REPORT ASCO 2016 CHICAG0: RESPIRATORY ONCOLOGY

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10 MESSAGE HIGHLIGHTS

Early stage non-small cell lung cancer

1. ***Nandroparine anticoagulation added to adjuvant chemotherapy (NVALT 8)***. This study originally planned to recruit 600 patients, but closed with about 200 because of poor accrual. There was no difference in outcome with nandroparine.
2. ***Secondary analysis of the 1500 patients in bevacizumab adjuvant study (ECOG 1505).*** Cisplatin was combined with several modern chemotherapies. No difference in outcome was seen between cis-vinorelbine, cis-gemcitabine, cis-docetaxel, or cis-pemetrexed in non-squamous tumors.

Locally advanced non-small cell lung cancer

3. ***Role of proton therapy in concurrent chemoradiotherapy for unresectable stage III.*** A small RCT did not detect any advantage of proton therapy over IMRT in this setting. Larger RCTs on this important question are ongoing.

Advanced non-small cell lung cancer

4. ***First line treatment for oligometastatic disease (OMD).***
   - In highly selected patients with OMD who did not progress after induction systemic treatment (≥4 cycles of chemotherapy or ≥3 months of TKI in oncogene driven tumors), a local consolidative therapy (radiation, surgery, or combination) was associated with improved progression-free survival (PFS), but overall survival (OS) data are still awaited.
   - In the specific setting of cancer with a limited (1-4) number of brain metastases, a RCT confirmed that WBRT should not be routinely recommended as it did not impact on OS and negatively affected cognitive functioning compared to SRS.
5. ***Second line treatment.*** A study confirmed taxane-based chemotherapy + angiogenesis inhibition to be superior to docetaxel alone in non-squamous NSCLC. Updated OS data, but no new data, on anti-PD-1/PD-L1 immuno-oncology therapy.
6. ***ALK-TKI.*** In addition to ceritinib (ASCO 2015), brigatinib and alectinib (ASCO 2016) are other active next generation TKIs for ALK+ NSCLC patients. In a Japanese first-line study, alectinib at 300 mg BID was superior to crizotinib.
7. ***TKI targeting other oncogenes detected by NGS testing in adenocarcinoma.***
   - EGFR: update on two AZD 3th generation TKIs in brain or leptomeningeal metastases confirms their good intracranial activity.
   - Update of promising phase I-II results for other targeted agents are tabulated in full text.
   - Expanded genomic testing in stage IV lung adenocarcinoma and associated targeted therapies did provide survival benefit in the Lung Cancer Mutational Consortium II experience.

Small cell lung cancer and mesothelioma

8. ***Radiotherapy schedule in stage I-III SCLC (CONVERT).*** In a large RCT, RT with a total dose 45 Gy in 30 BID fractions over 3 weeks or a total dose 66 Gy in 33 OD fractions over 6.5 weeks delivered similar survival outcomes. Both are acceptable regimens for standard practice.
9. ***Anti-CTLA-4 immunotherapy in relapsed mesothelioma (DETERMINE).*** Tremelimumab 10 mg/kg q4w for 7 doses, then q12w, did not improve OS in mesothelioma progressing after one or two prior therapies**.**

Supportive care

10. **Role of follow-up and palliative care (PC).** One RCT studied early supportive care by weekly web-based patient-reported symptom assessment, resulting in a significant OS benefit compared to standard follow-up. Another RCT confirmed QOL improvement of integrated early PC by an at least a monthly PC visit in incurable lung cancer.

At the ASCO 2016 congress, 169 abstracts in the field of respiratory oncology were presented (189 in 2015): 20 oral presentations (including 3 in a clinical science symposium), 24 poster discussion items, and 125 posters.
In the past, we used to concentrate mainly on phase 3 randomized controlled trials (RCTs), i.e. >100 patients per arm). The clinical trial and regulatory landscape has changed substantially over the last years, with an increasing contribution of expanded ph1 trials in biomarker driven populations. From all of these data, we try to concentrate on data 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://meetinglibrary.asco.org/subcategories/2016%20ASCO%20Annual%20Meeting, also in J Clin Oncol 2016 volume 34 Supplement 15 (abstracts #8500-8569 and #9000-9098).

