 trial (NEJ026, n=228) which evaluated the superiority of **"*1L erlotinib + bevacizumab*" vs. "*1L erlotinib alone*".**

In a preplanned interim analysis, a superior PFS with a HR 0.61 (95%CI 0.42-0.88; mPFS 16.9 vs. 13.3 ms was reported. No difference in ORR (72 vs 66%). Significantly higher toxicity rates were observed in the bevacizumab arm (including 22% grade 3 hypertension), leading to discontinuation of bevacizumab for AEs in 30% of patients. The OS data are still immature.

6/ Advanced NSCLC new TKIs for other oncogene addictions

#9019: Squamous NSCLC with PI3K mutation, cell cycle alteration, or FGFR alteration: the: umbrella ph2 LungMAP protocol found limited efficacy of TKI targeted therapies, but continued evaluation of novel targets and therapeutics is planned.

#9016/9048: METex14 mutant NSCLC: ph2 with the type 1b MET-inhibitor tepotinib (n=36). TKI hits the target with ORR 60%.

#9062 MET amplified (MET/CEP7 ratio ≥4) NSCLC: update on ph1 crizotinib (n=20) showed ORR 40% and mPFS 6.7m.

#102: RET FISH+ NSCLC: ph1 with LOXO-292 (n=38). Drug hits the target with ORR 77%. Vandetanib+everolimus (n=16) in abstract **#9035** gave an ORR of 62%.

#100: HER2 amplified NSCLC: update in the ph2 trial with ado-trastuzumab-emtansine showed an ORR of 43% and a mPFS of 7m.

#9015: EGFR exon 20 insertion NSCLC: ph1 TAK-788 ORR 40%.

#9043 ALK+ NSCLC: update on ALEX, ph3 trial of alectinib versus crizotinib, confirms superior efficacy with mPFS 34.8 vs. 10.9 m (HR 0.43) and median DOR 33.1 vs. 11.1 m.

#9093 ALK+ NSCLC: update on sequential crizotinib followed by alectinib showed a median combined PFS of 22.9 m and a 5-year OS of 59%. Considering this as a historical comparator, patients may derive greater benefit from first-line alectinib.

#9032 ALK+ NSCLC: update on ph2 lorlatinib after alectinib (n=62) showed ORR 40% and PFS 5.5 m, with intracranial ORR 41%, and median DOR 11.6 m.

7/ Genomics

#LBA8501: The Circulating Cancer Genome Atlas (CCGA) is a prospective multi-institutional longitudinal cohort study designed for comprehensive genome-wide sequencing analysis for untreated early stage lung cancer detection from paired plasma cell-free DNA and white blood cell (clonal hematopoiesis). Currently 12,292 of 15,000 participants are enrolled (70% cancer and 30% non-cancer), and a pre-specified case-control interim analysis on a first training set (n=1785) and test set (n=1015) was presented at this ASCO. Accounting for clonal hematopoiesis allowed high specificity (>98%) thus minimizing false positives, while the sensitivity was 48-56% in stage I-IIIA and 85-93% in stage IIIB-IV. While prior attempts at blood-based assays have been unsuccessful, these preliminary data support the promise of using cfDNA-based sequencing to develop an early cancer detection test with high specificity.

#8516: The Cancer Genome Atlas Research Network conducted a comprehensive integrated genomic study of malignant pleural mesothelioma. They found an overall prevalence of BAP1 alterations in 57%, a strong expression in epithelioïd mesothelioma of the immune checkpoint molecule VISTA, and a novel subtype of mesothelioma characterized by extensive LOH and inactivating mutations in p53 and SETB1. These findings raised new promising biomarkers for further investigation of targeted therapeutic options instead of empiric therapy in unselected mesothelioma patients.

8/ New avenues for relapsed advanced SCLC

#8507: A ph2 single arm study (TRINITY; n=339) of Rova-T in in ≥3L relapsed/refractory SCLC with DLL3-expression demonstrated an overall ORR of 12.4%. DLL3-high (IHC >75%) patients were most likely to benefit with ORR 14.3% (24% in 3L) and mOS 5.6 months. Frequency of G3/4 AEs was 53%, with pleural/pericardial effusions, edema and photosensitivity as most important ones, resulting in drug interruption in 10%. Rova-T is currently being evaluated in a 2L biomarker-selected ph3 study (TAHOE).

#8506: A ph2 multi-cohort study (Keynote-158; n=92) evaluated pembrolizumab 200mg IV q3w in patients who progressed on or were intolerant to standard therapy in advanced SCLC. The primary endpoint ORR was 18.7%, with a promising 35.7% in PD-L1 positive and a low 6% in PD-L1 negative patients. Responses were durable: mDOR not reached and >12 m in 73% of responders. Median OS was 8.7 m with a promising median OS 14.9 m (95%CI 5.6-NR) in PDL1+ patients. Pembrolizumab plus standard chemotherapy is being evaluated in a 1L ph3 study (Keynote-604).

#8518: A ph1/2 study (n=21) of durvalumab monotherapy in relapsed advanced SCLC observed a ORR 10% and 1-year OS rate 28%. No TRAE leading to discontinuation were observed.

