REPORT ASCO 2017 CHICAG0: RESPIRATORY ONCOLOGY

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10 MESSAGE HIGHLIGHTS

Early stage NSCLC

1. ***First report of adjuvant Gefitinib in resected stage II-III EGFR mutated NSCLC (CTONG 1104).*** Disease-free survival 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 overall survival (OS).

Advanced NSCLC targeted therapy

3. ***First-line Dacominitib vs. Gefitinib in EGFR mut+ NSCLC (ARCHER 1050).*** This randomized ph3 study showed superiority of the 2nd generation EGFR TKI Dacomitinib with respect to progression-free survival (PFS) and duration of response (DoR). Skin and gastro-intestinal toxicity was increased compared to Gefitinib, and should be taken into account. 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 ph2 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 ph2 study using this biomarker, Ado-trastuzumab emtansine (T-DM1) showed a promising partial response rate (44%), however with 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±Ipilimumab in relapsed SCLC (ChM 032).*** In the non-randomized cohort of this study, the updated 1-year OS with Nivo-Ipi 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 versus 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.

At the ASCO 2017 congress, 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.
We give most attention to phase 3 (ph3) 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 with the # sign to the respective abstracts in http://abstracts.asco.org/199/IndexView_199.html, also in J Clin Oncol volume 35 Suppl 15, 2017 (abstracts #8500-8586 and #9000-9107).

NSCLC – EARLY STAGES (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. Little progress since then, neither with 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 (**Figure 1**).

Figure 1: #8500: Gefitinib as adjuvant therapy in *EGFR* mut+ resected early stage NSCLC (CTONG 1104).
Patient setting
Completely resected stage II-IIIA (N1-N2) NSCLC.
Comparison
Gefitinib 250 mg/d for 2 years (n=99)
versus
Four cycles of adjuvant cisplatin-vinorelbine chemotherapy (n=102)
Outcome
Primary: disease-free survival (DFS): median 28.7 *vs.* 18.0 m in control arm. HR 0.60 [0.42-0.87], *P*=0.005. 3-year DFS 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* mut+ resected NSCLC.

There are problems with this study. First, 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. Second, 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 that there is no place for molecular testing nor for targeted agents in early-stage NSCLC in standard practice.

#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. 5-year OS was 37.1% for LR and 39.1% for RR patients.

#8519 looked at the value of analysis of circulating tumor DNA (ctDNA) in the follow-up after radical therapy for stage I-III NSCLC. A highly sensitive 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+ had significantly worse DFS and OS. Moreover, the post-treatment MRD status had a 100% PPV and a 93% 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.

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 is brain metastases, especially in patients with adenocarcinoma. One abstract studied the role of prophylactic cranial irradiation (PCI) in this setting (**Figure 2**).

Figure 2: #8502: PCI in radically treated stage III NSCLC (NVALT 11).
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)
versus
Observation (n=88)
Outcome
Primary: incidence of symptomatic brain metastases at 24 m: 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 m (*P*=0.52).
Author conclusion
Underpowered trial. PCI reduces symptomatic brain metastases without effect on OS.

This study does not lead to advice PCI in standard practice. First, it was underpowered and did not lead to improved OS. Second, the benefit in symptomatic brain metastasis occurrence was offset by the large increase of neurological symptoms in patients without brain metastases (36% with PCI, 11.3% with observation).

ADVANCED NSCLC TARGETED THERAPIES

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 ph3 trial comparing a 2nd generation TKI to a 1st generation TKI in the in the first-line setting (**Figure 3**).

Figure 3: #9007: Dacomitinib versus Gefitinib as 1st line in EGFR mut+ advanced NSCLC (ARCHER 1050).
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)
versus
Gefitinib 250 mg QD (n=225)
Outcome
Primary: PFS by blinded independent review: HR 0.59 [0.47-0.74]. Median PFS 14.7 *vs.* 9.2 m
Observations: ORR 75% vs. 72%, DoR 14.8 *vs.* 8.3 m OS data not mature yet. 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 compared to Gefitinib with a manageable safety profile.

