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Letter from Prof Rolf Stahel

Dear Colleagues

It is my pleasure to present this ETOP slide set which has been designed to highlight and summarise key findings in thoracic cancers from the major congresses in 2014. This slide set specifically focuses on the European Society for Medical Oncology Congress and is available in 3 languages – English, Italian and Japanese.

The area of clinical research in oncology is a challenging and ever changing environment. Within this environment we all value access to scientific data and research which helps to educate and inspire further advancements in our roles as scientists, clinicians and educators. I hope you find this review of the latest developments in thoracic cancers of benefit to you in your practice. If you would like to share your thoughts with us we would welcome your comments. Please send any correspondence to etop@etop.eu-org.

I would like to thank our ETOP members Drs Solange Peters and Martin Reck for their roles as Editors – for prioritising abstracts and reviewing slide content – also Dr Serena Ricciardi for overseeing translation to Italian. The slide set you see before you would not be possible without their commitment and hard work.

And finally, we are also very grateful to Lilly Oncology for their financial, administerial and logistical support in the realisation of this complex yet rewarding activity.

Yours sincerely,
Rolf Stahel
President, ETOP Foundation Council

ETOP Medical Oncology Slide Deck Editors 2014

Focus: Stage III & IV NSCLC & related biomarker data

Dr Solange Peters

Multidisciplinary Oncology Center, Lausanne Cancer Center, Lausanne, Switzerland

Focus: Stage I & II NSCLC/other malignancies & related biomarker data

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Contents

- Biomarkers
- Early stage and locally advanced NSCLC – Stages I, II and III
- Advanced NSCLC – Not radically treatable stage III and stage IV
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  - Later lines
- Other malignancies
  - SCLC and mesothelioma
  - Rare tumours

Biomarkers

167O: Prognostic and predictive biomarkers for ACT (adjuvant chemotherapy) in resected non-small cell lung cancer (R-NSCLC): LACE-Bio – Seymour LK et al

- **Study objective**
  - To identify predictive and prognostic biomarkers of overall survival for adjuvant chemotherapy in resected NSCLC
- **Study design**
  - Data from LACE-Bio (which is based on the LACE meta-analysis project), a fully annotated database and tissue bank (comprising ~1500 samples) from 4 randomised trials, was used to compare adjuvant chemotherapy with non-treated control
  - Immunohistochemical (including hematoxylin and eosin [H/E], histochemical) biomarkers of prognostic/predictive significance from one trial were cross-validated in the three other trials
    - A pooled analysis combining all 4 trials was performed when only a trend for such effects was observed
- **Key results**
  - While a number of biomarkers were identified in single studies that could have predictive or prognostic value, cross-validation with the other studies did not confirm the utility of the majority of markers (see table on next slide)

LACE, Lung Adjuvant Cisplatin Evaluation

Seymour et al. Ann Oncol 2014; 25 (suppl 4): abstr 167O

167O: Prognostic and predictive biomarkers for ACT (adjuvant chemotherapy) in resected non-small cell lung cancer (R-NSCLC): LACE-Bio – Seymour LK et al

- **Key results (cont.)**

Marker	Trial 1st tested in	Predictive?	Prognostic?	Validated?
ERCC1	IALT	Yes	Yes	No
Lymphocyte infiltrate	IALT	No	Yes	Prognostic (OS & DFS)
Mucin	CALGB	No	Yes	No
β-tubulin	JBR10	Trend	Yes	Prognostic (OS & DFS)
P27	IALT	Yes	No	No
FASL	IALT	Trend	No	Predictive (OS)
FAS/FASL	IALT	Yes	Yes	No
BAX	IALT	Trend	No	No
Cyclin E/P16*	IALT, JBR10	No	No	No
P53*	IALT, JBR10, CALGB	Yes**	Yes**	No

- **Conclusion**
  - Immunohistochemical assays from single trials may be misleading and should be validated before being implemented

*Exploratory pooled analyses; **in at least one trial
CALGB, Cancer and Leukemia Group B;
IALT, International Adjuvant Lung Trial

Seymour et al. Ann Oncol 2014; 25 (suppl 4): abstr 167O

1174O: Prognostic and predictive roles of EGFR copy number and KRAS mutation status from the RADIANT trial of adjuvant erlotinib (E) versus placebo (P) – Shepherd FA et al

- **Study objective**
  - To determine if KRAS mutation status or EGFR copy number are prognostic and predictive of response to erlotinib in patients with completely resected stage IB–IIIA NSCLC
- **Study design**
  - Tissue samples from the randomised RADIANT study were analysed
  - Association of KRAS M+ status (n=828) or EGFR copy number (n=921) and baseline characteristics were evaluated with Cox models to determine prognostic role of EGFR count in EGFR WT, plus KRAS M+ in the full analysis set and KRAS in adenocarcinoma EGFR WT, as well as their predictive roles in DFS and OS
- **Key results**
  - Only EGFR M+ was associated with high baseline EGFR copy number
- **Conclusion**
  - Neither KRAS status or EGFR copy number were prognostic or predictive of response to adjuvant erlotinib

Shepherd et al. Ann Oncol 2014; 25 (suppl 4): abstr 1174O

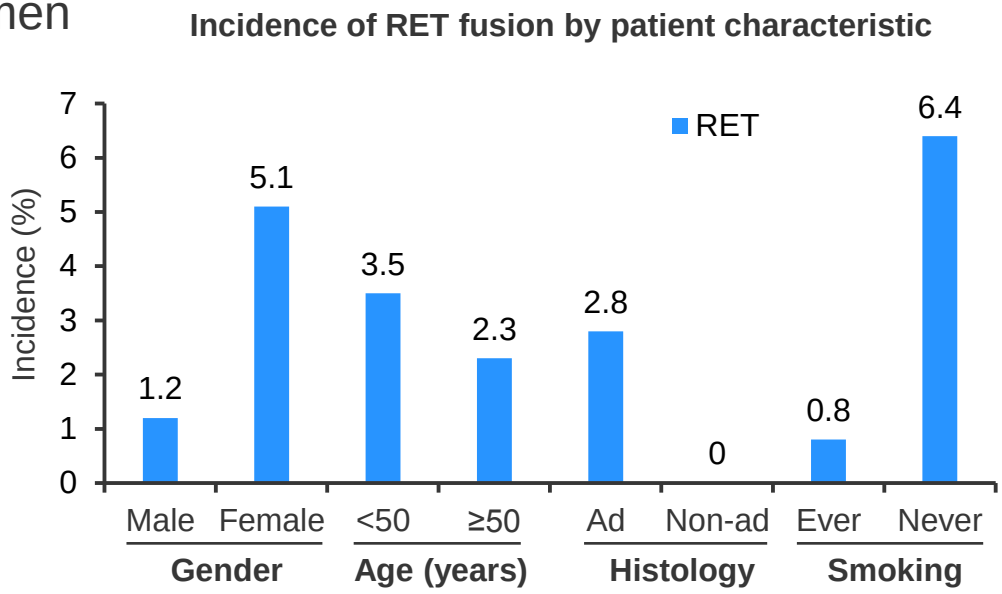
1227PD: Nationwide genomic screening for RET fusion in advanced EGFR mutation-negative non-squamous lung cancer and development of molecular targeted therapy in Japan: LC-SCRUM-Japan – Yoh K et al

- **Study objective**
  - To screen for rare driver mutations in NSCLC and develop individualised targeted therapies for these patients
- **Study design**
  - Prospective observational study in patients with advanced or recurrent EGFR mutation negative non-squamous NSCLC
  - Tumour samples screened with RT-PCR; primarily for RET, ROS1 and ALK
    - Positive results validated with break-apart FISH
- **Key results**
  - As of July 2014, a total of 940 patients were enrolled (608 male, median age 64 years and 93% had adenocarcinoma)
  - Of these 842 (90%) tumour samples had been screened
  - RET-fusion positive NSCLC was detected in 24 patients, ROS1 in 36 patients and ALK in 16 patients

Yoh et al. Ann Oncol 2014; 25 (suppl 4): abstr 1227PD

1227PD: Nationwide genomic screening for RET fusion in advanced EGFR mutation-negative non-squamous lung cancer and development of molecular targeted therapy in Japan: LC-SCRUM-Japan – Yoh K et al