NSCLC – EARLY STAGES (STAGE I, II, RESECTABLE IIIA)

In 2004, the IALT study demonstrated the advantage of adjuvant cisplatin-based chemotherapy, which was confirmed in the LACE meta-analysis for completely resected stage II and IIIA tumors, and is accepted as the standard of care.
To date, we still haven't made any progress from there: phase III adjuvant randomized controlled trials (RCTs) with pharmacogenetic tailoring of the chemotherapy, with targeted agents such as gefitinib, erlotinib, or bevacizumab, or with immunotherapy such as the MAGE-A3 vaccine did not improve overall survival (OS).
This year, a RCT with adjuvant nandroparine, a low molecular weight heparin, was presented (**Figure 1**).

Figure 1: #8506: nandroparine added to adjuvant chemotherapy in early stage NSCLC (NVALT 8 study).
Patient setting
Completely resected stage II-IIIA NSCLC.
Comparison
Four cycles of adjuvant cisplatin-based chemotherapy + 16 weeks nandroparine s.c. daily (n=99)
versus
Four cycles of adjuvant cisplatin-based chemotherapy (no placebo control, n=102)
Outcome
Primary: relapse-free survival (RFS): 47.8 m *vs.* 36.1 m in control arm. 3-year RFS 57 vs. 50%.
Observations: the trial suffered from low accrual and the statistics were adapted during the trial from a planned 600 patients to an achieved 200 patients.
No significant differences in bleeding events. More grade ≥ 3 neutropenia with nandroparine (p=0.002).
Conclusion
Underpowered study. No improvement in outcome with nandroparine.

Another presentation detailed the use of different cisplatin-based regimens and their respective outcomes in the adjuvant ECOG1505 trial **(Figure 2**).

Figure 2: #8507: bevacizumab added to different cisplatin-based adjuvant therapies (ECOG 1505 study).
Patient setting
Completely resected stage IB >4 cm, II or IIIA NSCLC.
Comparison
Four cycles of adjuvant cisplatin-based chemotherapy + bevacizumab for 1 year (n=750)
versus
Four cycles of adjuvant cisplatin-based chemotherapy (no placebo control, n=750)
Outcome
Primary: OS: HR 0.99; p=0.91 (reported at WCLC 2015).
Observations: as bevacizumab had no effect at all, both arms could be fused to compare outcomes with four modern cisplatin-based regimens in the adjuvant setting. Cisplatin was combined with vinorelbine in 25%, docetaxel in 23%, gemcitabine in 19% and pemetrexed in 33% (the latter all non-squamous).
There was no significant difference in OS or DFS by chemo regimen. Toxicities were consistent with known profiles of the drugs, but patients with non-squamous tumors who received pemetrexed had significantly less grade 3-5 toxicity.
Conclusion
Similar performance of different cisplatin-based doublets in the adjuvant setting.

These data, together with other experiences, such as NVALT-8 and the TREAT study (Ann Oncol 2013; 24: 986-992) are important for standard practice. They point at possible alternatives for the quite toxic cisplatin-vinorelbine regimen in the adjuvant setting. Moreover, a Japanese study planned with 800 patients will compare cis-vinorelbine and cis-pemetrexed in completely resected adenocarcinoma.

NSCLC – LOCALLY ADVANCED STAGE III

For patients with unresectable stage III NSCLC, a concurrent approach with cisplatin-based chemotherapy plus 60-66 Gy thoracic radiotherapy is the established standard of care since many years.
Just as for early stages, little progress over the last decade here as well: phase III RCTs with higher radiotherapy doses (74 Gy), more modern chemotherapy such as cisplatin-pemetrexed for non-squamous tumors, addition of targeted agents such as cetuximab, or consolidation with the MUC1 vaccine Tecemotide did not improve OS.
One abstract studied the role of proton therapy in this setting in a small RCT (**Figure 3**).

