1232PD: Lung cancer harboring Her2 mutation: epidemiological characteristics and therapeutic perspectives *Julien Mazieres*

1233PD: Efficacy and patient (pt)-reported outcomes (PROs) with selumetinib (AZD6244, ARRY-142866; SEL) + docetaxel (DOC) in KRAS-mutant advanced non-small cell lung cancer (NSCLC): a randomized, phase II trial *Pasi Janne*

1191PD: Clinical activity of crizotinib in patients with advanced nonsmall cell lung cancer (NSCLC) harboring ROS1 gene rearrangement *Sai-Hong Ou*

Discussant: Rafael Rosell



Disclosure slide

• The discussant has no conflicts of interest to declare.



Mutation spectrum in Adenocarcinoma

BRAF mutation NRAS mutation HER2 mutation RET translocation OTHER KRAS mutation EGFR mutation ALK translocation PIK3CA mutation CTNNB1 mutation ROS1 translocation

ROS1	Crizotinib
HER2	PF299804
	Afatinib (BIBW2992)
MEK	MEK162
	GDC-0973
	GSK1120212
	MSC1936369B
<mark>PI3K</mark> / MTOR	GDC-0980
	BEZ235
	SAR245409

Mutations in TP53 and STK11/LKB1 are common occurrences, not included in pie chart due to high overlap with other mutations Heist & Engelman. Cancer Cell 2012





Imielinski et al. Cell 2012

Overall survival in patients with advanced stage (IIIB/IV) disease



Arcila et al. CCR 2012





83% with 12 bp insertion duplicating amino acids YVMA at codon 775 6% frequency of EGFR/KRAS/ALK-negative

More frequent in never-smokers with moderately or poorly differentiated adenocarcinoma

VIENNA 2012

Arcila et al. CCR 2012 www.esmo2012.org 1232PD: Lung cancer harboring Her2 mutation: epidemiological characteristics and therapeutic perspectives *Julien Mazieres*



Clinical and biological characteristics of HER mutated patients, n=46.

	No	value
Age at diagnosis, years	46	
Mean		61
SD		12.99
Median		60
	No	%
Gender	46	
Women	30	65.21
men	16	0.35
	10	0.00
Tobacco	46	
never	24	52.2
former	8	17.4
current	11	23.9
unknown	3	65
	Ŭ	0.0
Tumor stage	46	
l anner enge	11	23.9
i.	1	2.17
III	11	23.9
IV	23	50
unknown	0	0
	Ū	0
Metastasis sites for stage IV	23	
lung	6	26.1
brain	3	13
bone	2	87
Multiples organs	10	43.5
Other or unknown	10	40.0 Q 7
	۷ ک	0.7



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Stage I, II, III vs. IV



Overall median survival for stage IV vs. early stage: 22.9 months vs. 68.2 months

DCR of 96% for trastuzumab-based therapies (n = 15), 100 % for afatinib (n = 4) but no response to lapatinib (n = 2) and to masatinib (n = 1).



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42 yrs female with HER2 mutation treated with trastuzumab and docetaxel after failure of two conventional chemotherapy regimens

02/11/2012





02/08/2012





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Phase II, double-blind, randomized, placebo-controlled, multi-center trial; NCT00890825



- Docetaxel was administered every 21 days; selumetinib/placebo administered daily
- Following completion of patient enrollment, the primary endpoint was changed from PFS to OS, without changing the sample size[‡]
 - OS analysis was planned for after approximately 58 events; HR 0.57, 80% power assuming a 1-sided 10% significance level



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Baseline patient characteristics

Selumetinib + docetaxel	Placebo + docetaxel
n=44	n=43
21 (47.7) / 23 (52.3)	20 (46.5) / 23 (53.5)
59.5 (26–79)	59 (37–76)
39 (88.6)	38 (88.4)
5 (11.4)	5 (11.6)
5 (11.4) / 39 (88.6)	1 (2.3) / 42 (97.7)
21 (47.7) / 23 (52.3)	21 (48.8) / 22 (51.2)
36 (81.8)	33 (82.5)
3 (6.8)	6 (14.0)
2 (4.5)	1 (2.3)
2 (4.5)	0 (0.0)
1 (2.3)	3 (7.0)
	Selumetinib + docetaxel n=44 21 (47.7) / 23 (52.3) 59.5 (26-79) 39 (88.6) 5 (11.4) 5 (11.4) / 39 (88.6) 21 (47.7) / 23 (52.3) 36 (81.8) 3 (6.8) 2 (4.5) 2 (4.5) 1 (2.3)



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Patient-reported outcomes

- There was a numerical improvement in the change from baseline in symptom burden with selumetinib+docetaxel compared with placebo+docetaxel, throughout the assessment period
- In a post-hoc analysis:
 - The proportion of patients with a clinically meaningful improvement in LCS score was greater for selumetinib+docetaxel than placebo+docetaxel (44% vs 24%; odds ratio 2.50; 80% Cl 1.34, 4.77; 1-sided p=0.029)
 - The time to deterioration of LCS score was also in favour of selumetinib+docetaxel (HR 0.33; 80% CI 0.22, 0.49; 1-sided p=0.0002)