LUX-Lung 7 (ESMO-ASIA 2016) was a ph2b 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 ph3 with a stronger statistical design. Dacomitinib offers a possible new 1st line option for advanced EGFR mut+ NSCLC without CNS metastases. Median PFS is high (14.7 m), however toxicity should be taken into account (e.g. 66% of patients in de 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 ph3 FL-AURA study (3rd generation Osimertinib versus Gefitinib or Erlotinib in 1st line therapy) may also determine the approach to EGFR mut+ advanced NSCLC.

ALK-TKIs
Crizotinib is the current standard-of-care for newly diagnosed ALK+ 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 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+ NSCLC patients who previously received 1 or more ALK TKIs. At this ASCO meeting, ph3 data for Alectinib versus Crizotinib in treatment-naïve patients and ph2 data for Lorlatinib in TKI-pretreated patients were presented (**Figures 4 and 5**).

Figure 4: #LBA19008: Alectinib vs. Crizotinib as first-line therapy in *ALK*-positive advanced NSCLC (ALEX)
Patient setting
ALK-TKI naïve ALK+ (immunohistochemistry) advanced NSCLC, asymptomatic CNS metastases allowed.
Randomization
Alectinib 600 mg BID (n=152)
versus
Crizotinib 250 mg BID (n=151)
Outcome
Primary: Investigator assessed PFS: HR 0.47 [0.34-0.65]; median PFS NR [17.7-NR] *vs.* 11.1 m [9.1-13.1].
Observations: ORR 83% vs. 76%. Median DoR 11.1 m vs. NR. Significant reduction in risk of CNS progression: HR 0.16 [0.10-0.28]. OS data immature. Safety: grade 3/4 AEs 41 vs. 50%. Fatal AEs 3% vs. 5%
Author conclusion
Alectinib demonstrated superior PFS and less AEs compared with Crizotinib.

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

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 ph1/2 study (ESMO 2016) showed good activity of Lorlatinib with ORR of 57% and 42%, respectively in ALK+ NSCLC patients previously treated with 1 or ≥ 2 ALK TKIs. The ph2 expansion portion of this study was presented at this ASCO meeting.

Figure 5: #9006: Lorlatinib in patients with ALK+ NSCLC with one or more prior ALK TKI (ph2 trial).
Patient setting
ALK+ or ROS1+ 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 on 4 of these. Exp1 (ALK+, no prior TKI) and exp6 (ROS1+) will be reported later.
Treatment
Lorlatinib 100mg QD
Outcome
Primary (exp2-5, ≥1 prior ALK TKI, n=82): ORR by independent review: 32.9%. 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 AEs (46.6%), most common hyperlipidemia (17%) successfully managed with lipid-lowering agents. Only 3% discontinued due to treatment-related AE, no fatal events.
Author conclusion
Lorlatinib showed significant activity in previously treated ALK+ patients, also in the CNS.

This study confirms that Lorlatinib is highly active in heavily pretreated ALK+ NSCLC, especially in the CNS. The place of Lorlatinib in first-line setting (compared to Crizotinib) will be explored in the ph3 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 ado-trastuzumab 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 ASCO meeting, results of T-DM1 in HER2-mutated (**Figure 6**) and HER-overexpressing NSCLC **(#8509**) have been reported.

Figure 6: #8510: Ado-trastuzumab emtansine in HER2 mutant NSCLC (ph2 basket trial).
Patient setting
HER2-mutant previously treated NSCLC.
Treatment
Ado-trastuzumab emtansine 3.6mg/kg IV q3w (n=18)
Outcome
Primary: ORR: 44% (partial response in 8/18 patients)
Observations: median PFS of 4 m (3.0-NR). Median DoR 5 m (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.

#8509 reported the results of a ph2 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 m) in both groups. Interestingly, among the 4 responders in the IHC3+ group, 3 also had confirmed HER2 amplification. 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 **(#9070**) 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.

Overall, although responses are short-lived (median PFS 4 m), 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 (**Figure 7**).

Figure 7: #8511: Impact of MET inhibitors on survival in MET exon 14 mutant NSCLC (retrospective).
Patient setting
MET exon 14 mutated advanced NSCLC.
Treatment
Received MET TKI (n=27)
versus
Never received MET TKI (n=34)
Outcome
Primary: 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.