- **Key results (cont.)**
  - Of those RET-fusion positive
    - Most (n=17, 71%) were women
    - All had adenocarcinoma
    - Median age was 62 years (range 41–79)
    - The majority (79%) had never smoked



- **Conclusions**
  - RET fusion was present in 2.8% of patients with advanced EGFR mutation-negative non-squamous NSCLC
  - A phase II trial, the LURET study, is underway in Japan to examine vandetanib in patients with advanced RET fusion-positive NSCLC

Yoh et al. Ann Oncol 2014; 25 (suppl 4): abstr 1227PD

Early and locally advanced NSCLC
Stages I, II and III

1177PD: EGFR del19/L858R activating mutation (M+) subgroup in RADIANT: Baseline characteristics, prognostic role, and disease-free survival (DFS) by stage – Altorki NK et al

- **Study objective**
  - To examine the prognostic role of EGFR mutation (M+) in NSCLC
- **Study design**
  - Exploratory analyses were performed on data from the RADIANT study to compare EGFR WT and M+ patients with respect to baseline characteristics and DFS
- **Key results**
  - Of 973 randomised patients, 161 were EGFR M+ and 703 were WT
    - The EGFR M+ group had significantly more smaller tumours (<40 mm, 70% vs. 49%) and adenocarcinoma (91% vs. 52%), but higher stage (IB 47% vs. 52%; II: 29% vs. 34%; IIIA: 22% vs. 14%) than the WT group
  - Among placebo recipients, DFS was worse for EGFR M+ compared with WT (median 28.5 vs. 55.1 months; p=0.23)
  - A non-significant effect was observed with regards to erlotinib treatment and DFS across disease stages IB (n=75; HR 0.52; p=0.14) and II (n=47; HR 0.51; p=0.09), but not IIIA (n=36; HR 1.12; p=0.78)
- **Conclusions**
  - No significant prognostic effect with EGFR M+ status was observed, but conclusions are limited because of the small sample size
  - EGFR M+ status may be associated with higher disease stage and other variables

Altorki et al. Ann Oncol 2014; 25 (suppl 4): abstr 1177PD

1179PD: Prognostic impact of immune microenvironment markers in tumor and stroma in resectable NSCLC – Usó M et al

- **Study objective**
  - To examine the prognostic role of immune-related gene expression in resectable NSCLC
- **Study design**
  - Retrospective analyses were performed on primary tumour tissue samples from 117 patients with early stage NSCLC
  - RT-PCR was used to determine expression of Treg markers including CD127, CD25, FOXP3, CTLA-4, IL-10, TGFβ-1, LAG-3, GITR, TNFα, CD4 and CD8
- **Key results**
  - CD25, FOXP3, CTLA-4 and TGFβ-1 were over-expressed in both tumour and stroma; TNFα expression was low
  - OS and PFS were significantly worse among patients with lower CD8 expression in the tumour (37.2 vs. 81.2 months; $p<0.001$ and 19.4 vs. 81.2 months; $p=0.001$, respectively). Similarly, OS was significantly worse for low CD4 (49.2 vs. 81.2 months; $p=0.018$) and LAG-3 (36.2 vs. 69.0; $p=0.024$) expression

Usó et al. Ann Oncol 2014; 25 (suppl 4): abstr 1179PD

1179PD: Prognostic impact of immune microenvironment markers in tumor and stroma in resectable NSCLC – Usó M et al

- **Key results (cont.)**
  - Patients with high CD25 and low CD127 (‘Treg’ profile) in stroma had worse PFS (median 12.7 vs. 35.4 months, p=0.004)
  - Those patients with higher levels of the ratio FOXP3 stroma/FOXP3 tumour, FOXP3 stroma/CD4 tumour and FOXP3 stroma/ CD8 tumour had significantly worse OS and PFS (table)

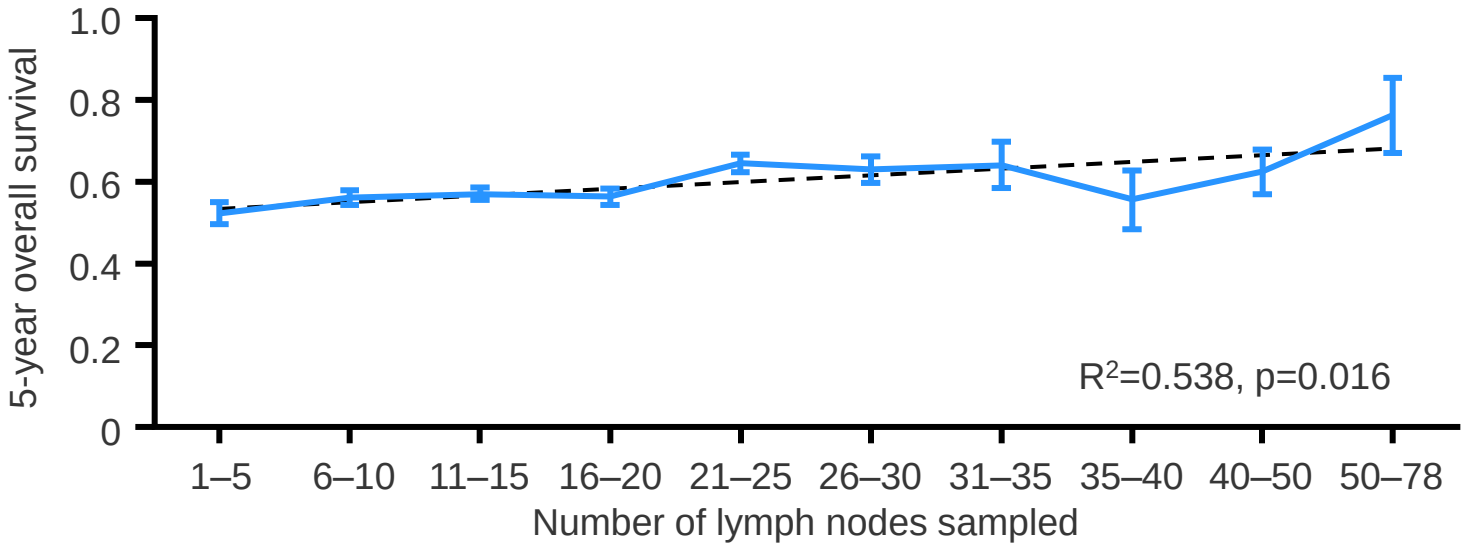
Ratio	mOS (months)	p value	mPFS (months)	p value
FOXP3 stroma/FOXP3 tumour	NR vs. 42.9	0.002	NR vs. 19.4	0.001
FOXP3 stroma/CD4 tumour	81.2 vs. 46.6	0.012	37.8 vs. 19.4	0.013
FOXP3 stroma/CD8 tumour	74.3 vs. 46.4	0.025	37.8 vs. 23.0	0.042

- **Conclusions**
  - Within the tumour microenvironment there are immune biomarkers that may play an important prognostic role in patients with early NSCLC

Usó et al. Ann Oncol 2014; 25 (suppl 4): abstr 1179PD

1176O: Impact of harvested lymph nodes count on staging and survival at radical resection for non-small cell lung cancer: A minimum of 14 lymph nodes should be sampled – Liang W et al

