Highlights in thoracic oncology

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During ASCO 2016, 190 abstracts were presented in the lung cancer track: 18 oral presentations, 22 discussion sessions and 172 posters. This report will highlight 7 selected phase III trials and 3 small but promising phase I/II trials.

This year's ASCO focused on the promising and exciting domain of immunotherapy with checkpoint inhibitors. Of special interest were the data in first line treatment of NSCLC, the combination of PD-L1 and CTLA-4 antibodies, and the phase I/II results in mesothelioma, small cell lung cancer and thymic carcinoma.

Other highlights of ASCO 2016 in the field of thoracic oncology included updated results of new targeted therapies for patients with defined molecular targets and for patients with acquired resistance after first-generation EGFR or ALK-inhibitors.

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Early stage non-small cell lung cancer (NSCLC)

E1505-trial: Adjuvant chemotherapy with or without bevacizumab for early stage NSCLC: outcomes based on chemotherapy subsets

Adjuvant cisplatin-based chemotherapy for completed resected early stage NSCLC provides a modest overall survival (OS) benefit of around 5%. Bevacizumab, an antibody to VEGF, improved outcomes with platinum-based chemotherapy in advanced stage non-squamous NSCLC in the E4599 study. E1505 was designed to evaluate the addition of bevacizumab to adjuvant chemotherapy in early stage resected NSCLC.[1]

Patients with resected early stage NSCLC were randomised (1:1) to chemotherapy alone or chemotherapy with bevacizumab (15 mg/kg every 3 weeks for up to 1 year). The chemotherapy regimen consisted of planned 4 cycles of every 3-week cisplatin (75 mg/m2 d1) with investigator's choice of vinorelbine (V) (30 mg/m2 d1,8), docetaxel (D) (75 mg/m2 d1), gemcitabine (G) (1200 mg/m2 d1,8), or pemetrexed (P) (500 mg/m2 d1). Pemetrexed was added in 2009 for non-squamous patients only.

The trial was stopped early for futility. When patients were pooled across the arms with or without bevacizumab and divided into non-squamous and squamous cohorts, there was no significant difference in OS (primary endpoint) or disease free survival (DFS) by chemotherapy regimen. Toxicities were consistent with known profiles of the drugs.[1]

In summary, no differences in OS or DFS were observed between 4 different adjuvant cisplatin based chemotherapy regimens for surgically resected early stage NSCLC patients.

Locally advanced NSCLC

Bayesian randomised trial comparing intensity modulated radiation therapy versus passively scattered proton therapy for locally advanced NSCLC

In a Bayesian randomised trial of intensity-modulated radiotherapy (IMRT) *vs.* 3D proton therapy (3DPT), both with concurrent chemotherapy, for locally advanced NSCLC, the rates of treatment failure as well as the time to treatment failure (TTF) (either grade 3 radiation pneumonitis (RP) or local recurrence (LR) within 12 months) were assessed. Of the 255 patients enrolled in the study, 149 were randomly allocated to IMRT (N=92) or 3DPT (N=57), and 106 received NRIMRT (N=70) or NR3DPT (N=36).[2]

The rates of treatment failure at 12 months were 20.7%

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in all patients, 15.6% in IMRT and 24.6% in 3DPT groups. The corresponding median TTF was 10.5 months in the entire treatment population and in the IMRT and 3DPT groups. The rates of RP were 8.7% in all patients, 7.2% in IMRT, and 11.0% in the 3DPT groups. The rates of LR on the other hand were 23.5%, 22.8% and 24.6% in all, in IMRT, and in 3DPT patients, respectively. The median time to LR was 13.0 months in the entire population and 12.7, and 13.4 months in the IMRT and 3DPT patients.[2]

In summary, no differences in treatment failure were found between IMRT and 3DPT in this randomised trial. However, we have to take into account that in this trial, "passive scattering 3DPT" is compared to IMRT, in other words, a 'poor-mans PT' is compared to optimised IMRT. In order to exclude a real benefit from PT, a comparison between Pencil Beam Scanning (instead of passive scattering) and IMRT is needed.