Although retrospective in nature and with some imbalances 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 en KRAS.

#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.

ADVANCED NSCLC IMMUNOTHERAPY

The first positive and therefore groundbreaking study on immunotherapy for 1st line therapy was presented at the ESMO 2016 meeting: 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 – PFS – was strongly positive with a HR of 0.50 (95%CI 0.37-0.68, *P* < 0.001). Moreover, the HR for OS was 0.60 (95%CI 0.41-0.89, *P* = 0.005). At this ASCO, data on progression after the first and next line of therapy (so-called "PFS2") and updated OS data were reported (**Figure 8**).

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

#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). Atezolizumab post progression was associated with high frequency of stable or reduced size of target lesions, a median OS of >1 year and a tolerable safety profile. This is exploratory, and perhaps suggestive of prolonged treatment benefit consistent with post-progression gain in OS.

#9011 gave the 3-year read-out of the phase 1 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 19.0% in the pre-treated cohort.

#9012 was 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 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.

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 the ASCO 2016 meeting, 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 (**Figure 9**). 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.

Figure 9: #8503: Randomized expansion cohort comparing Nivolumab to Nivolumab-Ipilimumab in relapsed SCLC (Checkmate 032 expansion).

Patient setting

Stage IV SCLC relapsing after chemotherapy (including at least a platinum-based regimen).

Randomization

Nivo 3 mg/kg q2w (n=147)

versus

Nivo 1 mg/kg and Ipi 3 mg/kg q3w x 4, followed by Nivo 3 mg/kg q2w (n=95).

Outcome

Primary: ORR 12% with Nivo *vs.* 21% with Nivo-Ipi.

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 Nivo-arm, 11% in the combination group. Five treatment-related deaths (1 in Nivo, 4 in combined arm).

Author conclusion

Durable responses are observed with Nivo and Nivo-Ipi in patients with previously treated SCLC.

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.

#8517 was an interesting abstract reporting comprehensive 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.

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 the ASCO 2016 meeting, single agent immunotherapy with the anti-CTLA4 antibody tremelimumab did not improve OS in the 2nd/3rd line mesothelioma setting. This year, results with anti-PD1 or combined anti-PD1 and anti-CTLA4 were reported (**Figure 10**).

Figure 10: #LBA8507: Phase 2 RCT with Nivolumab or Nivolumab-Ipilimumab in relapsed mesothelioma (IFCT 1501 MAPS2).

Patient setting

Malignant mesothelioma progressing after one or two prior therapies.

Randomization

Nivo 3 mg/kg q2w (n=63)

versus

Nivo 3 mg/kg q2w and Ipi 1 mg/kg q6w (n=62).

Outcome

Primary: DCR at 12 weeks >40%. In the early analysis, this was 40% in the Nivo group, 52% in the combination group.

Preliminary OS looks promising, but median follow-up was only 10.4 m. Grade AEs were 10% in the Nivo arm, 18% in the Nivo-Ipi arm. Three treatment-related deaths in the combined arm.

Author conclusion

Meaningful increase in 12 week DCR compared to historical control.

The DCR rate 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. 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.

#8514 was a large retrospective cohort of anti-PD-1 therapy in mesothelioma. 46 patients with unresectable pleural/peritoneal mesothelioma, all but 3 pre-treated with a median of 2 treatment lines. All but 1 patients had Pembrolizumab. The median OS 8.0 months (95%CI: 2.3-11.9), the median DoR was not yet reached. Both PFS and OS better in case of PD-L1 tumor expression ≥5% (HR 0.26, *P* = 0.10) and PD-L1 ≥50% (HR 0.17, *P* = 0.11).

For your calendar:
ESMO 2017: 8-12 September, Madrid.
WCLC 2017: 15-18 October, Yokohama, Japan
Respiratory Oncology Update 2017: 11 November, La Hulpe
https://www.update-respiratoryonco.be/en/Programme_20_818.html
ELCC 2018: 11-14 April, Geneva.
ASCO 2018: 1-5 June, Chicago.
ESMO 2018: 19-23 October, Munich.