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Murine co-clinical trial





Loss of SOCS3 activates JAK2 pathway

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15

Days

1191PD: Clinical activity of crizotinib in patients with advanced nonsmall cell lung cancer (NSCLC) harboring ROS1 gene rearrangement *Sai-Hong Ou*



Phase 1 Study of Crizotinib (PROFILE 1001) ROS1-Positive NSCLC Expansion Cohort

 Patients with ROS1-positive NSCLC enrolled into a ROS1 expansion cohort of a Phase 1, single-arm, dose-escalation study (NCT00585195)

ROS1-rearangement confirmed using a break-apart FISH assay

- Patients received oral crizotinib 250 mg BID
- 23 patients enrolled and treated as of August 20, 2012:
 - 16 patients on-treatment at cut-off
 - Median age 47 years (range 31–72)
 - 78% of patients were never-smokers
 - All patients had adenocarcinoma histology
 - None of 18 tested cases were positive for *ALK*-rearrangement.
- Most AEs were of grade 1 severity
 - The most common AE was visual impairment (91%), a common crizotinib side effect with little impact on patients' quality of life

Summary of Tumor Responses in Evaluable Patients with Advanced ROS1+ NSCLC*



*Response-evaluable population excluding patients with early death/indeterminate response (n=19). [†]Tumor ROS1 FISH-positive, but negative for ROS1 fusion gene expression. [‡]Crizotinib held for >6 wks prior to first scans which showed PD. +, Treatment ongoing. For ongoing patients, duration of response/SD is the time from first documentation of tumor response/first dose to last available on treatment scan. For discontinued patients, duration is to the time of PD or death. Duration is in wks. Data in the database as of August 20, 2012. *Ou et al*



Baseline

After 4 weeks of crizotinib



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A novel fusion KDELR2-ROS1 has recently been described. (Govindan et al. Cell 2012)





HCC78 cells and samples positive for SLC34A2-ROS1 fusion express equivalent levels of the long and short transcripts. Samples positive for the CD74-ROS1 fusion express only the short transcript. The SDC4-ROS1 fusion express a predominant long from and a minor short form.



Davies et al. CCR 2012 www.esmo2012.org



Acquaviva et al. Biochimica et Biophysica Acta, 2009

- CD74-ROS, like FIG-ROS, is a potent oncoprotein transforming fibroblast cells through activation of the canonical signaling pathways SHP-2, STAT-3, and MAPK.
- The SLC34A2-ROS fusion kinase is unable to activate these pathways and incapable of transformation. (Jun et al. Cancer Res 2012)

also

- HCC78 cells are less sensitive to ROS1 inhibition than SDC4-ROS1 expressing Ba/F3 cells. (Davies et al. CCR 2012)
- ROS1 gene fusions in NSCLC cases with SCC (Davies et al. CCR 2012)



- Druggable driver mutations include the frequent KRAS mutations and the uncommon HER2 mutations and ROS1 fusion kinases
- HER2 exon 20 insertions in 6% of EGFR/ALK/KRAS-negative tumors – more frequently in never-smokers. Benefit from treatment with HER2 inhibitors (afatinib, trastuzumab).
- KRAS mutations ⇒ benefit from second-line selumetinib/docetaxel
- Co-clinical selumetinib trial in mice and preclinical studies indicate that TP53/LKB1 mutations hamper selumetinib effect.
- BIM mRNA expression could be a predictive marker of the effect of MEK inhibitors.
- ADAM17 is commonly overexpressed in NSCLC, and several components of the NOTCH pathway are activated (NOTCH3, HES1). (GSIs elevate BIM expression in the H460 cell line. GSItreated, KRAS-driven NSCLC downregulates ERK and cause tumor arrest.) KRAS tumors could be rescued with selumetinib plus an Akt inhibitor when EPHA3 is low.



- ROS gene rearrangements occur in 1-2% of NSCLCs, defining a new genetic subtype of NSCLC (*Rikova et al. Cell 2007; Li et al. PLoS ONE 2011; Bergethon...Ou et al. JCO 2012; Takeuchi et al. Nat Med 2012; Davies et al. CCR 2012; Rimkunas et al. CCR 2012*).
- Estimated number of new cases per year worldwide: 12-27000.
- ROS fusion-positive patients tend to be younger, never-smokers, with adenocarcinoma (SCC cases have also been described), presenting with stage IV disease.
- ROS fusion partners include, among others, SLC342, CD74-ROS and SDC4-ROS1. The relevance of the splicing forms needs to be clarified.
- Prospective studies should include the type of ROS fusion partner to further understand the clinical activity of the clinically available ALK/MET inhibitor crizotinib.

