Highlights in respiratory oncology

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This article will briefly discuss the top stories in the field of respiratory oncology presented during the 2018 annual meeting of the American Society of Clinical Oncology (ASCO). For a complete overview of abstracts we refer to the official meeting website: https://am.asco.org.

1) ADVANCED NSCLC 1ST LINE: IO VERSUS CHEMOTHERAPY

The plenary session of the 2018 annual ASCO meeting featured the presentation of the KEYNOTE-042 study. In this randomized controlled trial (RCT), 1,274 untreated patients with NSCLC without targetable drivers and a PD-L1 score of ≥1% were randomized to: *pembrolizumab 200 mg q3w vs. platinum-based chemotherapy*. Chemotherapy consisted of either carboplatin-pemetrexed with optimal maintenance pemetrexed for non-squamous histologies, or carboplatin-paclitaxel. The primary endpoint of the study was overall survival (OS). The OS in PD-L1 ≥50%, ≥20%, and ≥1% are depicted in *Table 1*. Grade 3-5 drug-related AEs were less frequent with pembrolizumab (17.8% *vs.* 41.0%).[1]

2) ADVANCED NSCLC 1ST LINE: CHEMOTHERAPY + IO VERSUS CHEMOTHERAPY (HISTOLOGY ORIENTED)

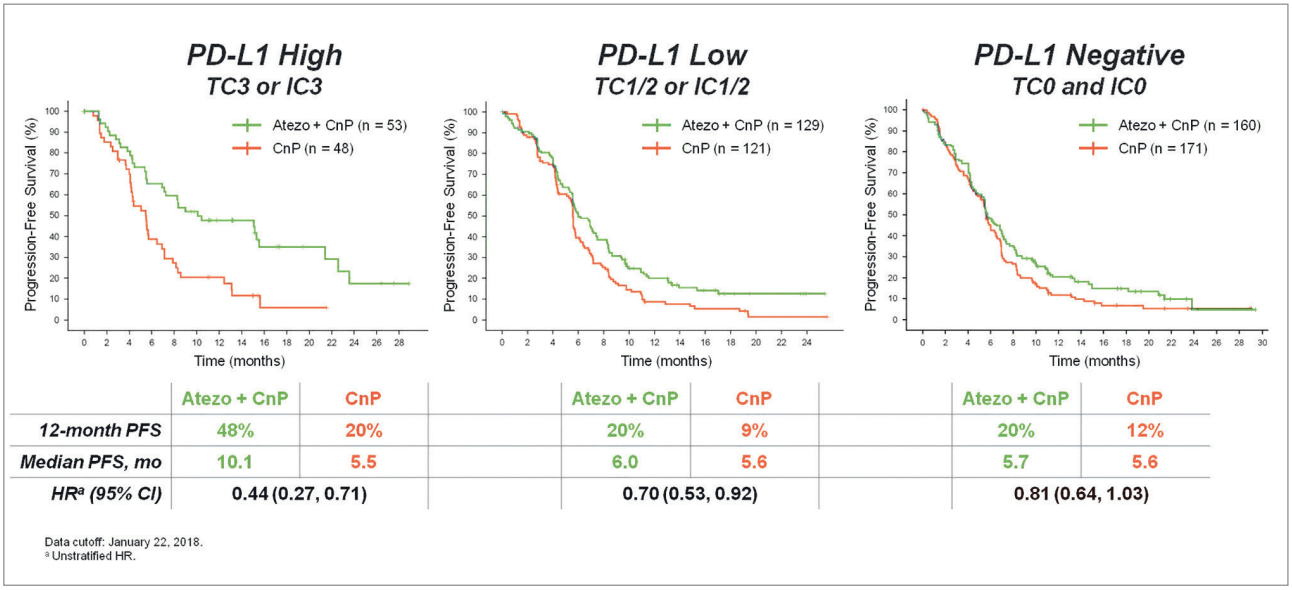
Abstract LBA9000 brought the results from IMPower 131.[2] This is the first report available from a randomized trial in this setting focusing on squamous NSCLC. Patients were randomly assigned to: *atezolizumab 1200 mg q3w + carboplatin-paclitaxel (A), atezolizumab 1200 mg q3w + carboplatin-nab-paclitaxel (B), or carboplatin-nab-paclitaxel (C)*. The primary analysis of investigator-assessed PFS for arm B (343 patients) *vs.* arm C (340 patients) was presented. The median PFS was 6.3 months in arm B *vs.* 5.6 months in arm C (HR[95%CI]: 0.72 [0.60-0.85]; 1-year PFS 24.7 *vs.* 12%; p=0.0001). This PFS benefit was present in all PD-L1 positive subgroups, but was most pronounced in TC3 or IC3 patients (*Figure 1*). 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 median OS (14 months in both arms), but curves tended to separate after 15 months with a currently immature 2-year OS of 32 *vs.* 24% (*Figure 1*).[2]