Figure 3: #8500: Randomized comparison of intensity-modulated radiotherapy (IMRT) *vs.* 3D proton therapy (3DPT) with concurrent chemotherapy for unresectable locally advanced NSCLC.
Patient setting
Unresectable stage III NSCLC.
Randomization
Concurrent chemotherapy and IMRT (n=149)
versus
Concurrent chemotherapy and 3DPT (n=57).
Outcome
Primary: rates of and time to treatment failure (TF). TF defined as either grade ≥ 3 radiation pneumonitis or local recurrence within 12 months. **TF rates at 12 m were 15.6% in IMRT *vs.* 24.6% in 3DPT groups.**
Observations: grade ≥3 radiation pneumonitis rates were 7.2% in IMRT *vs.* 11.0% in 3DPT groups. Incidence of local recurrence was 22.8% in IMRT *vs.* 24.6% in 3DPT.
Conclusion
No significant differences were found between IMRT vs. 3DPT in TF in this small randomized trial.

In contrast with these negative randomized data, a possible superiority for proton therapy (PT) over standard RT was reported in a retrospective analysis of the North-American NCDB (National Cancer Data Base), time interval 2004-2012 (**#8501**). The number of patients with PT was low (n=348) compared to the total number (n=140,383). On multivariate analysis, standard RT was associated with an increased risk of death relative to PT (HR 1.46, $p < 0.001$). There were imbalances in treatment approaches, as nearly all PT was in academic centers. For the time being, the place of PT still needs to be defined in standard practice. Large phase 3 studies are ongoing (e.g. RTOG 1308).

NSCLC – ADVANCED STAGE

First line treatment in the setting of oligometastatic disease (OMD)

There is a subgroup of stage IV patients with few metastases at diagnosis, so-called OMD. Several, mainly retrospective single center, series have suggested that OMD patients may survive longer than 2-3 years or may remain disease-free for many years, on the condition that all detectable deposits are treated radically with radiation treatment and/or surgery in addition to systemic treatment. For the first time, a RCT in the OMD setting of NSCLC was reported at this ASCO. The study was closed early due to significant PFS benefit observed in the local therapy arm of the study (**Figure 4a**).

Figure 4a: #9004: Open label ph2 RCT in NSCLC with ≤3 (N+ included as 1 site) metastases.

Patient setting

NSCLC with ≤3 metastases and no RECIST progression after induction therapy (chemo ≥4 cycles; TKI ≥3 months).

Randomization

Local Consolidative Therapy (LCT) of all sites +/- observation or maintenance systemic treatment (n=25)

versus

Observation or maintenance systemic treatment (n=24).

Outcome

Primary: PFS: median 11.9 *vs.* 3.9 m; HR not reported; p=0.005. Subgroup EGFR/ALK negative (n=40) HR 0.41 [0.19-0.90]; p=0.022.

Observations: study stopped early by DSMC due to efficacy in experimental arm at median FU of 19 months. OS data not yet mature, but 11 pats in the no-LCT arm did cross-over to LCT arm.

Prognostic factors: number of metastases: 1 *vs.* 2-3, p=0.043; oncodriver : ALK/EGFR *vs.* none, p=0.035.

Safety: no grade 4-5 toxicity, while 20% grade 3 toxicity in LCT arm.

Conclusion

In selected patients with oligometastatic NSCLC (63% solitary metastasis with cN0!) who do not progress after induction systemic treatment, LCT is associated with improved PFS without additional toxicity compared to standard of care.

The very low number of highly selected – most likely biased selection – patients in addition to the premature discontinuation of the study in the view of a primary endpoint dealing with PFS instead of OS does *not* support a change in institutional practice based on the results of this phase II study, but awaiting the results of ongoing confirmatory studies looking at overall survival is justified.

The addition of whole-brain radiotherapy (WBRT) to stereotactic radiosurgery (SRS) is known to deliver a significant improvement in intracranial tumor control, but no impact on OS, in patients with a limited (≤3) number of brain metastases. Neurosurgery is generally indicated in patients with (single) brain metastasis of ≥3cm or brain metastasis with neurological deficit or severe edema. It is however unknown whether

adjuvant salvage SRS is as good as adjuvant WBRT after surgical resection for a limited number of residual brain metastases. An interesting study on this topic was reported (**Figure 4b**).