Metastatic NSCLC (pan-wildtype)

Local consolidative therapy to delay progression in patients with oligometastatic NSCLC who receive induction systemic therapy: results of a multi-institutional phase II randomised study

In this study, appropriate induction systemic therapy was defined as either ≥4 cycles of platinum doublet therapy or ≥3 months of erlotinib/crizotinib for patients with EGFR mutations/ALK fusions, respectively. Patients were randomised to receive either local consolidative therapy (LCT, [chemo]radiation or surgical resection of all sites) with or without systemic therapy *vs.* systemic therapy alone. The primary endpoint of the trial was PFS.[3]

Based on the DSMC recommendation, the study was closed early due to significant efficacy benefit observed in the study arm. At a median follow-up time of 16.2 months, the median PFS in the LCT arm was 14.4 months as compared to 3.9 months in the no-LCT arm (HR: 0.36; p=0.013). The median OS has not yet been reached and patients continue to be followed for this endpoint.[3]

In conclusion, in oligometastatic NSCLC patients (≤3 metastases) without progression after IST, immediate LCT with or without systemic therapy improved the PFS as compared to systemic therapy alone.

Overall survival in patients with lung cancer using a web-application-guided follow-up compared to standard modalities: Results of phase III randomised trial

A web-application for an early detection of symptomatic relapse, complications and early supportive care in high-risk lung cancer patients between visits was developed. A dynamical analysis of the weekly self-reported symptoms automatically triggered physician visit. This was a national multi-institutional phase III prospective randomised study to compare a web-application follow-up (experimental arm) for which patient's self-scored symptoms that were sent to the oncologist on a weekly basis (between planned visits) and a clinical routine assessment with a CT-scan (every 3-6 months or at investigator's discretion). High-risk lung cancer patients without progression and with a 0-2 performance status (PS) after an initial treatment were included. In the experimental arm, an e-mail alert was sent to the oncologist when some predefined clinical criteria were fulfilled: imaging was then quickly prescribed. The primary objective was to detect an improvement of 12% in 9 months survival in favour of the experimental arm.[4]

In total, 121 patients were included in the intent-to-test survival analysis (90% were stage III/IV, median age: 65 y): 60 in the experimental and 61 in the standard arm. Median follow-up was 9 months. The median OS was found to be 19 months in the experimental arm as compared to 11.8 months with the standard CT follow-up (p=0.0014; HR[95%CI]: 0.33[0.16-0.67]) and the PS at the first relapse was 0-1 for 81.5% (experimental) versus 35.3% of the patients (p<0.001) (*Figure 1*).[4]

In summary, this trial shows a significant survival improvement using a web-application-guided follow-up. Moreover, this approach led to a better performance status at relapse, an earlier supportive care and a reduction of routine imaging.

CheckMate 012: safety and efficacy of first-line nivolumab and ipilimumab in advanced NSCLC

In CheckMate 012, a total of 148 patients with advanced NSCLC received N+I (mg/kg) across 4 dose cohorts. The primary objective was safety, while secondary endpoints were ORR (RECIST v1.1) and 24-week PFS rate. In addition to this, exploratory endpoints were OS and efficacy by tumour programmed death ligand 1 (PD-L1) expression. Treatment-related (TR) adverse events (AEs) and select TRAEs were manageable. Across cohorts, ORRs ranged from 13%–39% and the median duration of response was not reached. Responses were noted regardless of PD-L1 expression, with a higher magnitude of benefit in tumours that expressed PD-L1. Of note, the efficacy with nivolumab plus ipilimumab was enhanced with increasing PD-L1 expression:

