Highlights in respiratory oncology

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At ASCO 2017, 195 abstracts in the field of respiratory oncology were presented (169 in 2016): 22 oral presentations (including 4 in a clinical science symposium), 24 poster discussion items, and 149 posters. In this summary, most attention will go to phase III randomized controlled trials (RCTs) and innovative data that are, or may become, relevant for the practicing clinician. As this report is only the "extract of the abstracts", the reader is referred to the respective abstracts published in J Clin Oncol volume 35 Suppl 15, 2017 (abstracts #8500-8586 and #9000-9107 and available on-line at http://abstracts.asco.org/199/IndexView_199.html

NON-SMALL CELL LUNG CANCER (NSCLC) (STAGE I, II, RESECTABLE IIIA)

Since the IALT study of 2004, adjuvant cisplatin-based chemotherapy is the standard of care for completely resected stage II and IIIA NSCLC. Since then, little progress was made with either pharmacogenetic tailoring of the chemotherapy, nor with targeted agents such as gefitinib, erlotinib, or bevacizumab in unselected patients, nor with immunotherapy such as the MAGE-A3 vaccine.

This year, a RCT with EGFR-TKI in a truly molecularly selected group was reported (*Table 1*).[1] There are problems with this study. First of all, this was not an early-stage cohort as standard staging with PET-CT staging was not used, and as two thirds of the patients had proven pN2 disease. Secondly, treatment was not in line with good practice as per ESMO guidelines. Consequently, both groups had a disappointing 3-year DFS of about 30%. This study has no impact on the current ESMO recommendations stating that there is no place for molecular testing or for targeted agents in early-stage NSCLC in standard practice.[1]

Abstract 8501 retrospectively looked at salvage therapies in patients with local recurrence (LR) or regional recurrence (RR) after stereotactic ablative radiotherapy (SABR) for early-stage NSCLC. The median time to relapse was 14 months. Salvage consisted of surgery (20% LR, 2% RR), re-irradiation (24% LR, 17% RR), radiofrequency ablation (15% LR), chemotherapy (15% LR, 26% RR), and chemoradiation (6% LR, 44% RR) based on a multidisciplinary tumor board discussion. The 5-year OS in this study was 37.1% for LR and 39.1% for RR patients.[2]

Abstract 8519 looked at the value of analyzing circulating tumor DNA (ctDNA) in the follow-up after radical therapy for stage I-III NSCLC. A highly sensitive next generation sequencing (NGS) assay detected ctDNA in 93% of the pre-treatment samples and 46% of the 4-month post-therapy samples (the latter are patients with so-called molecular residual disease, MRD+). MRD+ patients had a significantly worse DFS and OS. Moreover, the post-treatment MRD status had a 100% positive predictive value (PPV) and a 93% negative predictive value (NPV) for later disease progression. This needs further validation, but could impact on follow-up strategy and early use of additional adjuvant therapy in the future.[3]

NSCLC: LOCALLY ADVANCED STAGE III

For most patients with stage III NSCLC, chemoradiotherapy, preferably in a concurrent approach, is the standard of care, with a role for additional surgery in selected patients.

One common type of relapse consists of brain metastases, especially in patients with adenocarcinoma. One abstract studied the role of prophylactic cranial irradiation (PCI) in this setting (*Table 2*). This study does not support PCI in standard practice. First of all, it was underpowered and did not lead to improved OS. Secondly, the benefit in symptomatic brain metastasis occurrence was offset by the large increase of neurological symptoms in patients without brain metastases (36% with PCI *vs.* 11.3% with observation).[4]

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TABLE 1. Abstract 8500: Gefitinib as adjuvant therapy in EGFR mutation-positive resected early stage NSCLC (CTONG 1104).[1]	
Patient setting:	Completely resected stage II-IIIA (N1-N2) NSCLC.
Comparison:	Gefitinib 250 mg/d for 2 years (N=99) vs. 4 cycles of adjuvant cisplatin-vinorelbine chemotherapy (N=102).
Primary endpoint:	Disease-free survival (DFS): median 28.7 vs. 18.0 m in control arm. HR[95%CI]: 0.60[0.42-0.87], p=0.005. 3-year DFS rate: 34% vs. 27%.
Observations:	Grade 3-4 adverse events less common with gefitinib: 12.%3 vs. 48.3%, p< 0.001.
Author conclusion:	Adjuvant gefitinib should be considered as an option in *EGFR* mutation-positive, resected NSCLC.