#8517: A ph1 dose expansion study (n=30) with durvalumab + tremelimumab in relapsed advanced SCLC observed ORR 13% with a mDOR of 18.9 months and 1-year OS rate 42%. No treatment-related AEs leading to discontinuation were observed.

9/ New avenues for 1L advanced mesothelioma

#8505: The addition of bevacizumab to standard 1L cisplatin-pemetrexed chemotherapy has proven able to enhance OS in a ph3 RCT (ASCO 2015). The impact on quality of life, measured by QLQ-C30 and QLQ-LC3 questionnaires and analyzed as HRQoL deterioration-free survival (QFS), was reported now. No deterioration in HRQoL was observed with a trend towards delayed pain worsening (HR 0.84, p=0.08) and significant improvement in peripheral neuropathy (HR 0.74, p=0.003). Therefore, platinum-pemetrexed + bevacizumab could be considered for these patients.

#8514: A ph2R SWOG S0905 trial (n=92) evaluated another anti-angiogenesis agent, the VEGFR-TKI cediranib. 1L patients received platinum-pemetrexed with/without cediranib. The trial did not meet its primary endpoint of PFS, and toxicity with cediranib was important (G3/4 64 vs. 54%).

#8503: A ph2 single arm study (DREAM) is the first to evaluate a cytotoxic/immunotherapy combination in 1L mesothelioma: durvalumab + platinum-pemetrexed (6 cycles) followed by durvalumab maintenance for 52 weeks. PFS at 6 months (PFS6) is the primary endpoint. The first stage (n=31) reported a promising activity with a PFS6 rate of 65%, a confirmed iRECIST ORR 58% and DCR 87%, and a mPFS of 7.3 m (95%CI 5.8-11.0). Further evaluation is warranted given the promising activity and tolerability.

10/ New avenues for radiotherapy in NSCLC

At the presidential session of the ESMO 2017 meeting, the results of the PACIFIC trial (durvalumab maintenance therapy vs. placebo in stage III unresectable NSCLC radically treated with chemoradiotherapy) have been presented. There was an impressive improvement with durvalumab, PFS 16.8 vs. 5.6 m, HR 0.52, time to death or distant metastasis 23.2 vs. 14.6 m, HR 0.52. Toxicity was manageable with a grade 3-4 pneumonitis rate of 3.4%. This was the first expansion of the benefits of IO therapy to non-metastatic NSCLC. Several abstracts at ASCO 2018 were in the same setting.

#8500 reported on a ph2 trial (93 patients) of concurrent chemoradiotherapy with consolidation pembrolizumab 200 mg q3w in unresectable stage III NSCLC (NCT02343952). The primary endpoint – median time to metastatic disease or death – was not yet reached, but the estimates of 1- and 2-year OS rates were 80.5% and 68.7%, better than expected with chemoradiotherapy alone.

#8510 was the very first trial to report on IO therapy administered concurrently with radiotherapy in unresectable stage III NSCLC, a matter of high scientific interest according to preclinical models. The NICOLAS trial, within the European Network ETOP (NCT 02434081), was a front-runner in this setting. Hence, safety defined as the rate of grade ≥3 pneumonitis at 6 months post RT was the primary endpoint. Patients received 3 cycles of platinum-based chemotherapy (platinum + etoposide, vinorelbine or pemetrexed) and radical RT of 66 Gy. Nivolumab treatment (240 mg / Q4W) started concurrently to RT. An interim report on safety (21 patients) was presented. The most frequently observed adverse events were fatigue an anemia. No pneumonitis grade ≥3 occurred in the first 21 patients.

#9023 was a nice Dutch ph2 RCT on enhancing the efficacy of pembrolizumab in stage IV NSCLC by the use of stereotactic ablative radiotherapy (SABR), based on the potential of radiation of increased tumor antigen release, improved antigen presentation and T-cell infiltration (NCT02492568). 72 patients with stage IV relapsed NSCLC were randomly assigned to:
"*SABR on a single metastatic site before pembrolizumab 200 mg q3w*" vs. "*pembrolizumab alo*ne".
The primary endpoint – objective response rate (ORR) at 12 weeks – was 41% in the SABR arm vs. 19% in the control arm. Median PFS was 1.8 months in the control arm vs 6.4 months in the SABR arm (HR 0.55; *P*=0.04). Grade ≥3 toxicity was experienced in 22% of patients in the control arm vs 17% in the experimental arm.

Full abstracts of this ASCO meeting can be found at:
https://meetinglibrary.asco.org/browse-meetings/2018%20ASCO%20Annual%20Meeting?filters=JTVCJTdCJTIyZmllbGQlMjIlM0ElMjJNZWRpYVR5cGVzJTIyJTJDJTIydmFsdWUlMjIlM0ElMjJBYnN0cmFjdHMlMjIlMkMlMjJxdWVyeVZhbHVlJTIyJTNBJTIyQWJzdHJhY3RzJTIyJTJDJTIyY2hpbGRyZW4lMjIlM0ElNUIlNUQlMkMlMjJpbmRleCUyMiUzQTAlMkMlMjJuZXN0ZWRQYXRoJTIyJTNBJTIyMCUyMiU3RCU1RA%3D%3D

For your calendar:
Respiratory Oncology Update 2018: 10 November, 2018 La Hulpe.
https://www.update-respiratoryonco.be/en/Home_10_6_12.html