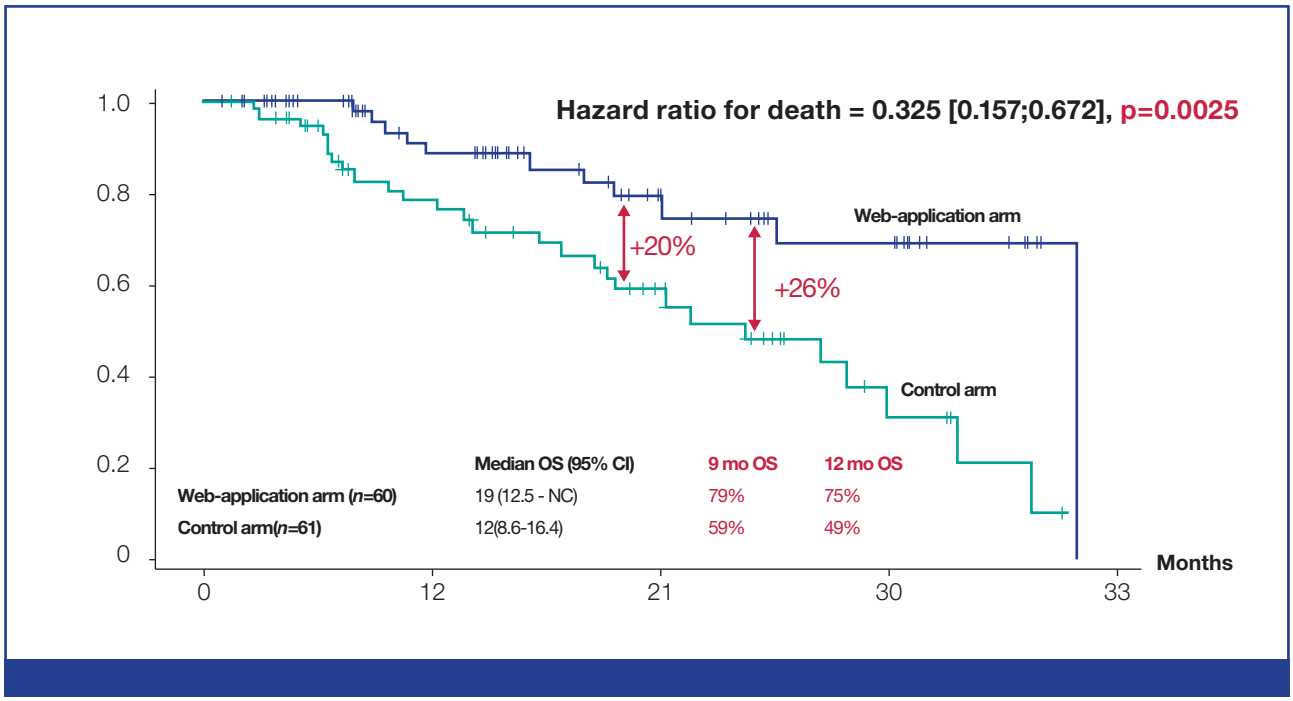

Figure 1. Overall survival in patients with lung cancer using a web-application-guided follow-up compared to standard modalities: median OS 19 *vs.* 12 months (HR 0.33).[4]

≥1% tumour PD-L1 expression: 57% ORR; 83–90% 1-year OS rates; ≥50% tumour PD-L1 expression: 92% (12/13) ORR.[5]

In summary, first line therapy with nivolumab and ipilimumab demonstrates clinical activity and a manageable safety profile.