ADVANCED NSCLC: TARGETED THERAPY

EGFR-TKIS

Second-generation EGFR TKIs have the potential to be more effective than 1st generation EGFR TKIs, since they irreversibly inhibit three members of the ErbB family (EGFR/HER2 and HER4). The ARCHER1050 trial is the first randomized phase III trial comparing a 2nd generation TKI to a 1st generation TKI in the in the first-line setting (*Table 3*).[5]

LUX-Lung 7, presented at ESMO-ASIA 2016, was a phase IIb comparison of the 2nd generation TKI afatinib with gefitinib. Afatinib significantly improved PFS (HR 0.73 [0.57-0.95]), however at the cost of increased skin and gastro-intestinal toxicity. This dacomitinib study was a phase III study with a stronger statistical design. Dacomitinib offers a possible new 1st line option for advanced *EGFR* mutation-positive NSCLC without CNS metastases. The median PFS was high at 14.7 months, however toxicity should be considered (e.g. 66% of patients in the dacomitinib group needed a dose reduction *vs.* 8% with gefitinib). Moreover, drug activity should be confirmed in a larger group of non-Asian patients. Finally, results from the phase III FL-AURA study (3rd generation osimertinib *vs.* gefitinib or erlotinib in 1st line therapy) may also determine the approach to EGFR mutation-positive advanced NSCLC.

ALK-TKIs

Crizotinib is the current standard-of-care for newly diagnosed ALK-positive lung adenocarcinoma (albeit not reimbursed in Belgium). However, acquired drug resistance invariably occurs and the central nervous system (CNS) is a common site of relapse. Next-generation drugs have proven to be effective in disease control, also in the CNS. By now, the 2nd generation TKIs ceritinib, alectinib and brigatinib are FDA approved in case of resistance to crizotinib. The 3rd generation TKI lorlatinib recently received the 'breakthrough therapy designation' status for use in ALK-positive NSCLC patients who previously received 1 or more ALK TKIs. At ASCO 2017, phase III data for alectinib versus crizotinib in treatment-naïve patients and phase II data for lorlatinib in TKI-pretreated patients were presented (*Tables 4 and 5*).[6,8]

TABLE 2. Abstract 8502: PCI in radically treated stage III NSCLC (NVALT 11).[4]	
Patient setting:	Radically treated stage III NSCLC (concurrent or sequential chemoradiotherapy with or without surgery).
Comparison:	PCI (dose either 36 Gy/18F, 30 Gy/12F, 30 Gy/10F) (N=87) vs. Observation (N=88).
Primary endpoint:	Incidence of symptomatic brain metastases at 24 months: 4/86 (4.6%) in PCI vs. 25/88 (28.4 %) (p< 0.0001).
Observations:	- The study aimed to randomize 300 patients in order to have 90% power. Due to slow accrual, the target number of randomized patients was reduced to 175. - Seven (8.1%) patients had metastatic brain imaging with PCI, 26 (29.7%) with observation (p< 0.001). - There was no difference in OS: median 24.2 vs. 21.9 months (p= 0.52).
Author conclusion:	Underpowered trial. PCI reduces symptomatic brain metastases without an effect on OS.

TABLE 3. Abstract LBA9007: Dacomitinib vs. gefitinib as 1st line in *EGFR* mutation-positive advanced NSCLC (ARCHER 1050).[5]	
Patient setting:	Stage IIIB/IV NSCLC with a common activating EGFR mutation (exon 19 del or exon 21 L858R). No CNS metastases allowed.
Randomization:	Dacomitinib 45 mg QD (N=227) vs. gefitinib 250 mg QD (N=225).
Primary endpoint:	PFS by blinded independent review: HR[95%CI]: 0.59[0.47-0.74]. Median PFS 14.7 vs. 9.2 months.
Observations:	ORR 75% vs. 72%, DoR 14.8 vs. 8.3 months, OS data not yet mature. No benefit was observed in the small subgroup of non-Asian patients (<25%).
Safety:	Most frequent grade 3 AEs: acneiform rash (13.7%) and diarrhea (8.4%) vs. ALT elevation (8.5%).
Author conclusion:	Dacomitinib demonstrated superior PFS over gefitinib with a manageable safety profile.