Abstract 105 reported the 2nd interim analysis of the KEYNOTE-407 study. In this trial, 560 untreated patients with squamous NSCLC were randomly assigned to *pembrolizumab 200 mg q3w + carboplatin-(nab)paclitaxel vs. placebo + carboplatin-(nab)paclitaxel*. The primary endpoint of 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%).[3]

Both of these trials are of interest for the first-line therapy

Table 1. OS in function of PD-L1 expression in the phase III KEYNOTE-042 study.[1]

	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] P	0.69 [0.56-0.85] P=0.0003		0.77 [0.64-0.92] P=0.0020		0.81 [0.71-0.93] P=0.0018	



	Atezo + CnP	CnP	Atezo + CnP	CnP	Atezo + CnP	CnP
12-month PFS	48%	20%	20%	9%	20%	12%
Median PFS, mo	10.1	5.5	6.0	5.6	5.7	5.6
HR[a] (95% CI)	0.44 (0.27, 0.71)		0.70 (0.53, 0.92)		0.81 (0.64, 1.03)	

Data cutoff: January 22, 2018.
[a] Unstratified HR.

FIGURE 1. Investigator assessed PFS in PD-L1 subgroups for Arm B vs. Arm C in the IMpower 131 study.[2]

of squamous NSCLC, although chemotherapy is not standard use in Europe. Data with platinum-gemcitabine are eagerly awaited.

Garrasino et al. reported on HR-QoL data in the KEYNOTE-189 study. In this large double-blind, phase 3 trial, 616 patients with non-squamous NSCLC were randomized to *Pembrolizumab 200 mg q3w + platinum-pemetrexed*, or *Placebo + platinum-pemetrexed*.[4] 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 studies. 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.[4]

Finally, abstract 9002 reported the interim OS findings of the IMPower150 study. This is a randomized controlled trial (RCT) including 1,202 patients with non-squamous NSCLC. Patients were randomized to one of the following arms: *atezolizumab 1200 mg q3w + carboplatin-paclitaxel* (A), *atezolizumab 1200 mg q3w + carboplatin-paclitaxel-bevacizumab* (B) and *carboplatin-paclitaxel-bevacizumab* (C).[5] 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.* 16.4 months in PD-L1 positive patients and 17.1 *vs.* 14.1 months 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 in patients with liver metastases (N=94; HR: 0.54).[5] Remarkably, there was little OS difference between arm A and arm C (HR 0.88; *P*=0.204). Grade 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)

Borghaei et al. presented a further analysis from the very large (1,739 randomized patients) and very complex phase 3 CHECKMATE-227 trial.[6] This study was designed with 3 arms in tumors with ≥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 2018, 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 (Figure 2).* This analysis revealed that the PFS was improved with the combination (HR: 0.74; 1-year PFS 26 *vs.* 14%). Of note, this PFS benefit was more pronounced in non-squamous (HR: 0.68) than in squamous NSCNC (HR: 0.92).[6]