Metastatic NSCLC (with oncogenic driver mutations)

EGFR mutations

Osimertinib activity in patients with leptomeningeal disease from NSCLC: updated results from BLOOM, a phase I study

Leptomeningeal (LM) disease is a severe type of NSCLC disease progression, associated with a poor prognosis. Osimertinib (AZD9291) is an oral, potent, irreversible epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) selective for activating T790M resistance mutations. Patients with EGFRm advanced NSCLC who had progressed on prior EGFR-TKI therapy and LM disease confirmed by positive cerebrospinal fluid (CSF) cytology were enrolled. Patients were treated with osimertinib 160 mg, once daily. In this study, osimertinib at 160 mg once daily demonstrates encouraging preliminary safety and activity in heavily pre-treated patients with LM disease from EGFR-mutant NSCLC.[6]

ALK rearrangements

Brigatinib in patients with crizotinib-refractory ALK-positive NSCLC: first report of efficacy and safety from a pivotal randomised phase 2 trial (ALTA)

In the phase II ALTA study, patients were stratified by presence of brain metastases at baseline and best response to prior crizotinib after which they were randomised (1:1) to receive oral brigatinib at 90 mg qd (arm A) or 90 mg qd for 7 d followed by 180 mg qd (arm B). The primary endpoint of this trial was investigator-assessed confirmed ORR per RECIST v1.1.[7]

In arm A, the investigator-assessed ORR was 46% as compared to 54% in arm B. The median PFS in arms A and B were 8.8 and 11.1 months, respectively. Most common grade ≥3 treatment-emergent AEs (arm A/arm B) included: increased CPK (3%/8%), hypertension (4%/5%), pneumonia (3%/5%), rash (1%/4%), increased lipase (3%/2%), and pneumonitis (2%/3%).7

In summary, in both study arms, brigatinib yielded substantial responses, with a robust PFS and an acceptable safety profile.

Alectinib versus crizotinib (CRZ) in ALK-inhibitor naïve ALK-positive NSCLC: primary results from the randomised phase III J-ALEX study

Alectinib showed promising efficacy and tolerability in the phase I/II study (AF-001JP). The randomised open-label phase III trial (J-ALEX study) was conducted to prove superior PFS of alectinib as compared to crizo-