The results of the phase III ALEX study largely confirm the previously reported Japanese J-ALEX study (ASCO 2016). Abstract 9064 brought an update of J-ALEX with an additional 10 months of follow-up. The updated PFS HR[95%CI] was 0.38 [0.26-0.44], with a median PFS of 25.9 [20.3-NR] *vs.* 10.2 months [8.3.3-12.0] with crizotinib.[7] The outstanding PFS in both studies (with a median PFS beyond 2 years!) and the strong CNS activity open the possibility for alectinib as the 1st line therapy for ALK-positive NSCLC. However, OS data still need to establish the final balance between sequential use of crizotinib followed by alectinib, or alectinib as only front-line drug.[6,7]

Resistance to 2nd generation ALK-TKIs also invariably develops. Lorlatinib is a potent 3rd generation ALK/ROS1 TKI that is active against almost all known ALK resistance mutations. Preliminary results from an ongoing phase 1I/II study, presented at ESMO 2016, showed good activity of lorlatinib with an ORR of 57% and 42%, respectively in ALK-positive NSCLC patients previously treated with 1 or ≥ 2 ALK TKIs. The phase II expansion portion of this study was presented at ASCO 2017.[8] This study confirms that lorlatinib is highly active in heavily pretreated ALK+ NSCLC, especially in the CNS.[8] The place of lorlatinib in first-line setting (compared to crizotinib) will be explored in the phase III CROWN study (NCT03052608). Reporting of the data is expected in Dec 2019.

HER2-DIRECTED THERAPY

HER2 overexpression is a well-known target in metastatic breast cancer. HER2 alterations are also present in NSCLC (e.g. mutations in 2%), but no targeted therapy for this patient group is approved yet. Based on the positive results in HER2-overexpressing breast cancer, the antibody adotrastuzumab emtansine (T-DM1) is currently being tested in NSCLC patients. However, the most relevant target for patient selection in NSCLC has yet to be defined. At this

TABLE 4. Abstract LBA9007: Abstract LBA9008: Alectinib vs. crizotinib as first-line therapy in ALK-positive advanced NSCLC (ALEX).[6]	
Patient setting:	ALK-TKI naïve ALK-positive (immunohistochemistry) advanced NSCLC, asymptomatic CNS metastases allowed.
Randomization:	Alectinib 600 mg BID (N=152) vs. crizotinib 250 mg BID (N=151).
Primary endpoint:	Investigator assessed PFS: HR[95%CI]: 0.47 [0.34-0.65]; median PFS NR [17.7-NR] vs. 11.1 months [9.1-13.1].
Observations:	ORR 83% vs. 76%. Median DoR 11.1 months vs. NR. Significant reduction in the risk of CNS progression: HR[95%CI]: 0.16 [0.10-0.28]. OS data immature.
Safety:	Grade 3/4 adverse events 41% vs. 50%. Fatal adverse events 3% vs. 5%.
Author conclusion:	Alectinib demonstrated superior PFS with less adverse events compared to Crizotinib.

TABLE 5. Abstract 9006: Lorlatinib in patients with ALK+ NSCLC with one or more prior ALK TKI (phase II trial).[8]	
Patient setting:	ALK-positive or ROS1-positive advanced NSCLC patients who progressed after prior TKI(s) and with PS 0-2. Asymptomatic untreated or treated CNS metastases allowed. Six expansion (exp) cohorts, this report was based on 4 of these. Exp1 (ALK-positive, no prior TKI) and exp6 (ROS1-positive) will be reported later.
Treatment:	Lorlatinib 100mg QD.
Primary endpoint:	(Exp2-5, ≥1 prior ALK TKI, N=82): ORR by independent review: 32.9% and intracranial ORR by independent review: 48.1%.
Observations:	Disease control rate (DCR) at 12 weeks: 56.1%. CNS DCR at 12 weeks: 75%.
Safety:	Grade 3/4 adverse events (46.6%), most common hyperlipidemia (17%) successfully managed with lipid-lowering agents. Only 3% discontinued due to treatment-related adverse events, no fatal events.
Author conclusion:	Lorlatinib showed significant activity in previously treated ALK+ patients, also in the CNS.