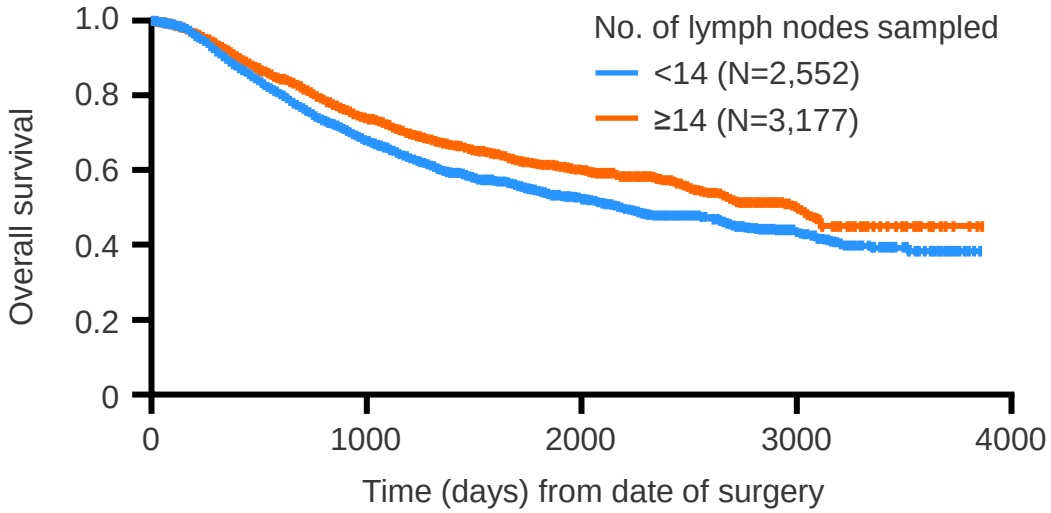
- **Study objective**
  - To examine the relationship between harvested lymph node count and OS or staging in patients with resectable NSCLC
- **Study design**
  - Tissue samples from a cohort of 5,729 patients in a Chinese register (2001–2008) were assessed; a second cohort of 546 patients were used to validate the results
- **Key results**
  - There was a positive correlation between the number of lymph nodes examined and 5-year OS (R^2=0.538, p=0.016)



Liang et al. Ann Oncol 2014; 25 (suppl 4): abstr 1176O

1176O: Impact of harvested lymph nodes count on staging and survival at radical resection for non-small cell lung cancer: A minimum of 14 lymph nodes should be sampled – Liang W et al

- **Key results (cont.)**
  - Greatest survival difference was identified at 14 lymph nodes examined (χ^2=27.2)
  - The median OS was significantly longer in patients who had ≥14 nodes harvested
  - Multivariate analysis confirmed the survival benefit when ≥14 nodes were harvested



Median OS: ≥14 LNs 100 months vs. <14 LNs 73 months (p<0.001)

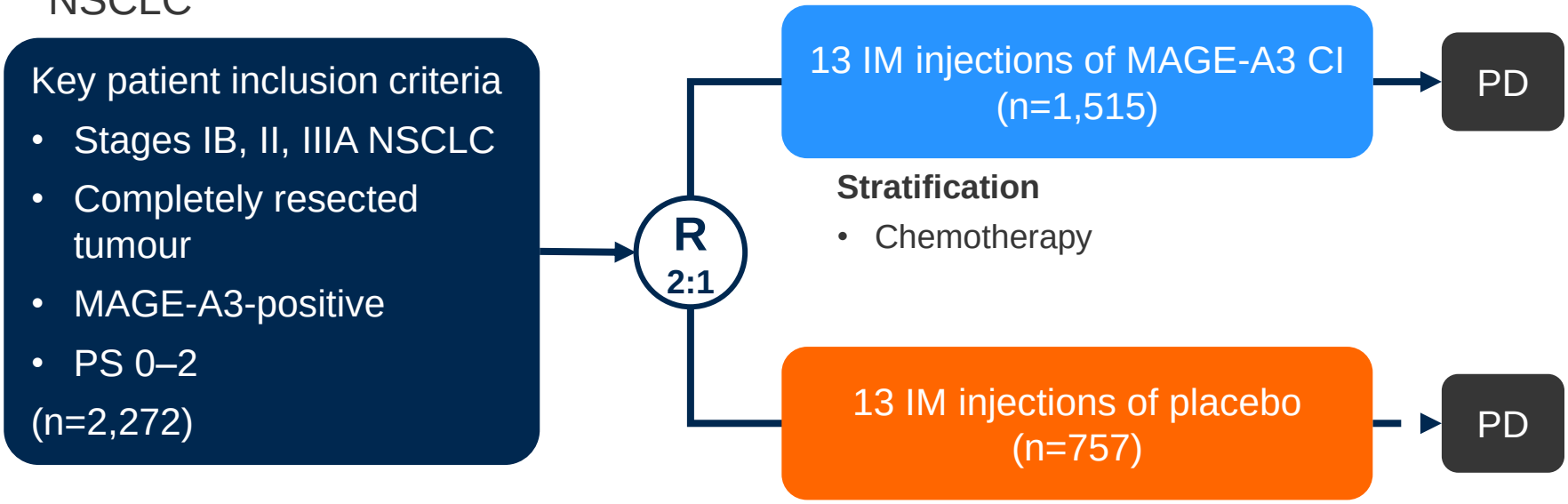
HR 0.73, 95% CI 0.66, 0.81; p<0.001

- **Conclusion**
  - The more lymph nodes harvested the greater the improvement in OS in patients who underwent radical resection for NSCLC; a minimum of 14 nodes should be harvested to accurately stage disease and improve patient survival

Liang et al. Ann Oncol 2014; 25 (suppl 4): abstr 1176O

1173O: MAGRIT, a double-blind, randomized, placebo-controlled phase III study to assess the efficacy of the recMAGE-A3 + AS15 cancer immunotherapeutic as adjuvant therapy in patients with resected MAGE-A3-positive non-small cell lung cancer (NSCLC) – Vansteenkiste JF et al

- **Study objective**
  - To determine if recMAGE-A3 + AS15 cancer immunotherapeutic (MAGE-A3 CI) as adjuvant therapy over 27 months improves DFS in patients with resected NSCLC



Primary endpoint

- DFS

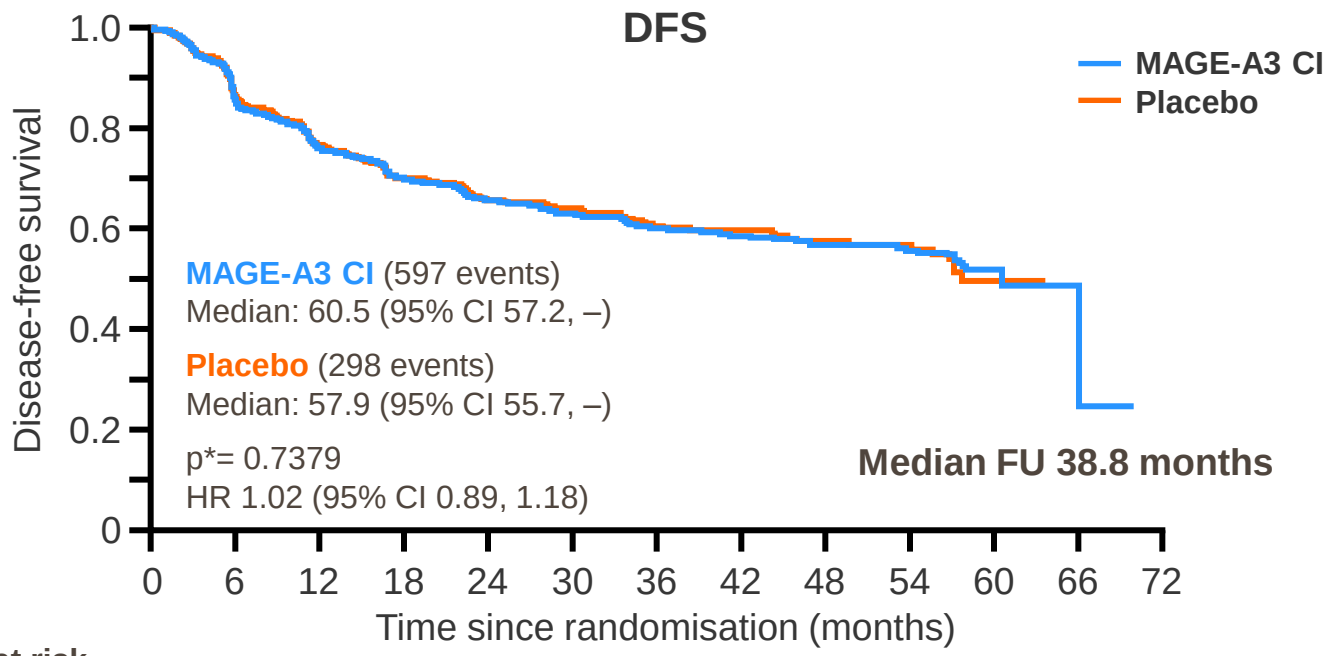
Secondary endpoints

- OS, lung cancer specific survival, immunogenicity
- Safety, health-related QoL

Vansteenkiste et al. Ann Oncol 2014; 25 (suppl 4): abstr 1173O

1173O: MAGRIT, a double-blind, randomized, placebo-controlled phase III study to assess the efficacy of the recMAGE-A3 + AS15 cancer immunotherapeutic as adjuvant therapy in patients with resected MAGE-A3-positive non-small cell lung cancer (NSCLC) – Vansteenkiste JF et al