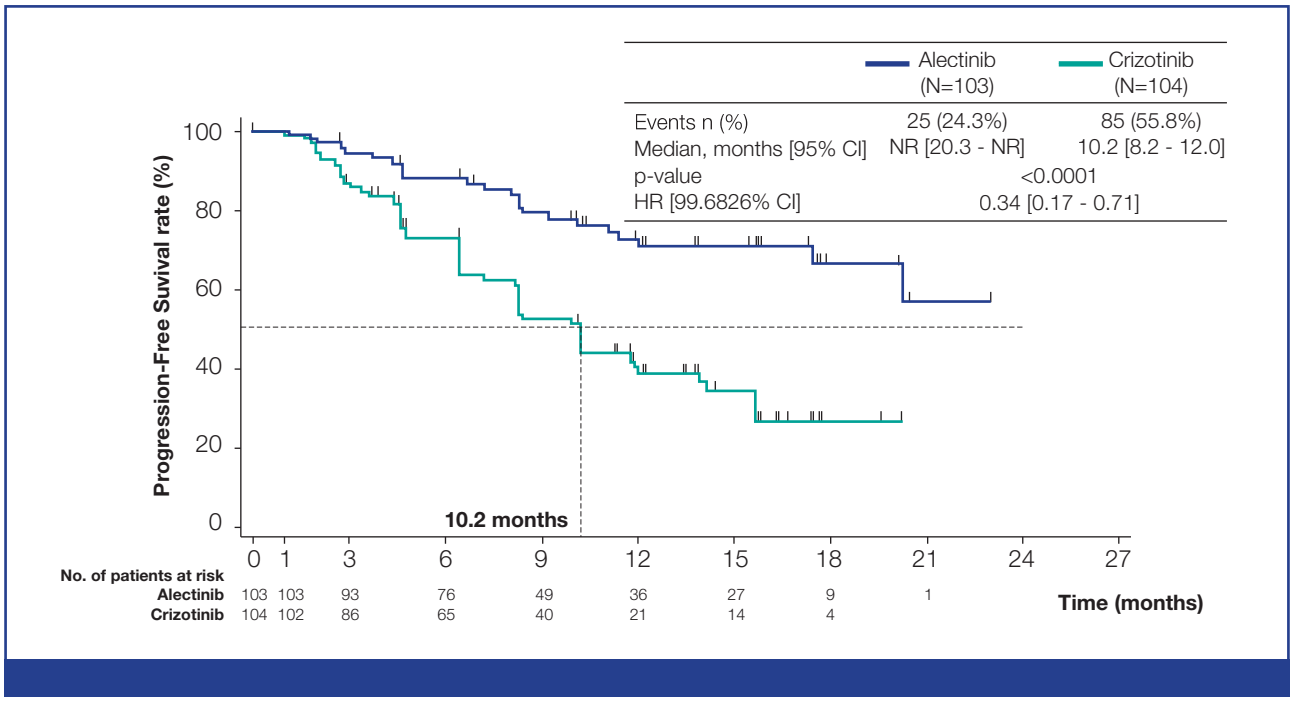

Figure 2. Alectinib versus crizotinib in ALK-inhibitor naïve, ALK-positive NSCLC: prolonged PFS with alectinib as compared to crizotinib (HR 0.34).[8]

tinib in ALK+ NSCLC patients without prior ALK inhibitor treatment.

In total, 207 Japanese ALK+ NSCLC patients were randomised 1:1 either to receive alectinib (300 mg b.i.d.) or crizotinib (250 mg b.i.d.). The primary endpoint was PFS. The HR for PFS of alectinib versus crizotinib was 0.34 (99.6826% CI: 0.17-0.70, stratified log-rank p=0.0001) (*Figure 2*).[8] The median PFS was not reached in the alectinib arm while it was 10.2 months (95%CI: 8.2-12.0) with crizotinib.[8]

In summary, alectinib demonstrated a significantly prolonged PFS as compared to crizotinib and was well tolerated with a favourable AE profile.

Small cell lung cancer

CONVERT: an international randomised trial of concurrent chemo-radiotherapy comparing twice-daily and once-daily radiotherapy schedules in patients with limited stage small cell lung cancer (LS-SCLC) and a good performance status

cCTRT is the standard of care for LS-SCLC patients with a good PS. However, there is no international consensus on a standard regimen. Twice daily (BD) radiotherapy has not been adopted widely due to concerns regarding logistics and toxicity. The aim of the study was to compare the OS and the toxicity of BD with once daily (OD) radiotherapy using modern conformal radiotherapy techniques given concurrently with chemotherapy.

Patients were randomised 1:1 to receive 45Gy in 30 BD fractions over 3 weeks or 66Gy in 33 OD fractions over 6.5 weeks starting on day 22 of cycle 1 chemotherapy (4 to 6 cycles of cisplatin 25 mg/m2 days 1-3 or 75 mg/m2 day 1 with etoposide 100 mg/m2 days 1-3), followed by PCI if indicated. RT was planned using 3D conformal or IMRT. The primary endpoint was 2-year survival and all analyses were by intention to treat.[9]

In total, 547 patients (274 BD and 273 OD) were recruited between April 2008 and November 2013 from 88 centres. At a median follow-up of 45 months, the two-year survival was 56% with BD and 51% with OD. The median OS was 30 months for BD as compared to 25 months with OD (HR[95%CI]: 1.17[0.95-1.45]; p=0.15) (*Figure 3*). Toxicities were comparable except for significantly more grade 3/4 neutropenia with BD than with OD (74% *vs.* 65%; p=0.03).[9]

In conclusion, OD radiotherapy did not result in a superior survival or worse toxicity than BD radiotherapy, supporting the use of either regimen for standard of care treatment of LS-SCLC with a good PS. Of note, the survival for both regimens was higher than previously reported. Moreover, with the modern RT techniques that were used, radiation toxicities were lower than expected.