ASCO meeting, results of T-DM1 in HER2-mutated (*Table 6*) and HER-overexpressing NSCLC have been reported.[9,10] Abstract 8509 reported the results of a phase II study with T-DM1 (3.6 mg/kg q3w) in *HER2*-overexpressing NSCLC (as assessed by IHC). Patients were analyzed in 2 cohorts: IHC2+ (N=29) and IHC3+ (N=20). The primary endpoint of the study was ORR: no responses were seen in IHC2+, while 4 partial responses were seen in the IHC3+ group (20%). The median PFS was low (<3 months) in both groups. Interestingly, among the 4 responders in the IHC3+ group, 3 also had confirmed *HER2* amplification.[10] This observation reinforces the question about what the relevant HER2 target is in NSCLC: overexpression, amplification or mutation? Based on the available data, HER2 mutation seems to be the better predictor for HER2-directed therapy.

The effect of the EGFR/HER2/HER4 TKI afatinib has also been explored in HER2-mutated NSCLC. The prospective ETOP niche trial was stopped prematurely because of futility: no responses were observed in the 13 recruited patients. In the ETOP trial, molecular analyses are ongoing to identify a subgroup of patients that may benefit from afatinib.[11] Overall, although responses are short-lived (median PFS 4 months), T-DM1 is at this moment the most promising targeted drug for *HER2*-mutated NSCLC.

MET-DIRECTED THERAPY

MET exon 14 mutations are present in 4% of non-squamous NSCLC, and enriched in atypical tumor types (22% of sarcomatoid tumors) and in elderly patients. Given the relatively high prevalence (comparable with ALK), *MET* mutations are important in the molecular screening of NSCLC. One abstract retrospectively studied the impact of MET-directed therapy on survival in MET mutated patients (*Table 7*).[12] Although retrospective in nature and with some imbalances

TABLE 6. Abstract 8510: Ado-trastuzumab emtansine in HER2 mutant NSCLC (phase II basket trial).[9]	
Patient setting:	HER2-mutant previously treated NSCLC.
Treatment:	Ado-trastuzumab emtansine 3.6mg/kg IV q3w (N=18).
Primary endpoint:	ORR: 44% (partial response in 8/18 patients).
Observations:	Median PFS of 4 months (3.0-NR). Median DoR 5 months (3.0-NR).
Safety:	Mainly grade 1 or 2 infusion reactions, thrombocytopenia and AST/ALT elevations. No dose reductions or treatment-related deaths.
Author conclusion:	Ado-trastuzumab-emtansine is active and well tolerated in patients with HER2-mutant NSCLC. Further development in a large multicenter study is warranted.

TABLE 7. Abstract 8511: Impact of MET inhibitors on survival in *MET* exon 14 mutant NSCLC (retrospective).[12]	
Patient setting:	*MET* exon 14 mutated advanced NSCLC.
Treatment:	Received MET TKI (N=27) vs. Never received MET TKI (N=34).
Outcome:	Median OS: 8.1 vs. 24.6 m, HR 0.11 [0.01-0.92].
Author conclusion:	The use of a MET TKI in MET exon 14 NSCLC patients results in a significant prolongation of survival.

between the 2 patient groups, this result matches data from the Lung Cancer Mutation Consortium (ASCO 2016) showing that, when a driver mutation is present, patients do best with targeted therapy. Hence, upfront testing for *MET* mutations is warranted in advanced non-squamous NSCLC and selected squamous NSCLC, especially in tumors without alterations in *EGFR, ALK, ROS1, BRAF* and *KRAS*.