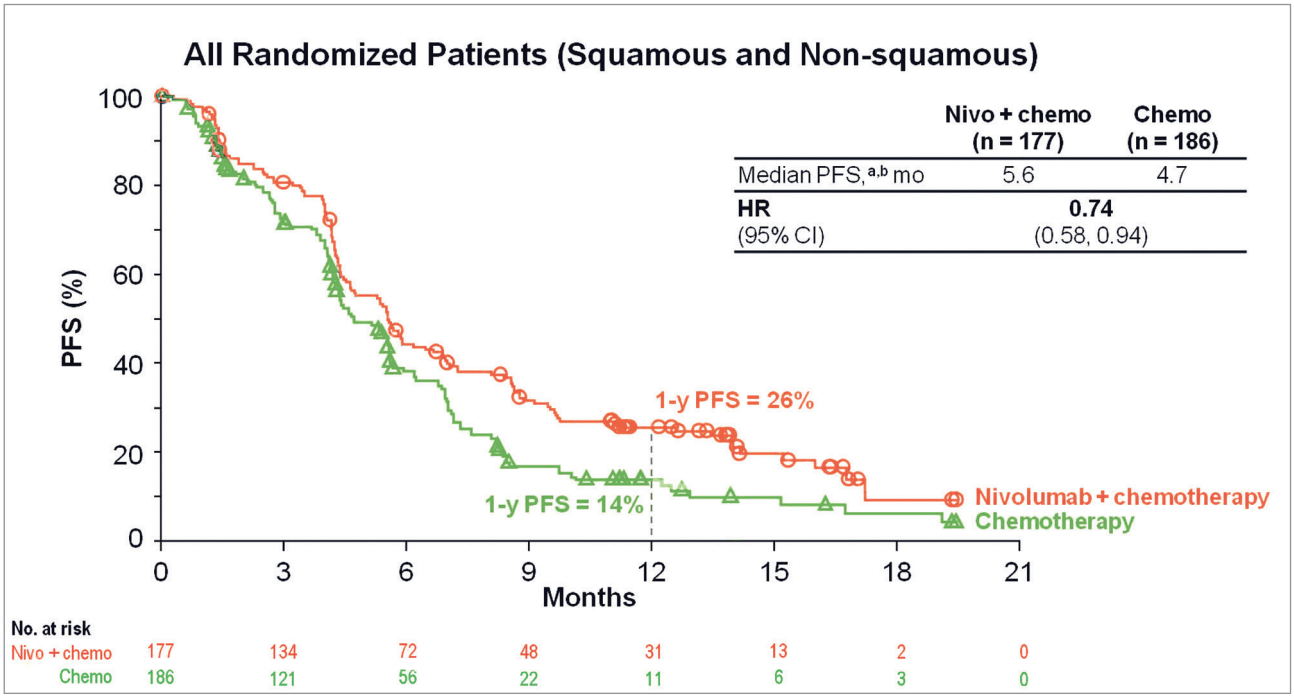


FIGURE 2. Nivolumab + chemotherapy vs. chemotherapy in patients with <1% tumor PD-L1 expression.[6]

4) ADVANCED NSCLC EGFR-TKIs

All previously published phase 3 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 ASCO 2018, two phase 3 trials (NEJ009 and ARCHER1050) and one phase 2 study could demonstrate an OS benefit of the experimental regimen over the 1st generation TKI gefitinib.