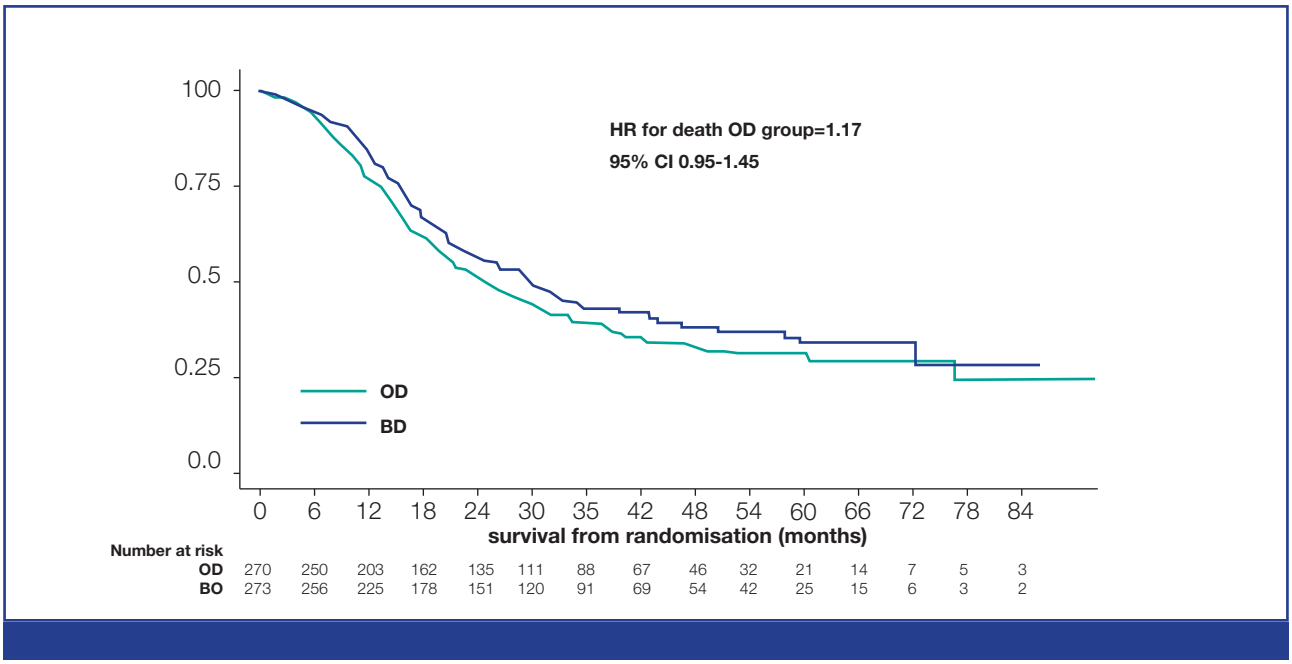

Figure 3. CONVERT trial: overall survival similar for OD and BD radiotherapy in patients with LS-SCLC.[9]

Italian multicentre phase III randomised study of cisplatin-etoposide with or without bevacizumab as first-line treatment in extensive stage small cell lung cancer (SCLC): GOIRC-AIFA FARM6PMFJM trial

Neo-angiogenesis is particularly abundant in SCLC and was previously shown to be associated with a poor prognosis. In the study at hand, patients were randomised to receive either etoposide 100 mg/m2 i.v. and cisplatin 25 mg/m2 on days 1-3 (or carboplatin AUC 5 in day 1) (arm A) or the same chemotherapy regimen combined with bevacizumab 7.5 mg/kg i.v. on day 1 (arm B), every 3 weeks and for a maximum of 6 courses. In the absence of progression after 6 cycles, patients in arm B continued bevacizumab alone until progression or for a maximum of 18 courses. The primary endpoint was OS. At a median follow-up of 35 months, the median PFS was 5.7 *vs.* 6.7 months (HR: 0.72), while the median OS was 8.9 *vs.* 9.8 months in arms A and B, respectively. The 1-year survival rate was 25% in arm A as compared to 37% in arm B (HR: 0.78).[10]

In summary, the addition of bevacizumab to platinum-etoposide in the first-line treatment of extensive stage SCLC leads to a statistically significant improvement in PFS, with an acceptable toxicity profile. However the observed increase in OS was not statistically significant.