- **Key results**
  - Median DFS was not significantly different between MAGE-A3 CI and placebo (60.5 vs. 57.9 months; HR 1.024, 95% CI 0.89, 1.18; p=0.7379)



Number at risk												
MAGE-A3 CI	1,515	1,257	1,115	1,013	887	656	476	339	220	127	19	2
Placebo	757	639	562	514	448	328	253	180	114	62	6	0

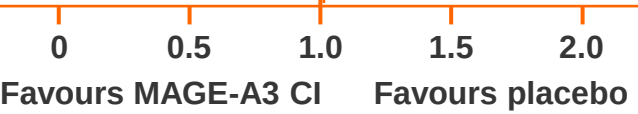
*Likelihood ratio test from Cox regression model stratified by chemotherapy and adjusted for baseline variables used as minimisation factors

Vansteenkiste et al. Ann Oncol 2014; 25 (suppl 4): abstr 1173O

1173O: MAGRIT, a double-blind, randomized, placebo-controlled phase III study to assess the efficacy of the recMAGE-A3 + AS15 cancer immunotherapeutic as adjuvant therapy in patients with resected MAGE-A3-positive non-small cell lung cancer (NSCLC) – Vansteenkiste JF et al

- **Key results (cont.)**
  - No difference in DFS was noted by according to any key covariate

Subgroup	Events/patients		HR (95% CI)	p value
	MAGE-A3 CI	Placebo		
Gender				0.1484
Female	154/370	67/178	1.226 (0.913, 1.646)	
Male	442/1141	235/577	0.954 (0.815, 1.118)	
Stage (TNM 6)				0.2123
IB or less	229/710	124/345	0.887 (0.713, 1.104)	
II	223/545	105/275	1.081 (0.857, 1.363)	
IIIa or more	144/256	68/135	1.191 (0.893, 1.590)	
Type of lymph node procedure				0.4742
Limited/minimal	326/802	155/400	1.061 (0.876, 1.284)	
Systematic	270/709	142/355	0.960 (0.783, 1.176)	
Histopathology				0.7507
Non-squamous cell carcinoma	345/735	166/355	1.027 (0.853, 1.236)	
Squamous cell carcinoma	251/776	131/400	0.980 (0.793, 1.211)	
Chemotherapy				0.4365
No-CT	289/727	153/363	0.955 (0.785, 1.162)	
CT	307/784	144/392	1.067 (0.876, 1.301)	
Overall	**596/1511**	**297/755**	**1.011 (0.880, 1.163)**	

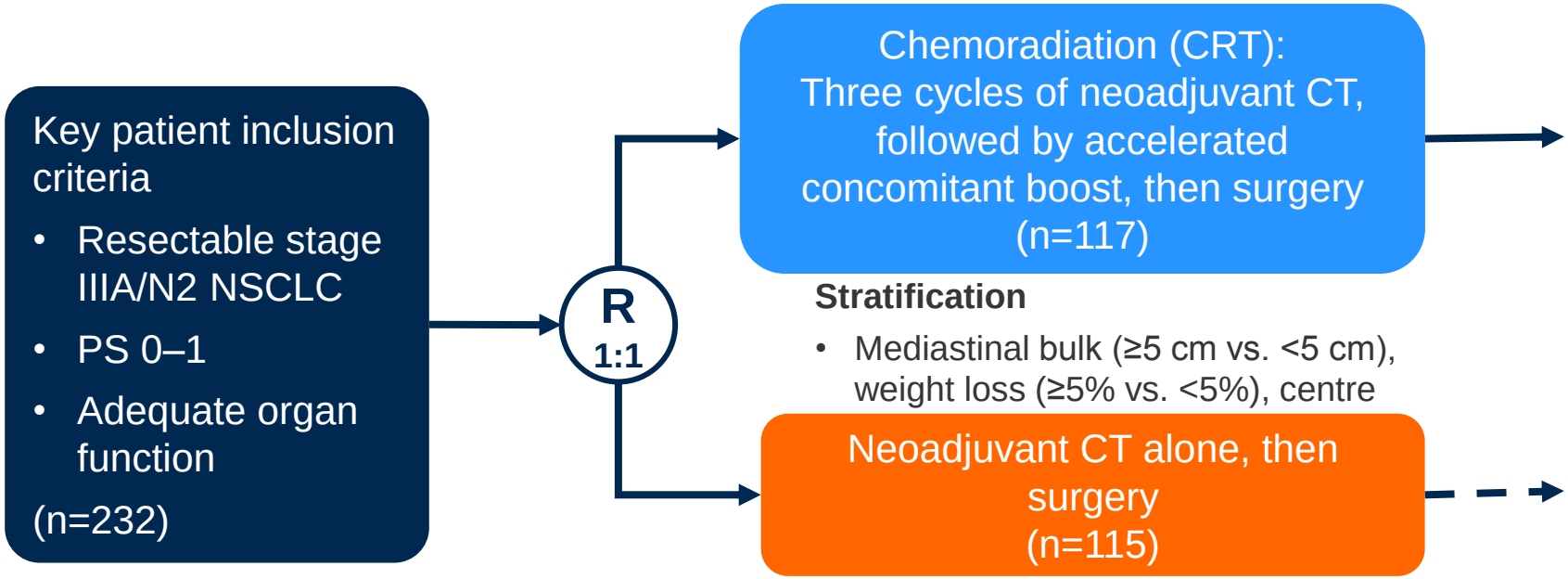


- **Conclusion**
  - MAGE-A3 CI did not increase DFS in patients with NSCLC, irrespective of prior adjuvant chemotherapy

Vansteenkiste et al. Ann Oncol 2014; 25 (suppl 4): abstr 1173O

1195O: Final results of the SAKK 16/00 trial: A randomized phase III trial comparing neoadjuvant chemoradiation to chemotherapy alone in stage IIIA/N2 non-small cell lung cancer (NSCLC) – Pless M et al

- **Study objective**
  - To determine if the addition of neoadjuvant radiotherapy (RT) improves outcomes in patients with stage IIIA/N2 NSCLC receiving neoadjuvant chemotherapy (CT) + surgery



Primary endpoint

- Event-free survival (EFS)

Secondary endpoints

- OS, post-operative 30-day mortality, ORR, failure pattern, rate of complete resection, operability