Abstract 8512 was a very interesting retrospective analysis exploring response of *MET* exon 14 NSCLC to immunotherapy. Of the 15 patients that received immunotherapy, only 1 (6.7%) had a partial response. In addition, no response occurred in the PD-L1 ≥50% group, neither in the group with higher mutation burden (which is generally low in *MET* exon 14 NSCLC). Hence, this abstract reinforces the use of targeted therapy in this situation.[13]

ADVANCED NSCLC: IMMUNOTHERAPY

The first positive and therefore groundbreaking study on immunotherapy for 1st line therapy was presented at the ESMO 2016: the Keynote 024 study compared pembrolizumab 200 mg q3w with platinum doublet chemotherapy in non-oncogene driven and highly PD-L1 expressing NSCLC. The primary endpoint of PFS was strongly positive with a HR[95%CI] of 0.50[0.37-0.68] (p< 0.001). Moreover, the HR[95%CI] for OS was 0.60[0.41-0.89] (p= 0.005). At ASCO 2017, data on progression after the first and next line of therapy (so-called "PFS2") and updated OS data were reported (*Table 8*).[14]

Abstract 9001 reported on the outcome of post-progression treatment in the phase III study comparing the anti-PD-L1 antibody atezolizumab to docetaxel in relapsed NSCLC (OAK study, also initially reported at ESMO 2016).[15] Atezolizumab post progression was associated with a high frequency of stable or reduced size of target lesions, a median OS of >1 year and a tolerable safety profile.[15] This is exploratory, and perhaps suggestive of prolonged treatment benefit consistent with post-progression gain in OS.

Abstract 9011 gave the 3-year read-out of the phase I KN 001 study with pembrolizumab. The plateau in survival was confirmed with a 3-year OS of 26.4% in the 1st line cohort, and of 19.0% in the pre-treated cohort.[16]

Finally, abstract 9012 features a very interesting retrospective analysis of immune-related adverse events (irAEs) in a large cohort of 482 patients treated with anti-PD(L)-1 +/- anti-CTLA-4 and treatment delay because of irAE. 71 (14.7%) had treatment delay related to an irAE, mostly grade 2 or 3. 32/71 (45%) were permanently discontinued after the irAE and 39/71 (55%) were retreated with an anti-PD(L)-1. In the

TABLE 8. Abstract 9000: PFS2 and updated OS results of pembrolizumab 1st line (Keynote 024).[14]	
Patient setting:	Advanced NSCLC with PD-L1 expression ≥50% (EGFR wild-type/ALK negative).
Randomization:	Pembrolizumab 200 mg q3w for 2 years (N=154) vs. platinum doublet chemotherapy (Pemetrexed maintenance allowed) (N=151).
Outcome:	Updated observations. PFS2 was significantly better in the experimental arm: HR[95%CI]: 0.54[0.40-0.72], with 52% of patients free from progression at 18 months in the pembrolizumab arm vs. 25% in the chemotherapy arm. With a median follow-up of 19 months, the OS remained significantly better with pembrolizumab (HR[95%CI] 0.63 [0.46-0.88], p= 0.003). The one-year OS rates were 70.3% vs. 54.8% with pembrolizumab and chemotherapy, respectively.
Author conclusion:	Despite increased cross-over from 1st line chemotherapy, updated OS data maintained consistent superiority of 1st line Pembrolizumab.

TABLE 9. Abstract 8503: Randomized expansion cohort comparing Nivolumab to Nivolumab-Ipilimumab in relapsed SCLC (Checkmate 032 expansion).[18]	
Patient setting:	Stage IV SCLC relapsing after chemotherapy (including at least a platinum-based regimen).
Randomization:	Nivolumab 3 mg/kg q2w (N=147) vs. nivolumab 1 mg/kg and ipilimumab 3 mg/kg q3w x 4, followed by nivolumab 3 mg/kg q2w (N=95).
Primary endpoint:	ORR 12% with nivolumab vs. 21% with nivolumab-ipilimumab.
Observations:	Responses were seen both in platinum-sensitive as well as platinum-refractory patients. Responses were durable. 5% of patients had to stop immunotherapy for AEs in the nivolumab arm vs. 11% in the combination group. Five treatment-related deaths (1 with nivolumab, 4 in combination arm).
Author conclusion:	Durable responses are observed with nivolumab and nivolumab-ipilimumab in patients with previously treated SCLC.