Safety and efficacy of single-agent rovalpituzumab tesirine (SC16LD6.5), a delta-like protein 3 (DLL3)-targeted antibody-drug conjugate (ADC) in recurrent or refractory SCLC

DDL3 is a novel target in neuroendocrine tumours with an aberrant cell surface expression in 80% of SCLC and large cell neuroendocrine cancers. Rovalpituzumab tesirine is a delta-like protein 3 (DLL3)-targeted antibody-drug conjugate (ADC). Patients with recurrent or refractory SCLC (after ≥1 prior treatment) were enrolled into this first-in-human study; escalating doses of rovalpituzumab tesirine were administered in a dose-ranging manner. The ORR (PR + CR) was 18% and the clinical response rate (SD + CR + PR) was 68% among all patients. Responses were greater among those patients with ≥50% of cells expressing DLL3; ORR was 39% and the clinical response rate was 89%. These are very promising results, especially given the manageable toxicity.[11]

Mesothelioma

Tremelimumab as second- or third-line treatment of unresectable malignant mesothelioma: results from the global, double-blind, placebo-controlled DETERMINE study

Malignant mesothelioma (MM) is an asbestos-induced cancer with increasing global incidence. The 1st-line treatment for these patients consists of pemetrexed + platinum and there are no approved 2nd-line therapies. CTLA-4 is a co-inhibitory receptor expressed on activated T-cells. Tremelimumab is a selective human IgG2 mAb inhibitor of CTLA-4 that promotes T-cell activation. Single-arm phase II trials of tremelimumab using 2 different doses and schedules achieved responses and

Key messages for clinical practice

1. It has been shown that there are no differences in OS or DFS between 4 different adjuvant cisplatin-based chemotherapy regimens for surgically resected early stage NSCLC patients; for clinical practice: do not restrict to cisplatin-vinorelbine adjuvant chemotherapy.
2. An important phase II trial in oligo-metastatic NSCLC (≤3 mets), showed a PFS benefit of more than 10 months for patients without progression after initial systemic therapy, treated with local consolidative therapy (radiotherapy or surgery) compared to systemic treatment only.
3. A randomised phase III trial showed a significant survival improvement using Web-application-guided follow-up that allowed better PS at relapse, earlier supportive care and reduction of routine imaging and costs. The compliance was very high (84%). Of course these results need to be confirmed in other trials. Although this trial highlights the importance of PRO and self-reported symptoms in NSCLC patients in follow-up. It should be encouraged to also incorporate PRO in treatment trials and probably in the near future also in routine clinical practice.
4. For patients with EGFR mutations and ALK rearrangements, new drugs are studied and presented: third generation TKI's with activity against T790M are promising. (osimertinib, rociletinib). For ALK-rearrangement, second and third generation drugs will become available soon (brigatinib, ceritinib, lorlatinib, alectinib). Alectinib has shown to be superior to crizotinib in the first line setting in Japanese patients. At present it is not yet clear what the optimal sequence is for all these ALK-inhibitors.
5. For SCLC-LD with a good PS, there was no international consensus on a standard regimen (OD or BD radiotherapy). CONVERT was designed to answer this question and compared OD to BD radiotherapy using modern conformal RT techniques. In this trial OD radiotherapy did not result in a superior survival or worse toxicity than BD radiotherapy, supporting the use of either regimen for standard of care treatment of LS-SCLC with good PS.
6. Tremelimumab monotherapy did not demonstrate superiority to placebo for the primary endpoint OS in the 2nd/3rd line treatment of mesothelioma. These negative results probably reflect the moderate mutational load compared to NSCLC and melanoma. The accrual of this trial was very rapid, demonstrating an important unmet need for patients with progressing mesothelioma.
7. Liquid biopsies can complement tissue biopsy. The liquid biopsy will become the first choice in diagnosis, but does not obviate biopsy in negative cases. It seems promising in follow-up of patients with EGFR mutations and acquired resistance. The test is rapid and less/non invasive. As such, a liquid biopsy can be of important value in patients in which biopsy or rebiopsy is difficult to perform.
8. DDL-3 targeted antibody drug conjugates are a promising new class of chemotherapeutic agents.
9. The landscape of immunotherapy for lung cancer is rapidly evolving. New promising results were presented in first line metastatic NSCLC (CheckMate 012). The combination of nivolumab and ipilimumab is promising with a good RR, although there is enhanced but manageable toxicity. With this combination more responses are seen in EGFR mutations and non-smokers. In recurrent SCLC (CheckMate 032), the combination of nivolumab and ipilimumab doubled the RR compared to monotherapy. Also in mesothelioma and in thymic carcinoma, checkpoint inhibitors and especially the combination of checkpoint inhibitors seem promising.
10. Further research in the domain of checkpoint inhibitors will focus on non-immunogenic tumours: how to render a tumour more immunogenic? The combination of chemotherapy, radiation or targeted therapy with checkpoint inhibitors can release antigen, affect the tumour microenvironment and consequently make a tumour more immunogenic.
11. Different questions in immunotherapy remain open: how to select patients? Should we use PDL-1 as biomarker or is mutation burden a better marker? What is the optimal duration of treatment? What about post-RECIST progression?