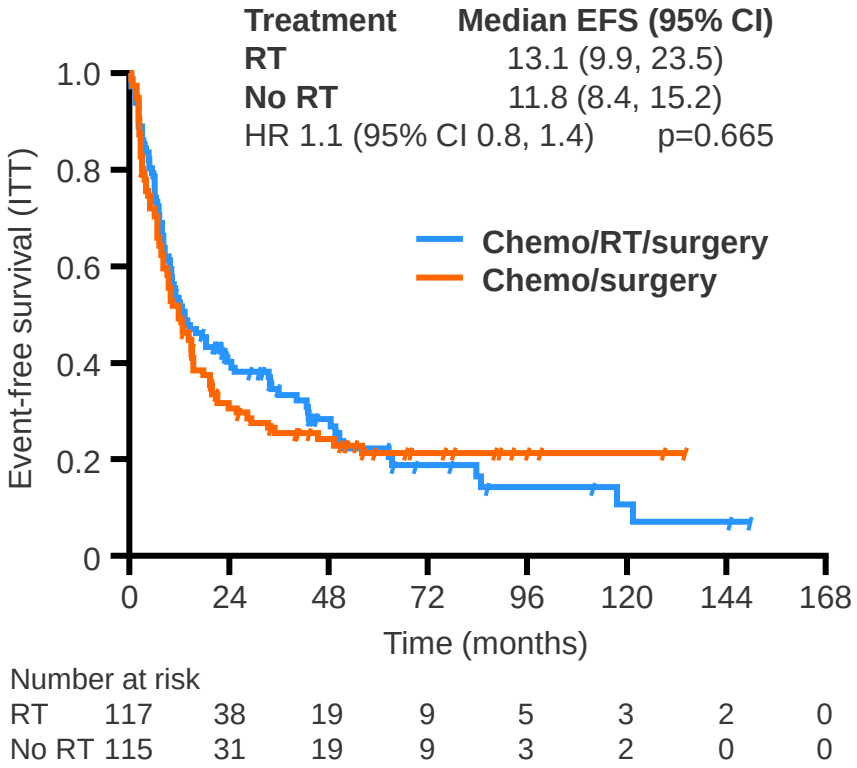
CT, cisplatin 100 mg/m^2 and docetaxel 85 mg/m^2 D1, q3w
RT, with 44 Gy in 22 fractions in 3 weeks

Pless et al. Ann Oncol 2014; 25 (suppl 4): abstr 1195O

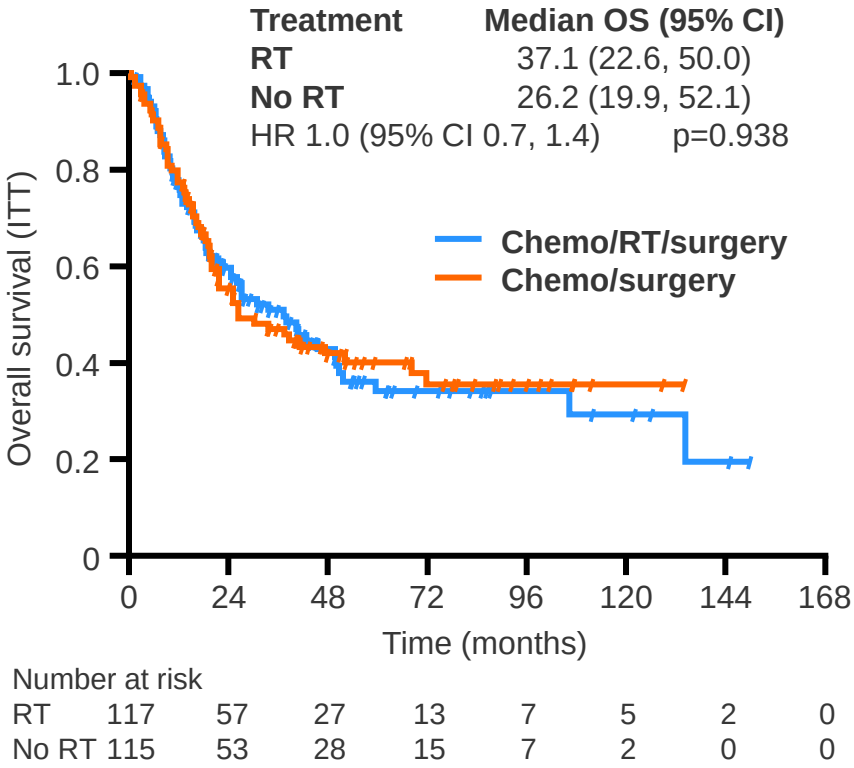
1195O: Final results of the SAKK 16/00 trial: a randomized phase III trial comparing neoadjuvant chemoradiation to chemotherapy alone in stage IIIA/N2 non-small cell lung cancer (NSCLC) – Pless M et al

- **Key results**
  - Neither EFS nor OS were significantly longer with CRT

EFS



OS



Pless et al. Ann Oncol 2014; 25 (suppl 4): abstr 1195O

1195O: Final results of the SAKK 16/00 trial: a randomized phase III trial comparing neoadjuvant chemoradiation to chemotherapy alone in stage IIIA/N2 non-small cell lung cancer (NSCLC) – Pless M et al

- **Key results (cont.)**

	CRT (n=117)	CT (n=115)
Objective response rate, %	61	44
Complete resection,%	91	81
pCR, %	16	12

  - CT was associated with substantial toxicity (febrile neutropenia was especially common), but RT was well tolerated

- **Conclusion**
  - While the addition of RT to CT in patients with stage IIIA/N2 NSCLC improved ORR, complete resection and pCR, these benefits did not translate into improved EFS or OS

pCR, pathological complete remission

Pless et al. Ann Oncol 2014; 25 (suppl 4): abstr 1195O

1196O: Postoperative radiotherapy in resected ypN2 stage III-N2 non-small cell lung cancer: Can modern conformal radiotherapy compensate for the poor outcome? – Billiet C et al

- **Study objective**
  - To determine the effect of modern postoperative radiotherapy (PORT) on OS in patients with persistent N2 NSCLC after induction chemotherapy
- **Study design**
  - From a prospective database, patients with resectable N2 NSCLC who had received induction chemotherapy and surgery were selected
  - Patients (n=103) without progressive disease after chemotherapy underwent resection; 95% of patients were staged with FDG-PET and 85% underwent brain imaging
    - Those with incomplete resection or persistent ypN2 status received 3D-PORT (n=53) to a dose of 50–66 Gy in 2/Gy fractions
    - Patients with a complete resection and with nodal downstaging to ypN0 or ypN1 did not receive PORT

Billiet et al. Ann Oncol 2014; 25 (suppl 4): abstr 1196O

1196O: Postoperative radiotherapy in resected ypN2 stage III-N2 non-small cell lung cancer: Can modern conformal radiotherapy compensate for the poor outcome? – Billiet C et al

- **Key results**
  - The median follow-up was 46.3 months
  - Of those who received resection:
    - The 5-year OS was 31.3%
    - Relapse-free survival was 29.8%
    - Cumulative local recurrence rate was 51.0%
  - Significant co-variables for 5-year OS (by multivariate analysis) were:
    - PORT (relative risk [RR] 0.441; p=0.017)
    - Downstaging after chemotherapy (RR 0.478; p=0.030)
    - Completeness of resection (RR 2.051; p<0.001)
- **Conclusions**
  - Although patients receiving PORT have adverse prognostic factors, PORT improved survival for patients with stage IIIA NSCLC and ypN0/1 or R1/R2
  - In patients with ypN0 and ypN1 there is high rate of local recurrence, which suggests PORT could also have utility in these patients

Billiet et al. Ann Oncol 2014; 25 (suppl 4): abstr 1196O

1198PD: German Clinical Registries: Neoadjuvant chemoradiotherapy in non small cell lung cancer – De Wit M et al

- **Study objective**
  - To examine survival outcomes following neoadjuvant chemoradiotherapy in patients with NSCLC in Germany
- **Study design**
  - Retrospective analysis of ADT and KoQK registries; this analysis focused on neoadjuvant therapy in patients with NSCLC
- **Key results**
  - A total of 129,740 patients with NSCLC were included in the analysis; 52.3% had squamous cell carcinoma, 32.5% adenocarcinoma, 5.2% large cell carcinoma and 10% other NSCLC
  - 15,325 patients (58.6%) had reached stage IIIB, while 10,819 (41.4%) were in stage IIIA
  - Treatment stages and sex showed no significant differences for survival, but patients receiving neoadjuvant treatment were younger (women 60 vs. 66 years, men 62 vs. 67 years)
  - Patients receiving neoadjuvant therapy lived longer than those not receiving neoadjuvant therapy (median 25 vs. 12 months) and also showed better therapeutic response but had more frequent local relapses or metastases
- **Conclusion**
  - Neoadjuvant therapy was associated with longer survival; whether this relates to the younger age and probably better ECOG at diagnosis remains unclear

De Wit et al. Ann Oncol 2014; 25 (suppl 4): abstr 1198PD

Advanced NSCLC

Not radically treatable stage III and stage IV

1st line

1223O: ASPIRATION: first-line erlotinib (E) until and beyond RECIST progression (PD) in Asian patients (pts) with EGFR mutation-positive (mut+) NSCLC – Park K et al