In the Japanese phase 3 NEJ009 trail, 344 patients were and randomly assigned to *carboplatin-pemetrexed+gefitinib, or gefitinib with platinum-based chemotherapy at progression.*[7] The protocol was amended for multiple prespecified primary endpoints with hierarchical testing (PFS1 - PFS2 - OS). The combination achieved a superior PFS1 with a HR of 0.49 (95%CI: 0.39-0.63) and a median PFS of 20.9 *vs* 11.2 months. This translated into a superior OS with a HR of 0.70 (95% CI 0.52-0.93) and a median OS 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 months). 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 first-line treatment of advanced *EGFR*-mutant NSCLC.[7]

Abstract 9004 reported the OS analysis of the phase 3 ARCHER 1050 trial testing the 2nd generation, irreversible, pan-HER TKI dacomitinib. In this trial 452 patients were randomly assigned to *dacomitinib 45 mg/d vs. gefitinib 250 mg/d.*[8] Of note, patients with (asymptomatic) brain metastases were not allowed in the trial. The primary endpoint of PFS was met with a median PFS of 14.7 *vs.* 9.2 months (HR[95%CI]: 0.59[0.47-0.74]), p<0.0001). Dacomitinib also demonstrated a significant improvement in the prespecified secondary OS endpoint with median OS of 34.1 *vs.* 26.8 months (HR[95%CI]: 0.76[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%. [8]

Finally, abstract 9013 featured a small randomized Latin American phase 2 trial of 116 patients evaluating the addition of metformin to a 1st or 2nd generation EGFR-TKI. The study showed an improvement in both PFS (median PFS 14 *vs.* 10 months; HR[95%CI]: 0.57[0.36-0.88]; p=0.011) and OS (median OS 31.7 *vs.* 17.5 months; HR[95%CI]: 0.50[0.28-0.90], p=0.02).[9]

Since the publication of FLAURA, osimertinib could be considered the new standard of care 1st line treatment for patients

with EGFR-mutant lung cancer.[10] In this trial, the median PFS was significantly longer with osimertinib than with standard 1st generation EGFR-TKI with a median PFS of 18.9 *vs.* 10.2 months (HR[95%CI]: 0.46[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 phase 2, single arm, first-line study with erlotinib-bevacizumab (BELIEF; N=109) demonstrated a median PFS of 13 months in the intent-to-treat (ITT) population and of 16 months in T790M positive tumors.[11]

Abstract 9007 reported the OS analysis of a smaller Japanese phase 2 RCT (J025567; N=154) initially presented at ASCO 2014, with a significantly longer PFS for erlotinib-bevacizumab *vs.* erlotinib (median PFS 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.[12] However, the recently published AURA and FLAURA trials with osimertinib, a third generation EGFR-TKI surpassing T790M resistance, make erlotinib as the control arm obsolete.

Abstract 9006 discussed a Japanese phase 3 trial (NEJ026, N=228) which evaluated the superiority of *first-line erlotinib + bevacizumab vs.* first-line *erlotinib alone*.[13] In a preplanned interim analysis, a superior PFS with a HR of 0.61 (95%CI: 0.42-0.88; median PFS 16.9 *vs.* 13.3 months). 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.[13]

6) ADVANCED NSCLC NEW TKIs FOR OTHER ONCOGENE ADDICTIONS

A series of interesting abstracts were presented discussing new TKIs in the setting of advanced NSCLC:

- Abstract 9019: Squamous NSCLC with PI3K mutation, cell cycle alteration, or FGFR alteration: the umbrella phase 2 LungMAP protocol found limited efficacy of TKI targeted therapies, but continued evaluation of novel targets and therapeutics is planned.[14]
- Abstracts 9016/9048: METex14 mutant NSCLC: phase 2 with the type 1b MET-inhibitor tepotinib (N=36). TKI hits the target with ORR 60%.[15,16]
- Abstract 9062: MET amplified (MET/CEP7 ratio ≥4) NSCLC: update on phase 1 crizotinib (N=20) showed an ORR 40% and a median PFS of 6.7 months.[17]
- Abstract 102: RET FISH+ NSCLC: phase 1 with LOXO-292 (N=38). Drug hits the target with ORR 77%. Vandetanib+everolimus (N=16) in abstract #9035 gave an ORR of 62%.[18,19]
- Abstract 100: HER2 amplified NSCLC: update in the phase 2 trial with ado-trastuzumab-emtansine showed an ORR of 43% and a median PFS of 7 months.[20]
- Abstract 9015: EGFR exon 20 insertion NSCLC: phase 1 TAK-788 ORR 40%.[21]
- Abstract 9043 ALK+ NSCLC: update on the ALEX, phase 3 trial of alectinib *vs.* crizotinib, confirms superior efficacy with a median PFS of 34.8 *vs.* 10.9 months (HR: 0.43) and a median DOR of 33.1 *vs.* 11.1 months.[22]
- Abstract 9093 ALK+ NSCLC: update on sequential crizotinib followed by alectinib showed a median combined PFS of 22.9 months and a 5-year OS of 59%. Considering this as a historical comparator, patients may derive greater benefit from first-line alectinib.[23]
- Abstract 9032 ALK+ NSCLC: update on phase 2 lorlatinib after alectinib (N=62) showed an ORR of 40% and a median PFS of 5.5 months, with an intracranial ORR of 41%, and a median DOR of 11.6 months.[24]