Figure 4b: #2003: Open label ph3 RCT in cancer with brain metastases (JCOG0504 trial).
Patient setting
Cancer with 1-4 brain metastases (with at least one with size ≥3 cm); PS 0-2; MRI documented.
Randomization
Adjuvant whole brain radiotherapy (WBRT) 37.5 Gy in 15 fractions (n=137)
versus
Adjuvant observation or stereotactic radiosurgery (SRS) 18-24 Gy for residual lesion(s) (n=134)
Outcome
Primary: OS: HR 1.05 [0.83-1.33]; median 15.6 *vs.* 15.6 m (non-inferiority design).
Observations: time to intracranial progression: median 10.4 [WBRT] *vs.* 4.0 m [SRS]; p<0.0001.
Progression in SRS group was treated with either SRS (up to 8 lesions) or WBRT (30% of patients during first year after randomization).
Demographics: 48% NSCLC; 73% had 1 brain metastasis ; 60% had no residual disease after surgery.
Toxicity: grade 2-4 cognitive dysfunction at 90 days: 16.4 *vs* 7.7%; proportion non-worsening MMSE score at 12 m: 45.3 *vs* 42.5%.
Conclusion
Salvage SRS resulted in non-inferior OS compared to adjuvant WBRT. Adjuvant WBRT did improve intracranial tumor control, but with neurocognitive decline and no impact on OS.

This RCT thus confirmed that salvage SRS is at least as good as adjuvant WBRT, this time in the setting where the largest (≥3cm) of 1-4 brain metastases is surgically resected and the residuals brain metastases are amended for irradiation.

Second-line chemotherapy
Two already published RCTs compared a taxane (docetaxel) and an anti-angiogenic agent (nintedanib or ramucirumab, respectively) to docetaxel alone, and both studies demonstrated superiority in terms of PFS and OS for the combination in non-squamous NSCLC. Similarly, an open label phase III trial (**#9005**) now demonstrated that weekly paclitaxel + bevacizumab resulted in superiority over docetaxel for ORR and PFS with 38% reduction in risk of disease progression. This makes the combination of a taxane and angiogenesis inhibitor the first choice in patients not eligible for immuno-oncology (I-O) drugs in second-line non-squamous NSCLC. This combination could also challenge the choice for I-O treatment in the second-line setting in patients with low or negative PD-L1 IHC.

At this ASCO, no new RCT data were presented in the field of I-O treatment. Survival updates were presented for second-line treatment with I-O drugs compared to docetaxel, i.e. Checkmate 017/057 (**#9025**), POPLAR (**#9028**), and KEYNOTE-010 (**#9024**), to support the observation that I-O treatment can result in durable response impacting on the tail of the survival curve. In addition, numerous posters were dealing with the areas of opportunity for mechanism-based biomarker development in anti-PD-1/PD-L1 therapies. The most studied were immunologic factors in the tumor (i.e. PD-L1 protein expression) and genetic factors (i.e. tumor mutational burden). PD-L1 IHC does correlate with ORR and OS for non-squamous NSCLC treated with pembrolizumab with increasing responsiveness for increased PD-L1 expression (**#9015**). PD-L1 IHC enriches for responsiveness but it remains unknown if PD-L1 staining is useful in selecting patients for I-O treatment in second line setting, i.e. if the negative predictive value (NPV) of PD-L1 IHC is satisfactory to exclude patients for I-O treatment. In addition, PD-L1 expression is heterogeneous in terms of tumor tissue expression and assays. Tumors with a high mutational density are more likely to derive clinical benefit from I-O therapy. There is a correlation between tumor mutation

burden (TMB) and outcome on PD-1/PD-L1 inhibition, but TMB threshold in lung cancer suffers from suboptimal NPV or PPV, so that it is unlikely to become the principle test to specifically rely on to guide I-O therapy (**#9017**). Most likely a multifactorial biomarker will be needed to guide anti-PD-1/PD-L1 I-O therapy.

ALK-TKIs

In ALK+ lung adenocarcinoma, the role of crizotinib has become very clear over the past years. However, acquired drug resistance always occurs, and next generation drugs have proven value for disease control (even good intracranial activity) of ALK+ NSCLC. Ceritinib has already been FDA/EMA approved in case of resistance to crizotinib. At this ASCO meeting, randomized ph2 data with brigatinib for crizotinib-refractory ALK+ patients, and ph3 data with alectinib for crizotinib-naive ALK+ patients were presented (**Figures 6a and 6b**).

Figure 6a: #9007: Phase 2 open-label randomized dose evaluation of brigatinib (ALTA study).