- **Study objective**
  - To examine the efficacy and safety of first-line erlotinib in patients with EGFR mutation (M+) NSCLC in Asia
- **Study design**
  - Phase II, open-label, single arm study involving patients aged ≥18 years with stage IV EGFR M+ NSCLC who received erlotinib 150 mg/day PO
  - Primary endpoint: PFS1 (time to RECIST PD/death)
  - Secondary endpoints: PFS2 (time to off-erlotinib PD if erlotinib was extended beyond RECIST PD), ORR, DCR, best objective response, OS and safety
- **Key results**
  - Of 207 patients, 171 had RECIST PD; 93 continued post-PD erlotinib
  - PFS1 median was 11.0 months (95% CI 9.2, 11.1)
  - PFS2 median was 14.1 months (95% CI 11.5, 14.8)
  - Difference between PFS1 and PFS2 in patients receiving post-PD erlotinib was 3.1months

Park et al. Ann Oncol 2014; 25 (suppl 4): abstr 1223O

1223O: ASPIRATION: first-line erlotinib (E) until and beyond RECIST progression (PD) in Asian patients (pts) with EGFR mutation-positive (mut+) NSCLC – Park K et al

- **Key results (cont.)**

	Post-PD erlotinib (n=93)	No post-PD erlotinib (n=78)	p-value
mPFS1, months (95% CI)	11.0 (9.1, 11.0)	7.4 (5.6, 9.2)	0.0096
Median depth of response, %	-48.7[a]	-42.2[b]	0.0389
Median time from baseline to best overall response, days	56	59	0.8840
Median time from best overall response to PFS1, days	169	113	0.0047
ECOG PS 0/1 at PFS1, %	95.7	78.2	0.0005
Grade ≥3 AEs at PFS1, %	19.4	19.2	0.9837

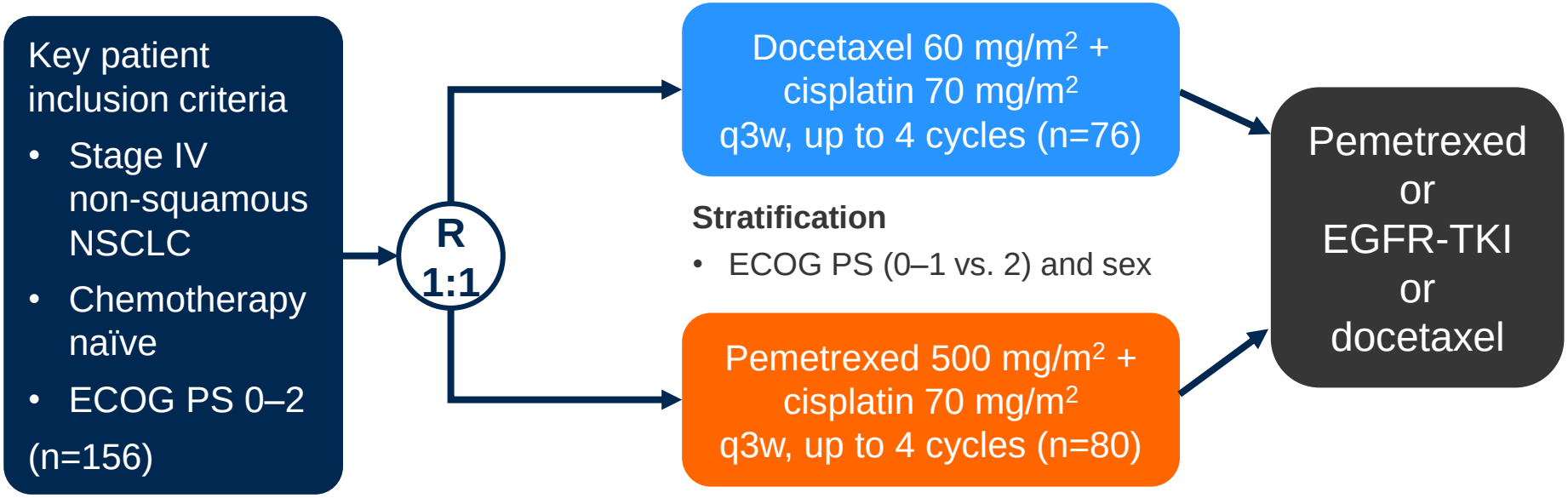
[a]n=90, [b]n=70

- **Conclusions**
  - Continuing erlotinib beyond RECIST PD is feasible in patients with EGFR M+ NSCLC
  - The optimal patient subset that will benefit from post-PD erlotinib remains to be validated

Park et al. Ann Oncol 2014; 25 (suppl 4): abstr 1223O

LBA41_PR: A randomized phase III study of docetaxel plus cisplatin versus pemetrexed plus cisplatin in first line non-squamous non-small cell lung cancer (NSq-NSCLC) – Kim Y et al

- **Study objective**
  - To prove the non-inferiority of docetaxel + cisplatin compared with pemetrexed + cisplatin in patients with non-squamous NSCLC