7) GENOMICS

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).[25] 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=1,785) and test set (N=1,015) was presented at ASCO 2018. 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.[25] 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.

The Cancer Genome Atlas Research Network conducted a comprehensive integrated genomic study of malignant pleural mesothelioma.[26] 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

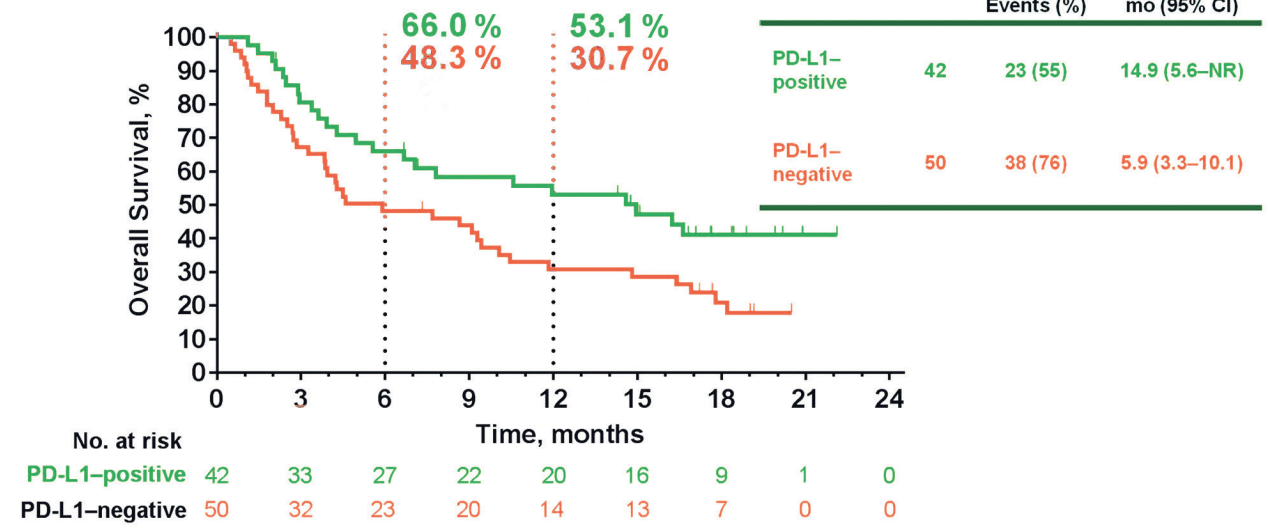


FIGURE 3. OS by tumor PD-L1 status in a phase II trial evaluating pembrolizumab in SCLC patients.[28]

findings raise 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

A phase 2 single arm study (TRINITY; N=339) of rovalpituzumab tesirine (Rova-T) in in ≥3rd line relapsed/refractory SCLC with *DLL3*-expression demonstrated an overall ORR of 12.4%. DLL3-high (IHC >75%) patients were most likely to benefit with an ORR 14.3% (24% in 3rd line) and a median OS of 5.6 months. The frequency of G3/4 AEs was 53%, with pleural/pericardial effusions, edema and photosensitivity as most important ones, resulting in drug interruption in 10%.[27] Rova-T is currently being evaluated in a 2L biomarker-selected phase 3 study (TAHOE).