Patient setting

Metastatic stage crizotinib-refractory ALK+ NSCLC with PS 0-2. Unstable CNS metastases not allowed and prior ALK-TKI other than crizotinib not allowed.

Randomization

Brigatinib 90 mg daily (n=112)

versus

Brigatinib 180 mg daily after 7-day lead-in at 90 mg (n=110).

Outcome

Primary: confirmed ORR (RECIST 1.1): 45 and 54%; confirmed DCR: 82 and 86%.

Observations: CNS objective response 36 *vs.* 67% for measurable brain metastases.

Post-hoc analyses: PFS HR 0.55 [0.35-0.86], median PFS 9.2 *vs* 12.9 m. OS HR 0.57 [0.31-1.05], 1-year OS 71 *vs* 80 %.

Safety: no pulmonary AE after dose escalation to 180 mg; dose reduction due to AE 7 *vs.* 20%; discontinuation due to AE 3 *vs.* 8%.

Conclusion

Brigatinib at 180 mg daily demonstrated substantial efficacy and safety, and has the potential to be promising new treatment for crizotinib-refractory ALK+ NSCLC. In addition, a first line phase 3 RCT of brigatinib 180 mg *vs.* crizotinib has been initiated.

Brigatinib in crizotinib refractory ALK+ patients has similar efficacy as ceritinib, reported at ASCO 2015 with a response rate of 49.2%, disease control rate of 79.5%, with signs of good intracranial activity, and a withdrawal rate due to AEs of 8.0%. These next generation ALK-TKIs are brought to the first line setting compared to crizotinib in RCTs now. The first such trial reported is J-ALEX in a Japanese patient cohort (**Figure 6b**).

Figure 6b: #9008: Phase 3 open-label RCT alectinib versus crizotinib (J-ALEX study).
Patient setting
Metastatic stage ALK-TKI naïve ALK+ (IHC+FISH) NSCLC in PS 0-2; stable CNS metastases allowed.
Randomization
Alectinib 300 mg BID (n=103)
versus
Crizotinib 250 mg BID (n=104).
Outcome
Primary: PFS by independent review: HR 0.34 [0.17-0.71]; median PFS NR [20.3-NR] *vs.* 10.2m.
Observations: ORR 91.6 vs 78.9%.
Safety: grade 3/4 AEs 26 vs. 52%; SAEs 15 vs. 26%; discontinuation rate due to AEs 8.7 *vs.* 20.2%.
Conclusion
At pre-planned interim analysis, alectinib demonstrated superior PFS and less AEs compared with crizotinib in Japanese patients.

Update on TKI targeting oncogenes detected by NGS testing in adenocarcinoma
Non-invasive genotyping is here to stay and can guide clinical care to detect actionable EGFR mutations, to detect exon 20 T790M resistance mutation, to monitor evolution of resistance, or to detect additional resistance mechanisms (**#9000 and #9001**).
There were a large number of abstracts updating on new drugs and targets, they are briefly summarized in our **Table**.

Table: new drugs and new targets

Abstract	Type	Compound	Target mutation	ORR	Main toxicity
#107	Phase II	Dafrafenib + trametinib	BRAF V600E	36/57 (63%)	Pyrexia, anemia, nausea, skin SQCC
#9012 #9014	Phase II Global registry	Vandetanib or cabozantinib	RET	29-47%	AHT, rash, diarrhea, QTc, liver, thrombocytopenia
#9002	Phase I	Osimertinib 160 mg	EGFR T790M with LM disease	7/21 (33%) on MRI	Rash, diarrhea
#9020	Phase II	Capmantinib	EGFR with cMET+	12/65 (18%)	Hypoalbuminemia, edema, decreased appetite
#9003	Phase I	AZD3759	EGFR with brain disease	6/21 (29%)	Rash, diarrhea
#9009	Phase I	Lorlatinib	ALK+	19/41 (46%)	Dyslipidemia
#9009	Phase I	Lorlatinib	ROS-1+	6/11 (55%)	Dyslipidemia
#108	Phase I	Crizotinib	MET exon 14 alteration	8/18 (44%)	Edema, nausea, diarrhea, vision disorder

Expanded genomic testing in 875 patients with stage IV lung adenocarcinoma and associated targeted therapies did provide survival benefit in the Lung Cancer Mutational Consortium II experience (2012-2015; 14 genes analysed using NGS) (**#11510**): driver without targeted therapy *vs.* driver with targeted therapy resulted in median OS of 1.5 *vs.* 2.7 years (P=0.013). No driver *vs.* driver with targeted therapy resulted in median OS of 1.7 *vs.* 2.7 years (P=0.006).

