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Maintenance treatment for advanced NSCLC

Previously two trials with gemcitabine continuation therapy following initial cisplatin + gemcitabine treatment have shown a trend towards improved overall survival in patients (pts) with advanced NSCLC (Brodowicz et al. Lung Cancer 2006; Pérol et al. ASCO 2010)

The PARAMOUNT trial is so far on the largest trial to evaluate the role of continuation maintenance treatment in this setting. In this trial pts with nonsquamous NSCLC who had not progressed during 1st-line treatment with pemetrexed + cisplatin were randomized to continuation treatment with pemetrexed or placebo. While the results for the primary endpoint (PFS) were already reported previously (HR 0.62; p<.0001; Lancet Oncology 2012), Paz-Ares et al (abstr. LBA7507) presented the favorable effects on overall survival during this year's meeting.

Table 1. Overall survival of continuation chemotherapy (PARAMOUNT)

OS from randomization	Pemetrexed	Placebo
Median OS	13.9 m	11.0 m
1-yr OS rate	58%	45%
2-yr OS rate	32%	21%
Overall survival HR	0.78 (p 0.0195)	

The survival benefit was observed amongst all subgroups; i.e. both pts with a response or stable disease following the 1st-line pemetrexed + cisplatin have a similar benefit (HR 0.81 and 0.76). Thus this trial demonstrated that continuation pemetrexed following pemetrexed + cisplatin is feasible, well tolerated, does not affect the ability to administer 2nd-line treatment and results in a significant improvement in survival. However before this treatment can be considered the standard of care for advanced nonsquamous NSCLC the questions of impact on symptom control /QoL and of cost-effectiveness will have to be addressed.

EGFR-TKIs for Treatment of molecularly selected NSCLC

Recently several trials comparing first-generation EGFR-TKIs (i.e. gefitinib and erlotinib) with platinum-doublets as 1st-line treatment of NSCLC tumors with activating *EGFR*-mutations have been reported. Given the significant improvements in response rate, PFS and symptom control/QoL, gefitinib and erlotinib have now become the preferred 1st-line treatment for pts with *EGFR*-mutation positive NSCLC. However while *EGFR*-mutations occur almost exclusively in nonsquamous NSCLC, none of these trials used cisplatin + pemetrexed as the comparator chemotherapy arm.

The LUX-Lung 3 trial (Yang et al abstr. LBA7500) is a worldwide trial randomizing pts with advanced adenocarcinoma of the lung harboring EGFR-activating mutations in a 2:1 fashion between afatinib (an irreversible ErbB family blocker of EGFR (ErbB1), HER2 (ErbB2), ErbB4, with in vitro activity against T790M *EGFR* mutation) and cisplatin + pemetrexed as 1st-line treatment. This trial met its primary endpoint of improved PFS by central independent review.

Table 2. Response rate (RR) and PFS in LUX-Lung 3

	Afatinin	Cis + Pem
RR (independent review)	56%	23%
Median PFS	11.1m	6.9m
1-yr PFS rate	32%	21%
Overall survival HR	0.58 (p 0.0004)	

The PFS-survival benefit was consistent across all relevant subgroups. No OS data were presented. The number of pts experiencing any drug-related AE grade ≥3 was similar in both arms, but the type of toxicity was markedly different: with afatinib the most common AE were diarrhea (95%), rash (62%) and paronychia (57%), and with cisplatin + pemetrexed this was nausea (66%), decreased appetite (53%) and vomiting (42%). Time to deterioration of lung-cancer related symptoms and QoL was better for the afatinib-arm. Thus afatinib offers another option for 1st-line EGFR-TKI treatment of EGFR-mutation positive pts. How afatinib compares to the 1st-generation TKIs gefitinib and erlotinib in this setting is not yet known, but will be addressed by the LUX-Lung 7 study (comparing afatinib vs gefitinib).