latter, the same irAE recurred in 10/39 (26%), a new irAE occurred in 9/39 (23%), and 20/39 (51%) had no subsequent irAE. The risk for a recurrent/new irAEs was mostly after an initial irAE that occurred <3 months after onset of therapy. Recurrent/new irAEs were successfully managed with immunosuppression in 17/19 (90%) patients, but 2 patients died. Only 3/39 (8%) of retreated patients had a response.[17]

SMALL-CELL LUNG CANCER (SCLC)

Treatment options for patients with stage IV SCLC who progress on platinum-based chemotherapy are limited. Topotecan is the only approved therapy, based on very modest results. At ASCO 2016, encouraging results were reported with rovalpituzumab-tesirine, an antibody-chemotherapy drug conjugate targeted to DLL3, which is highly (>50% cells staining) expressed in two thirds of SCLC. Rova-T, as it is now commonly called, currently undergoes further testing.

The other hope is this setting relies on immunotherapy. One abstract reported the longer-term follow-up of the initial cohort of patients in Checkmate 032 (initial report *Antonia et al,* Lancet Oncol 2016) and the results of the randomized expansion cohort (*Table 9*).[18] In the longer-term follow-up data, the objective response rate (ORR) was 11% for nivolumab, while it was 25% for the combination. More important, the 1-year OS was 27% with nivolumab and 40% with the combination.[18]

The 1-year OS of 40% in the follow-up of the non-randomized cohort is of interest in a setting of relapsed SCLC. The toxicity still is a matter of concern in these, often elderly, patients with smoking-induced comorbidity. In the randomized cohort, there were 5 treatment-related deaths in the present analysis. Optimally, there should be a selection biomarker here, but with the data presented so far, it is clear that – in contrast with NSCLC – it will not be PD-L1 expression. Further data are needed for implementation in clinical practice.[18]

Abstract 8517 was an interesting abstract reporting compre-

TABLE 10. Abstract LBA8507: Phase 2 RCT with Nivolumab or Nivolumab-Ipilimumab in relapsed mesothelioma (IFCT 1501 MAPS2).[20]	
Patient setting:	Malignant mesothelioma progressing after one or two prior therapies.
Randomization:	Nivolumab 3 mg/kg q2w (N=63) vs. nivolumab 3 mg/kg q2w and ipilimumab 1 mg/kg q6w (N=62).
Primary endpoint:	DCR at 12 weeks >40%. In the early analysis, this was 40% in the nivolumab group, 52% in the combination group.
Observations:	Preliminary OS data look promising, but median follow-up was only 10.4 months. Grade 3/4 adverse events were seen in 10% in the nivolumab arm vs. 18% in the nivolumab-ipilimumab arm. Three treatment-related deaths occurred in the combination arm.
Author conclusion:	Meaningful increase in 12 week DCR compared to historical control.

KEY MESSAGES FOR CLINICAL PRACTICE

Early stage NSCLC

1. First report of adjuvant gefitinib in resected stage II-III EGFR mutated NSCLC (CTONG 1104). DFS was significantly better with gefitinib, while grade 3-4 adverse events were less common. This study was not in a truly early-stage cohort and treatment was not according to ESMO guidelines. No practical consequences at present.

Locally advanced NSCLC

2. Role of prophylactic cranial irradiation (PCI) in radically treated stage III NSCLC (NVALT 11). In this underpowered trial, PCI significantly reduced occurrence of symptomatic brain metastases, but with a clear increase of non-metastasis-related neurologic deterioration, and without effect on OS.