SMALL CELL LUNG CANCER

Except for rare patients with very early stage SCLC – in whom surgery may play a role in the treatment plan – the standard approach for fit patients with stage I-III SCLC is four cycles of cisplatin-etoposide chemotherapy with concurrent radiotherapy. A landmark RCT from quite some time ago (N Engl J Med 1999; 340:265-271) compared 45 Gy of radiotherapy, delivered twice-daily accelerated (twice daily 1.5 Gy, over a 3 week period, BID) with once daily standard fractionated (1.8 Gy, over a 5 week period, OD). BID resulted in a clearly better outcome with a 47% and 26% OS rates at 2 and 5 years for BID, versus 41% and 16% for OD, at the cost of more grade 3 esophagitis. BID RT has not been adopted widely due to logistics and toxicity concerns. 45 Gy in a standard fractionation may, however, be a too low dose.
An important RCT led by the Manchester group in this setting was reported at this meeting (**Figure 8**).

Figure 8: #8504: Randomized comparison of two RT schedules in stage I-III SCLC (CONVERT study).
Patient setting
Stage I-III SCLC eligible for concurrent chemoradiotherapy (about 70% PET-CT staged).
Randomization
RT total dose 45 Gy in 30 BID fractions over 3 weeks starting with cycle 2 (n=274)
versus
RT total dose 66 Gy in 33 OD fractions over 6.5 weeks starting with cycle 2 (n=273).
Outcome
Primary: 2-year OS: 56% [95%CI 50-61] for BID *vs*. 51% [95% CI 45-57] for OD (HR 1.17, p=0.15).
Observations: median OS 30 *vs.* 25 months.
Toxicities were comparable except for significantly more grade 3/4 neutropenia (74% BID vs 65% OD, p=0.03).
Conclusion
This trial supports the use of either regimen for standard of care treatment of stage I-III SCLC in good PS.

Survival was better in both arms, compared to historical control, which may be related to the high proportion of patients with PET staged disease and the use of modern RT planning and delivery. In the light of the easier and shorter delivery time, the BID schedule remains the preferred one for the presenting author. On ongoing RTOG study now compares 45 Gy BID to 61.2 Gy OD and to 74 Gy OD.

Treatment options for patients with stage IV SCLC that progress on platinum-based chemotherapy are limited. In this respect, we mention **#LBA8505.** In this trial, the activity of rovalpituzumab-tesirine, a new antibody-chemotherapy drug conjugate in relapsed SCLC was reported. The antibody part is targeted to DLL3, which is highly (>50% cells staining) expressed in two thirds of SCLC. In these high expressing tumors, there was a promising response rate of 39%. This “targeted” agent for relapsed SCLC will undergo further testing.
In an Italian intergroup trial **(#8513**), bevacizumab was added to platinum-etoposide for stage IV SCLC. There was a one month difference in PFS, but no change at all in the primary endpoint OS.

MESOTHELIOMA

The standard first line systemic therapy for malignant pleural mesothelioma (MPM) is cisplatin-pemetrexed. There are at present no registered 2nd line options for this malignancy. As a sign of the high unmet need in this situation, a recent RCT with the anti-CTLA-4 antibody tremelimumab recently recruited very quickly and was reported at this meeting (**Figure 9**). Tremelimumab is a human IgG2 checkpoint inhibitor of CTLA-4 that promotes T-cell activation.

Figure 9: #8502: Phase 3 RCT with tremelimumab in relapsed mesothelioma (DETERMINE study).
Patient setting
Malignant mesothelioma progressing after one or two prior therapies.
Randomization
Tremelimumab 10 mg/kg q4w for 7 doses, then q12w (n=382)
versus
Placebo same schedule (n=189).
Outcome
Primary: OS: HR 0.92, p=0.408. Median OS 7.7 vs. 7.3 m.
Observations: grade ≥ 3 treatment-emergent AEs that were more frequent in the active arm were diarrhea (15%/1%) and colitis (7%/0%). For any grade AEs this was diarrhea (47%/19%), pruritus (27%/8%) and rash (21%/7%).
Conclusion
Tremelimumab monotherapy did not improve OS 2nd/3rd-line mesothelioma.