A phase 2 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 of ORR was 18.7%, with a promising 35.7% ORR in PD-L1 positive patients and a much lower (6%) ORR in PD-L1 negative patients. Responses were durable as the median DOR was not reached and exceeded 12 months in 73% of the responders. The reported median OS was 8.7 months with a promising median OS of 14.9 months (95%CI 5.6-NR) in PDL1+ patients (*Figure 3*).[28] Pembrolizumab plus standard chemotherapy is being evaluated in a first-line phase 3 study (Keynote-604).

A phase 1/2 study (N=21) of durvalumab monotherapy in relapsed advanced SCLC observed an ORR of 10% and a 1-year OS rate of 28%. No treatment-related AEs leading to discontinuation were observed.[29]

Finally, a phase 1 dose expansion study (N=30) with durvalumab + tremelimumab in relapsed advanced SCLC reported an ORR of 13% with a median DOR of 18.9 months and 1-year OS rate of 42%. No treatment-related AEs leading to discontinuation were observed.[30]

9) NEW AVENUES FOR FIRST-LINE ADVANCED MESOTHELIOMA

The addition of bevacizumab to standard first-line cisplatin-pemetrexed chemotherapy has proven able to enhance OS in a phase 3 RCT. The impact on quality of life, measured by QLQ-C30 and QLQ-LC3 questionnaires and analyzed as HRQoL deterioration-free survival (QFS), were reported.[31] 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).[31] Therefore, platinum-pemetrexed + bevacizumab could be considered for these patients.

The phase 2, randomized SWOG S0905 trial (N= 92) evaluated another anti-angiogenesis agent, the VEGFR-TKI cediranib. First-line 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%).[32]

A third interesting mesothelioma abstract discussed the data of the phase 2, single arm DREAM study. This is the first