Advanced NSCLC targeted therapy

3. First-line dacominitib *vs.* gefitinib in EGFR+ NSCLC (ARCHER 1050). This randomized phase 3 study showed superiority of the 2nd generation EGFR TKI Dacomitinib with respect to PFS and (DoR). Skin and gastro-intestinal toxicity was increased compared to gefitinib, which should be considered. Albeit, dacomitinib is a possible new treatment option for 1st line EGFR mut+ NSCLC.
4. First-line alectinib *vs.* crizotinib in ALK+ NSCLC (ALEX). The global ALEX study, confirmed previously reported Japanese data, i.e. that alectinib at 600 mg BID was superior to crizotinib. These data open the possibility for alectinib as the 1st line therapy for ALK+ NSCLC.
5. Lorlatinib in pre-treated ALK+ or ROS1+ NSCLC. In a dedicated phase 2 study, lorlatinib showed robust clinical activity in ALK+ advanced NSCLC patients who were heavily pretreated, most of them with CNS metastasis.
6. Targeted therapy for pre-treated HER2-mutated NSCLC. In contrast to overexpression in breast cancer, mutations in HER2 seem to best select NSCLC patients for HER2-directed therapy. In a small phase 2 study using this biomarker, ado-trastuzumab emtansine (T-DM1) showed a promising partial response rate (44%), however with a short-lived PFS (4 months).
7. Data to support the use of targeted therapy in MET exon 14 mutated NSCLC. MET exon 14 deletion is emerging as a promising actionable target and as a predictive biomarker for MET-directed therapy. A retrospective analysis confirmed use of a MET TKI significantly prolongs survival compared to non-targeted therapy.

Advanced NSCLC immunotherapy

8. Update of the landmark study with 1st line pembrolizumab in highly PD-L1 expressing NSCLC. The previously reported strong differences in PFS and OS *vs.* chemotherapy were maintained when the "PFS2" (i.e. the result of 2 lines) and updated OS were considered. This sets a sequence of immunotherapy followed by chemotherapy as the preferred choice in these patients.

SCLC and mesothelioma

9. Nivolumab with, or without ipilimumab in relapsed SCLC (ChM 032). In the non-randomized cohort of this study, the updated 1-year OS with nivolumab-ipilimumab was 40%, but the toxicity was a matter of concern. In the ongoing randomized cohort, there were 5 treatment-related deaths. Further study is needed.
10. Nivolumab *vs.* nivolumab-ipilimumab in relapsed mesothelioma (IFCT 1501). This study met its primary endpoint of a DCR rate >40% at 12 weeks in the initial analysis in both arms. The preliminary OS data look promising. It remains to be determined if single agent or combination immunotherapy will have the best risk/benefit balance in mesothelioma.

hensive genomic profiling of 300 large cell neuroendocrine carcinomas (LCNEC) in comparison with 887 SCLC tumors. Two major subsets of LCNEC emerged, a LCNEC-SCLC type (both TP53 and RB1 mutated) and a NSCLC-like type (wild type for TP53 and/or RB1, and often with adenocarcinoma like traces such as *KRAS*). It is thus useful to run NGS on LCNEC samples to look for this distinction, as this may give guidance to select the optimal chemotherapy.[19]

MESOTHELIOMA

There are at present no registered 2nd line options for patients with mesothelioma who relapse after standard 1st first

line therapy with cisplatin-pemetrexed. In a RCT reported at ASCO 2016, single agent immunotherapy with the anti-CTLA4 antibody tremelimumab did not improve the OS in the 2nd/3rd line mesothelioma setting. This year, results with anti-PD1 or combined anti-PD1 and anti-CTLA4 were reported (*Table 10*).[20] The DCR rate in this study indeed compares favorably with historical control, and the preliminary OS data look promising. This again needs to be balanced with the (at present) 3 treatment-related deaths.[20]

Further follow-up and relation of outcome to PD-L1 expression is awaited in order to judge if single agent or combination immunotherapy has the best risk/benefit balance in mesothelioma.

Abstract 8514 was a large retrospective cohort of anti-PD-1 therapy in mesothelioma. In total, 46 patients with unresectable pleural/peritoneal mesothelioma, all but 3 pre-treated with a median of 2 treatment lines. All but 1 patient received pembrolizumab. The median OS reached 8.0 months (95%CI: 2.3-11.9), while the median DoR was not yet reached. Both PFS and OS were better in patients with PD-L1 tumor expression ≥5% (HR: 0.26, p= 0.10) and PD-L1 ≥50% (HR :0.17, p= 0.11).[21]

FOR YOUR CALENDAR

ESMO 2017: 8-12 September, Madrid.

WCLC 2017: 15-18 October, Yokohama, Japan.

Respiratory Oncology Update 2017: 11 November, La Hulpe.

ELCC 2018: 11-14 April, Geneva.

ASCO 2018: 1-5 June, Chicago.

ESMO 2018: 19-23 October, Munich.

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