Primary endpoint

- PFS

Secondary endpoints

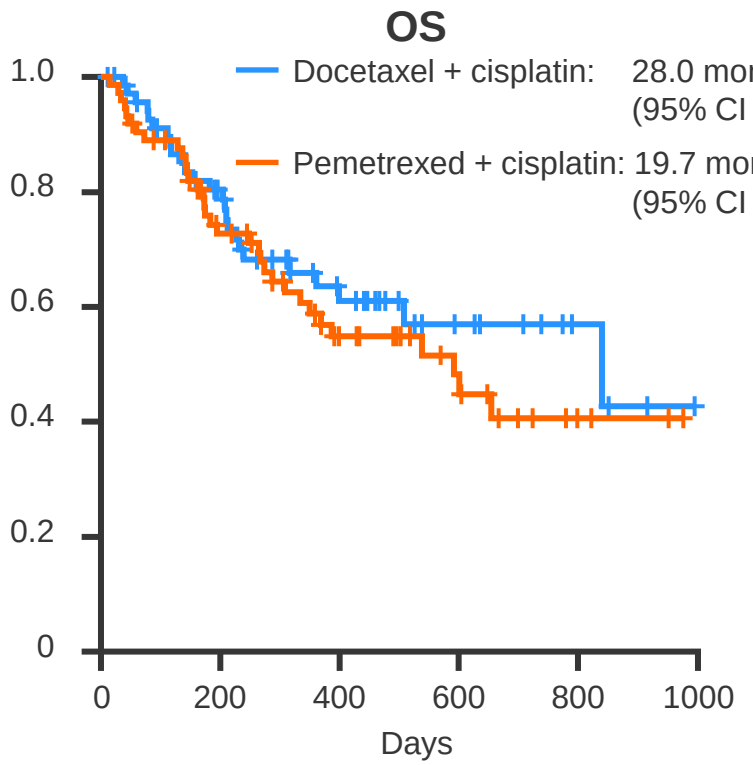
- Response rate, ORR and safety

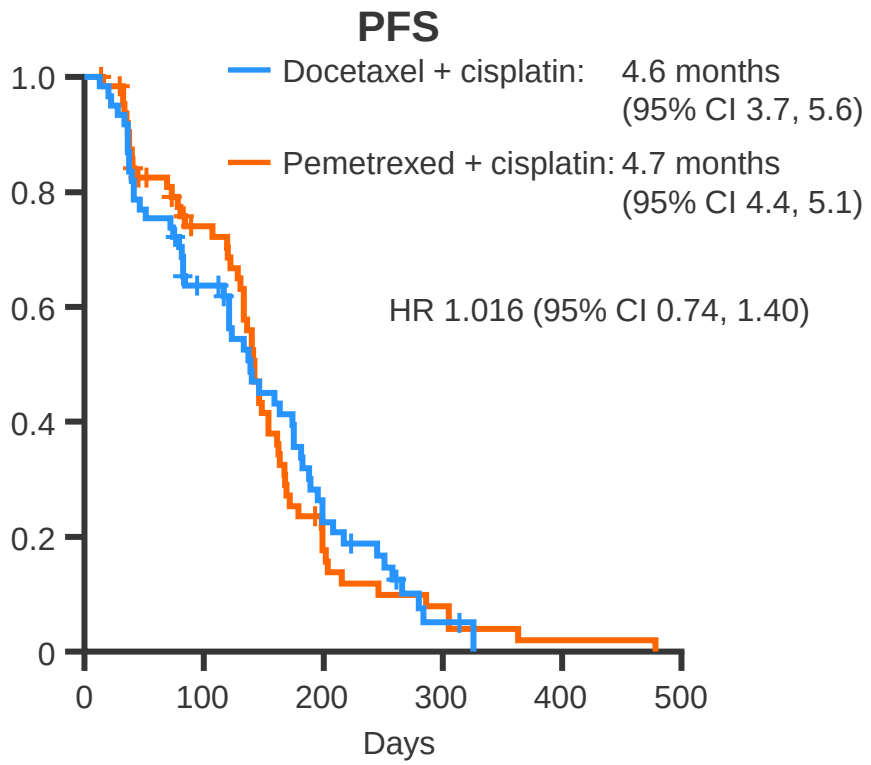
Note: the trial was closed early due to slow accrual and, therefore, the results should be interpreted with caution

Kim et al. Ann Oncol 2014; 25 (suppl 4): abstr LBA41_PR

LBA41_PR: A randomized phase III study of docetaxel plus cisplatin versus pemetrexed plus cisplatin in first line non-squamous non-small cell lung cancer (NSq-NSCLC) – Kim Y et al

- **Key results**
  - OS and PFS were similar between the two groups





  - Partial remission was observed in 33.3% of patients who received docetaxel + cisplatin, compared with 31.2% who received pemetrexed + cisplatin

Kim et al. Ann Oncol 2014; 25 (suppl 4): abstr LBA41_PR

LBA41_PR: A randomized phase III study of docetaxel plus cisplatin versus pemetrexed plus cisplatin in first line non-squamous non-small cell lung cancer (NSq-NSCLC) – Kim Y et al

- **Key results (cont.)**
  - Compared with pemetrexed + cisplatin, significantly higher rates of grade 3/4 neutropenia and febrile neutropenia, as well as a greater number of SAEs were observed with docetaxel + cisplatin

	Docetaxel + cisplatin (n=72)	Pemetrexed + cisplatin (n=77)
Neutropenia grade 3/4	10 (13.9%)**	1 (1.3%)
Febrile neutropenia	8 (11.1%)*	1 (1.3%)
Total number of SAE	42	24
Number of cases with SAE	29 (40.3%)*	17 (22.1%)

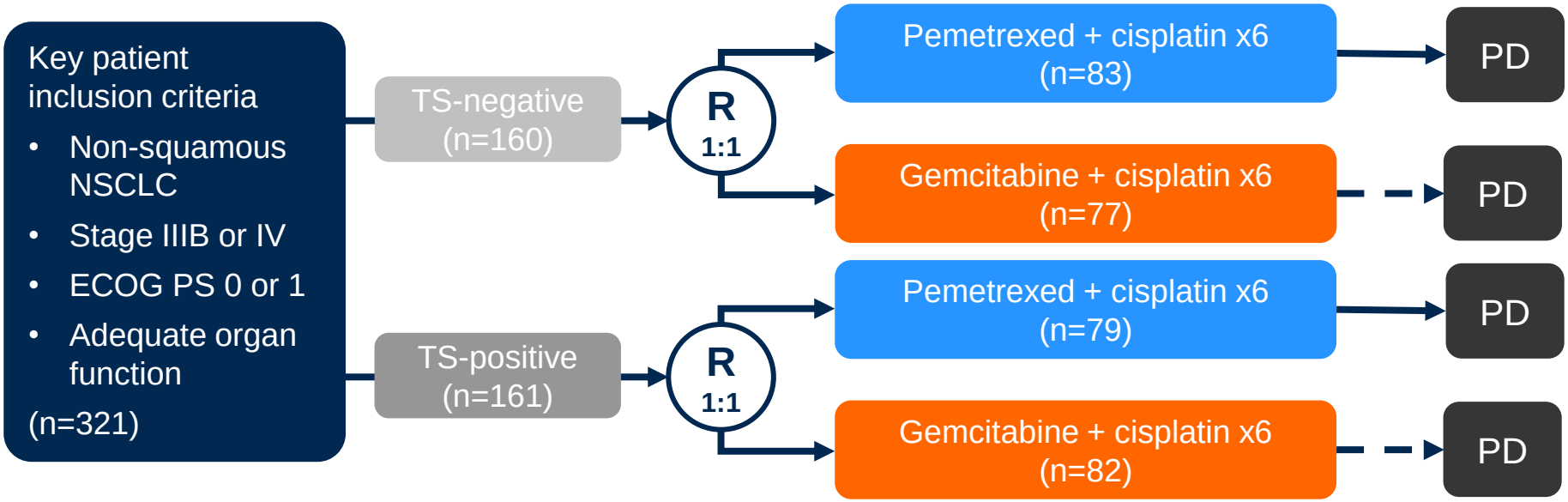
*p<0.05, **p<0.01

- **Conclusion**
  - In patients with non-squamous NSCLC, treatment with docetaxel + cisplatin produced similar PFS and response rate as pemetrexed + cisplatin, but was associated with more SAEs and toxicity

Kim et al. Ann Oncol 2014; 25 (suppl 4): abstr LBA41_PR

LBA42_PR: Cisplatin plus pemetrexed (CP) versus cisplatin plus gemcitabine (CG) according to thymidylate synthase expression in non-squamous NSCLC: A biomarker-stratified randomized phase II trial – Ahn M et al

- **Study objective**
  - To investigate whether thymidylate synthase (TS) expression is a predictive factor for pemetrexed + cisplatin compared with gemcitabine + cisplatin in patients with non-squamous NSCLC