In abstract **#8503**, the early results with the anti-PD-L1 checkpoint inhibitor avelumab in mesothelioma were presented. Patients had progression after a platinum-pemetrexed regimen and were selected for PD-L1 expression. Avelumab 10 mg/kg i.v. q2w was given until progression, unacceptable toxicity, or withdrawal. Five responses in 53 patients were noted (ORR 9.4%). Median PFS was 17 weeks. ORR was 14.3% in PD-L1 positive and 8.0% in PD-L1 negative tumors. Avelumab thus showed some clinical activity, both in PD-L1 positive and negative tumors.

SUPPORTIVE CARE

Patient reported outcomes (PROs) focusing on symptoms have proven a high sensitivity (86-100%) and very high negative predictive value (93-100%) to assess oncologic disease relapse, resulting in a 27% survival benefit at 1 year follow-up after first-line treatment for stage III-IV lung cancer in a non-randomized setting. At this ASCO, one RCT focused on the OS improvement through early supportive care by weekly PRO symptom assessment, while another RCT focused on QOL improvement of integrated early palliative care (PC) by an at least a monthly PC visit (**Figures 10a and 10b**).

Figure 10a: #LBA9006: Open-label multicenter ph3 RCT of web-application-guided versus standard follow-up after first line treatment of lung cancer.

Patient setting

Non-progressive stage II (N+) to IV lung cancer with PS 0-2 and symptom score <7 after first line treatment.

Randomization

Planned visit + CT scan q6-12 m *plus* weekly web-based patient-scored 12-symptoms (with programmed e-mail alert to oncologist resulting in further action, i.e. CT +/- early supportive care) (n=60)

versus

Standard follow-up with planned visit and CT scan q3-6 m (n=61).

Outcome

Primary: OS (at median FU 9 m): HR 0.33 [0.16-0.67]; p=0.0025; median 19 *vs.* 12 m; 1-year OS 75 *vs* 49%.

Observations: PFS was NS different between arms; PS 0-1 at first relapse: 77 *vs.* 33%, *P*<0.001; optimal treatment of relapse: 74 *vs.* 33%, P<0.001. Compliance to web-app 84%.

Both groups were baseline well balanced for age, PS, NSCLC/SCLC, maintenance treatment; only imbalance for stage (stage III/IV 96 *vs.* 72%).

Conclusion

Using web-application-guided follow-up resulted in significant OS improvement compared to standard follow-up. Web-application guided FU may improve QOL by allowing earlier supportive care and better PS at first relapse. This could explain why early supportive care may improve survival.

At ASCO 2010 Temel et al. demonstrated for the first time that early PC led to significant improvements in both QOL and mood. At this ASCO the same authors presented a confirmatory study extended to SCLC, mesothelioma and GI tumors.

Figure 10b: #10003: Open label ph3 RCT of early integrated palliative and oncology care (PC) versus standard oncology care.

Patient setting

Newly diagnosed incurable lung cancer (55%: NSCLC, SCLC, mesothelioma) or GI cancer; PS 0-2.

Randomization

At least monthly visit with PC integrated with oncology care (n=175)

versus

Usual oncology care (n=175).

Outcome

Primary: FACT-G at 12 weeks (86% completed): trend in improvement of QOL (p=0.09). Significant improvement in FACT-G at 12 weeks for lung cancer cohort only (p=0.03).

Observations: QOL at 24 weeks (69% completed): higher QOL at FACT-G (*P*=0.004) and less depression on PHQ-9 (p=0.047) for early PC. End-of-life preferences discussion: 30.2 *vs.* 14.5%, p=0.005.

Conclusion

Early PC significantly improved QOL and mood in lung cancer subtype only, and increased communication about end-of-life preferences in all patients with newly diagnosed cancer (55% lung cancer).

For your calendar:
ESMO 2016: 7-11 October, Copenhagen.
WCLC 2016: 4-7 December, Vienna.
ELCC 2017: 5-8 May, Geneva.
ASCO 2017: 2-6 June 2017, Chicago.
ESMO 2017: 8-12 September, Madrid.