In the phase II SELECT trial (Neal et al. abstr. 7010) 36 pts with completely resected stage IA-IIIA NSCLC harboring activating EGFR mutations were treated with erlotinib for 2 years (y) after completion of any standard adjuvant chemotherapy and/or radiotherapy. Only 1 patient progressed while on erlotinib treatment, yielding a 94% disease-free survival at 2 years, which compares favorably to genotype-matched controls. Eleven pts relapsed after stopping of erlotinib (range 2.5 – 24 months). Important to note is that in 6 of 8 rebiospy samples no EGFR-TKI resistance mechanism was found and that all 5 evaluable pts were sensitive to further erlotinib treatment. However, we still need the results of the randomized phase III trial Radiant before the use of erlotinib in the adjuvant setting can be considered in routine practice.

Garassino (abstr. LBA7501) presented the PFS results of the TAILOR trial, which compared docetaxel to erlotinib in second line treatment of EGFR wild-type NSCLC. Upon progression no crossover to the other treatment was allowed. The objective of the trial was to demonstrate superiority of docetaxel in terms of OS. The response rate (14% vs 2%), median PFS (3.4m vs 2.4m; HR 0,69) and PFS rate at 6 months (29% vs 17%) were all significantly in favor of the docetaxel arm. However it should be noted that there was a slight imbalance in smoking status and histology (i.e. ~10% more (ex-)smokers and squamous CA in erlotinib arm) and that there was no independent radiology review in this open-label study (i.e. an unprecedented 4% CR-rate in docetaxel arm). Thus the results of the OS analysis need to be awaited before any definitive conclusions can be drawn from this trial.

Treatment of *KRAS*-mutation positive NSCLC

KRAS mutations are the most common (15-20%) oncogenic alteration in NSCLC.

Shepherd et al (abstr. 7007) reported the prognostic and predictive effects of *KRAS*-mutations in 1532 pts from 4 Lace-BIO trials of adjuvant chemotherapy *vs* observation in completely resected NSCLC. *KRAS* mutation was found to be not significantly prognostic in resected NSCLC. *KRAS* mutation status overall is not significantly predictive of survival benefit from adjuvant chemotherapy but codon 13 mutations appear to have worse outcome with chemotherapy (HR 0.89 in wild-type; HR 0.95 in codon 12 and HR 5.78 in codon 13 mutations), In the observation arm there was an almost 3-fold increase in the rate of second primary cancers in *KRAS*-mutant NSCLC compared to *KRAS* wild-type. But in the adjuvant chemotherapy arm there was a 34% reduction of this rate in the *KRAS*-mutant cases compared to the

wild-type. Overall these results indicate that currently treatment decision for adjuvant chemotherapy should not be based on *KRAS* mutation status.

Chaft et al (abstr. 7014) analyzed the pathologic response to induction chemotherapy in *KRAS*-mutated versus non-mutated resected stage I-III non-squamous NSCLC. In their series of 51 pts they found that pts with tumors having ≥90% necrosis had improved survival. There were no pts with *KRAS* mutation that achieved ≥90% treatment effect in response to induction chemotherapy. Thus the effectiveness of chemotherapy may be reduced in *KRAS*-mutant NSCLC.

Currently there are no effective targeted therapies available for *KRAS*-mutation positive NSCLC. Janne et al. (abstr. 7503) prospectively evaluated selumetinib + docetaxel *vs* docetaxel + placebo in previously treated pts with advanced *KRAS* mutant NSCLC in a phase II trial (N 87) with OS as primary endpoint. Selumetinib is a selective inhibitor of MEK 1/2. OS was longer in the selumetinib-arm (9.4 m *vs* 5.2 mo; HR 0.80) but did not reach statistical significance. The secondary endpoints response rate (37% vs 0%) and PFS (5.3 m *vs* 2.1 m; HR 0.58) were significantly improved in the selumetinib + docetaxel arm. There was an increased toxicity in the combination arm (f.e. AEs leading to hospitalization 48% *vs* 20%; febrile neutropenia 18% *vs* 0%). Nevertheless this is the first prospective study to demonstrate a clinical benefit of a targeted therapy (selumetinib + docetaxel) for pts with *KRAS* mutant cancer.