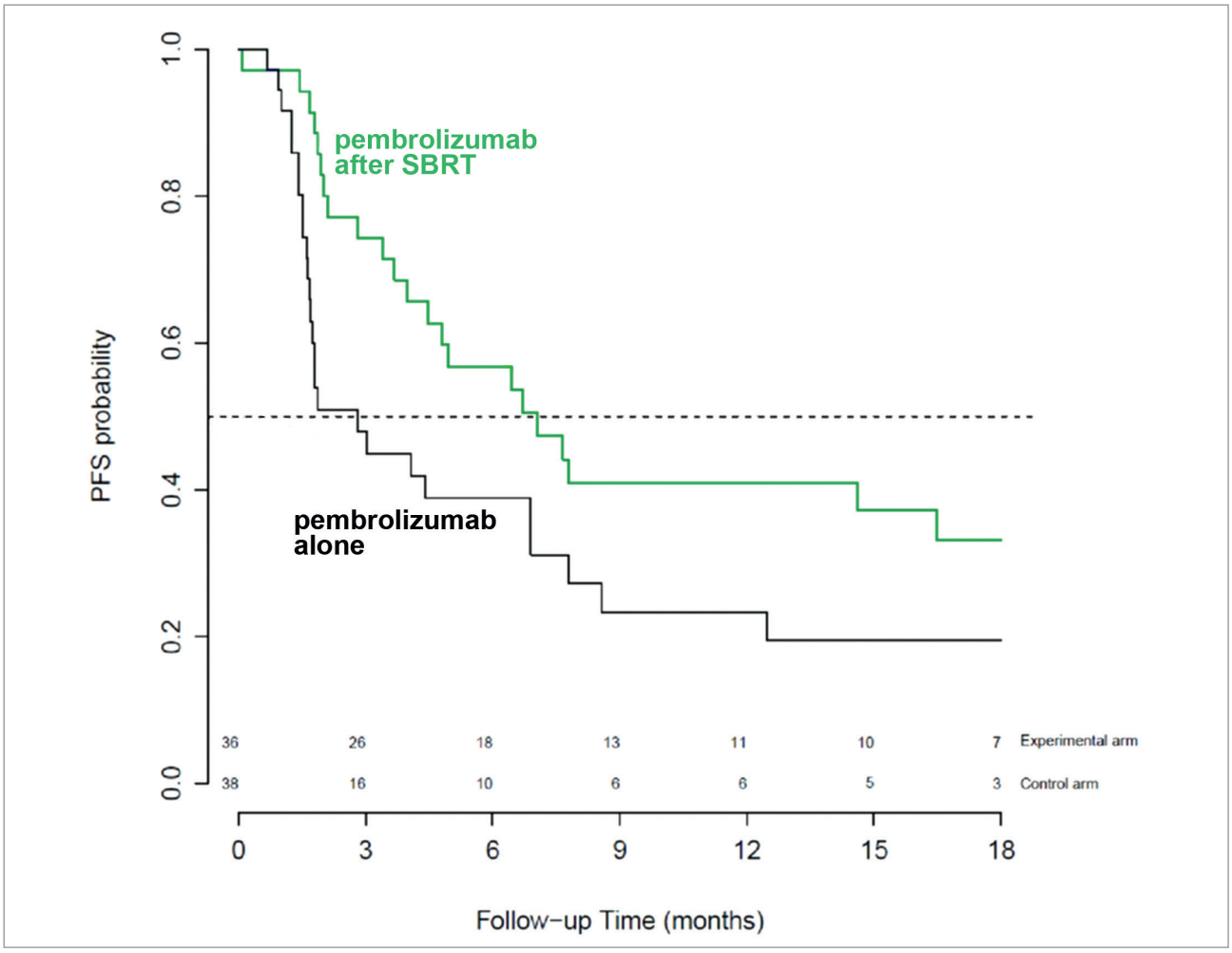


FIGURE 4. PFS in a randomized phase II study of pembrolizumab after stereotactic body radiotherapy (SBRT) versus pembrolizumab alone in patients with advanced NSCLC.[37]

study to evaluate a cytotoxic/immunotherapy combination in first-line mesothelioma: durvalumab + platinum-pemetrexed (6 cycles) followed by durvalumab maintenance for 52 weeks. The PFS rate 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 of 58% and a DCR of 87%. The median PFS was reported at 7.3 months (95%CI: 5.8-11.0).[33] 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) were presented.[34] There was an impressive PFS improvement with durvalumab, from 5.6 months to a median PFS of 16.8 months (HR: 0.52). Also the time to death or distant metastasis was significantly improved (median 23.2 *vs.* 14.6 months, HR: 0.52).[34] 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 in the same setting were presented at ASCO 2018.

Abstract 8500 reported on a phase 2 trial (N=93) 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%, which is better than what could be expected from chemoradiotherapy alone.[35]

Abstract 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.[36] The NICOLAS trial, within the European Network ETOP (NCT 02434081), was a frontrunner 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.

Finally, abstract 9023 discussed a Dutch phase 2 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). In total, 72 patients with stage IV relapsed NSCLC were randomly assigned to SABR *on a single metastatic site before pembrolizumab 200 mg q3w vs. pembrolizumab alone* (*Figure 4*). The primary endpoint was the ORR at 12 weeks and reached 41% in the SABR arm *vs.* 19% in the control arm. The median PFS was 1.8 months in the control arm as compared to 6.4 months in the SABR arm (HR[95%CI]: 0.55[; P=0.04). Grade ≥3 toxicity was experienced in 22% of patients in the control arm *vs.* 17% in the experimental arm.[37]

FOR YOUR CALENDAR

Respiratory Oncology Update 2018:
10 November, 2018 La Hulpe.

https://www.update-respiratoryonco.be/en/Home_10_6_12.html

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