durable disease control in mesothelioma patients.

The DETERMINE trial evaluated tremelimumab *vs.* placebo in patients with unresectable pleural or peritoneal MM. Eligible patients who progressed after 1–2 lines of prior therapy were randomised (2:1) to receive tremelimumab (10 mg/kg q4w for 7 doses, then q12w) or placebo. In total, 571 patients were randomised in this trial, with OS as the primary endpoint.[12]

With a median PFS of 7.7 months in the tremelimumab arm and 7.3 months in the placebo arm, no statistically significant difference in OS was seen (HR: 0.92, p=0.408). The most frequent treatment-emergent AEs with grade 3/4 severity (tremelimumab/placebo) were dyspnoea (9%/14%), diarrhoea (15%/1%) and colitis (7%/0%). Most frequent AEs (any grade) included: diarrhoea (47%/19%), dyspnoea (32%/37%), decreased appetite (29%/24%), fatigue (24%/32%), nausea (28%/20%), constipation (17%/28%), pruritus (27%/8%) and rash (21%/7%).[12]

In summary, tremelimumab monotherapy did not demonstrate superior OS to placebo in the second or third line treatment of mesothelioma.

Pathology

Epidermal growth factor receptor genotyping of matched urine, plasma and tumour tissue from NSCLC patients with rociletinib

Rociletinib is an oral inhibitor of mutant EGFR, including T790M. In this trial EGFR mutation detection in circulating tumour DNA from blood and urine was compared to that in matched tissue in TIGER-X (NCT01526928), a phase I/II study of rociletinib in patients with mutant EGFR positive advanced NSCLC.

EGFR status was assessed by the therascreen EGFR test (Qiagen) in tissue, BEAMing (Sysmex) in plasma, and a quantitative short footprint assay method that uses next-generation sequencing (Trovagene) in urine.

In T790M+ pts, response was similar whether T790M status was identified by tissue, plasma or urine. Plasma and urine testing identified T790M mutations missed by biopsy due to tumour heterogeneity or inadequate sample quality. These data suggest plasma and urine EGFR analyses complement tissue biopsies in EGFR TKI resistant NSCLC.[13]

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