Immunotherapy for metastatic NSCLC

Programmed death 1 (PD-1) is a key immune-checkpoint receptor expressed by activated T cells that mediates immunosuppression. Expression of the PD-1 ligand (PD-L1) has been found in NSCLC, while an increased expression of PD-L1 on tumor cells is correlated with a decreased number of tumor-infiltrating lymphocytes. Inhibition of the interaction between PD-1 and PD-L1 can enhance T-cell responses in vitro and mediate preclinical antitumor activity.

Julie Brahmer (abstr. 7509) presented updated results of a multidose phase I trial of the fully human anti-PD1 mAb BMS-936558 in pretreated pts with advanced NSCLC. In 76 pts evaluable for clinical activity, the objective response rates and the PFS rate at 24 weeks were 18% and 26% respectively

Table 3. Clinical activity of different dose levels of BMS-936558

Dose	N	ORR	PFS at 24 wks
1 mg/kg	18	6%	16%
3 mg/kg	19	32%	41%
10 mg/kg	39	18%	24%

Durable clinical benefits were observed in both squamous and non-squamous NSCLC. Preliminary data indicate that PD-L1 expression on the surface of tumor cells in pretreatment tumor biopsy samples may be associated with an objective response (ORR 36% vs 0% in PD-L1 positive vs negative tumors), suggesting that PD-L1 expression in tumors is a candidate molecular marker.

New molecular targets for NSCLC

ROS1 receptor tyrosine kinase gene rearrangements are found in ~1% of NSCLCs. These *ROS1* rearrangements lead to the expression of oncogenic ROS1 fusion kinases. Shaw et al. (abstr. 7508) examined the efficacy of crizotinib (a TKI of MET-, ALK- and ROS-kinase activity) in pts with advanced, *ROS1*-rearranged NSCLC. In 14 pts they observed a RR of 57%. The median duration of treatment of 26 weeks is

underestimated since 12 pts are still ongoing treatment. Thus *ROS1* rearrangements define a new molecular subset of pts with NSCLC for whom crizotinib therapy may be highly effective.

Using next generation sequencing Capelletti et al (abstr. 7510) identified genomic alterations in 24 NSCLC specimens. In 72% NSCLCs, at least one alteration was associated with a current clinical treatment or targeted therapy trial, including mutations in *KRAS, BRAF, EGFR, MDM2, CDKN2A, CCNE1, CDK4, NF1* and *PIK3CA.* They also indentified a novel gene fusion joining exons 1-15 of *KIF5B* to exons 12-20 of *RET*. In 643 additional tumors they identified 11 RET-fusion positive pts (1.7%) who were all wild type for known oncogenes (frequency of 6.3% (10/159)). In preclinical models *KIF5B-RET* cells show growth patterns consistent with oncogenic transformation and are sensitive to RET inhibitors such as sunitinib, sorafenib and vandetinib. These findings suggest that RET inhibitors should be tested in prospective clinical trials in NSCLC pts bearing *KIF5B-RET* rearrangements.

Govindan presented updated results from The Cancer Genome Atlas (TCGA) describing the genetics of squamous cell lung carcinomas (abstr. 7006). In 178 tumor samples high somatic mutation rates were found (mean 228 non-silent mutations/tumor) with near universal *TP53* mutation and frequent loss of *CDKN2A* function. Potential therapeutic targets for clinical trials with currently available drugs were identified in 75% of pts (including FGFRs, PI3 kinase pathway, EGFR/ERBB2 and cyclin/CDK complexes).

Pail and colleagues (abstr. 7505) found similar rates of “actionable” driver mutations using multiplex and next generation testing in 52 squamous cell lung carcinomas. They were able to detect “drugable” driver mutations in 63% tumors (*FGFR1* amplification 25%, PTEN mutation 17%, PTEN loss 11%, *PIK3CA* mutation 8% and *KRAS* mutation 2%).