Primary endpoint

- Response rate

Secondary endpoints

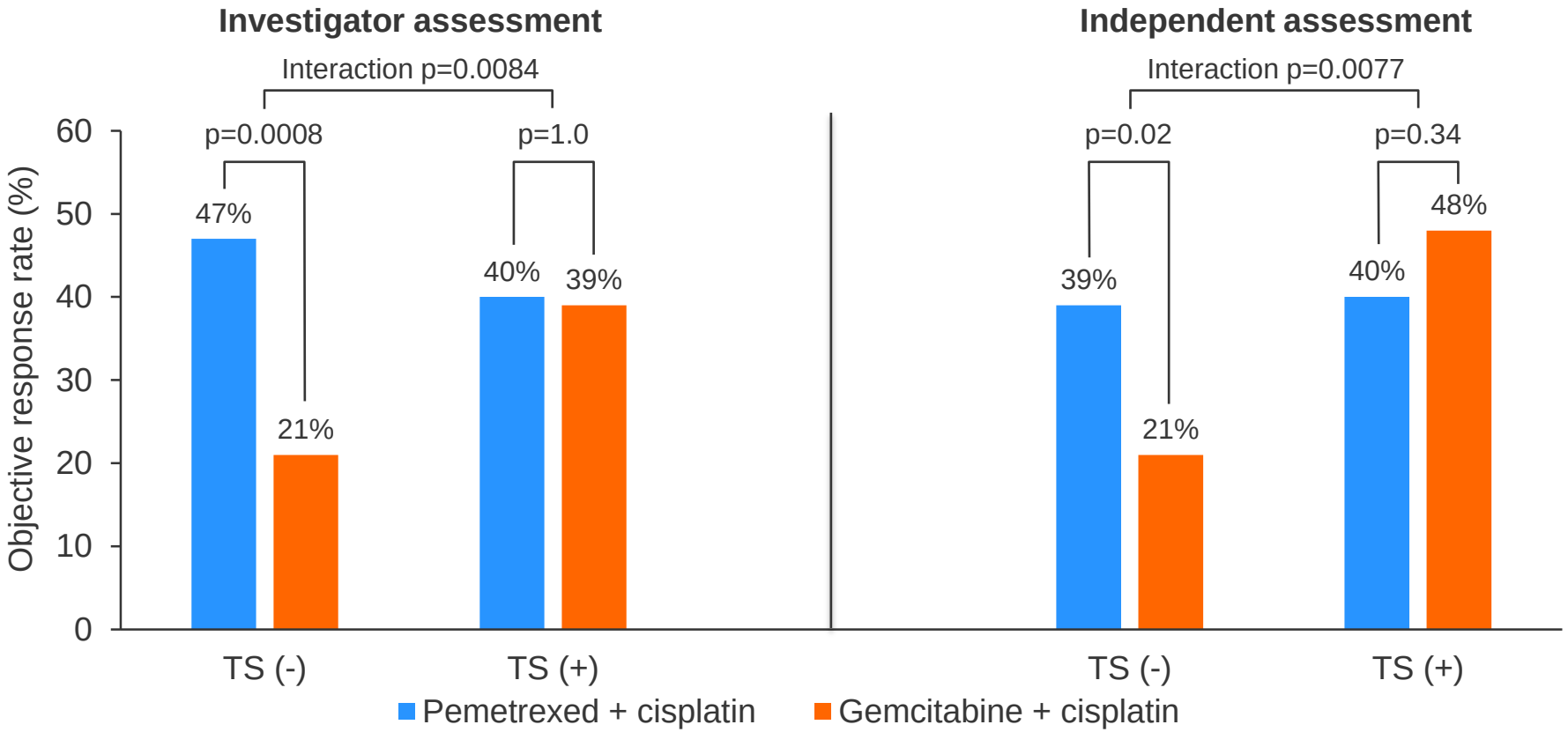
- PFS, OS
- Safety

Pemetrexed 500 mg/m^2 + cisplatin 70 mg/m^2 D1 q3w or gemcitabine 1000 mg/m^2 D1–D8 + cisplatin 70 mg/m^2 D1 q3w

Ahn et al. Ann Oncol 2014; 25 (suppl 4): abstr LBA42_PR

LBA42_PR: Cisplatin plus pemetrexed (CP) versus cisplatin plus gemcitabine (CG) according to thymidylate synthase expression in non-squamous NSCLC: A biomarker-stratified randomized phase II trial – Ahn M et al

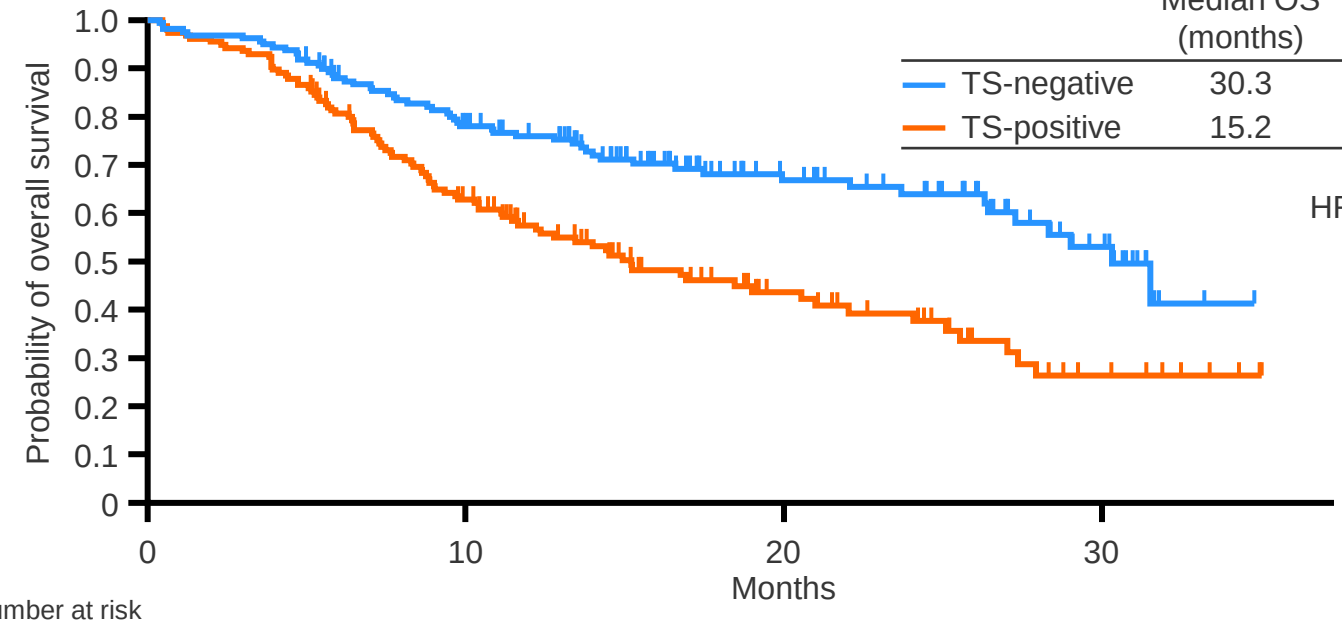
- **Key results**
  - In the TS-negative group, pemetrexed + cisplatin was more efficacious than gemcitabine + cisplatin, while in the TS-positive group efficacy was similar between treatments



Ahn et al. Ann Oncol 2014; 25 (suppl 4): abstr LBA42_PR

LBA42_PR: Cisplatin plus pemetrexed (CP) versus cisplatin plus gemcitabine (CG) according to thymidylate synthase expression in non-squamous NSCLC: A biomarker-stratified randomized phase II trial – Ahn M et al

- **Key results (cont.)**
  - Low expression of TS was asssociated with prolonged OS irrespective of treatment regimen



	Median OS (months)	95% CI	p value
TS-negative	30.3	26.4, not reached	<0.0001
TS-positive	15.2	11.5, 21.0	

HR 0.64, 95% CI 0.45, 0.90

Number at risk				
TS (-)	159	116	52	18
TS (+)	156	90	31	8

- **Conclusion**
  - TS is a predictive and prognostic biomarker

Ahn et al. Ann Oncol 2014; 25 (suppl 4): abstr LBA42_PR

1225O: Overall and intracranial (IC) efficacy results and time to symptom deterioration in PROFILE 1014: 1st-line crizotinib vs pemetrexed - platinum chemotherapy (PPC) in patients (pts) with advanced ALK-positive non-squamous non-small cell lung cancer (NSCLC) – Solomon B et al

- **Study objective**
  - To compare the efficacy of crizotinib with standard chemotherapy when used as first-line therapy in patients with advanced ALK+ NSCLC
- **Study design**
  - PROFILE 1014 is an open-label phase III study that randomised 343 patients to crizotinib 250 mg bid PO (n=172) or pemetrexed + cisplatin or carboplatin (PPC; n=171)
  - Patients were permitted to continue with or crossover to crizotinib following PD
  - Primary endpoint: PFS
  - Secondary endpoints: OS, intracranial TTP, time to deterioration in symptoms of chest pain, dyspnoea, or cough (TTDS) and safety
- **Key results**
  - Crizotinib, compared with PPC, significantly prolonged PFS (median 10.9 vs. 7.0 months; HR 0.45; 95% CI 0.35, 0.60; p<0.0001)
    - This effect was observed in most patient subgroups

PPC, pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2 or carboplatin AUC 5–6; all IV q3w for ≤6 cycles

Solomon et al. Ann Oncol 2014; 25 (suppl 4): abstr 1225O

1225O: Overall and intracranial (IC) efficacy results and time to symptom deterioration in PROFILE 1014: 1st-line crizotinib vs pemetrexed−platinum chemotherapy (PPC) in patients (pts) with advanced ALK-positive non-squamous non-small cell lung cancer (NSCLC) – Solomon B et al

- **Key results (cont.)**
  - OS and intracranial TTP was not significantly greater with crizotinib vs. PPC
  - TTDS was significantly longer with crizotinib (median 2.1 vs. 0.5 months; HR 0.62; p=0.0004)
  - Vision disorder and GI symptoms were the most common AEs associated with crizotinib treatment while those with PPC were consistent with previous reports in unselected NSCLC

- **Conclusions**
  - In patients with treatment-naïve advanced ALK-positive non-squamous NSCLC, crizotinib had an acceptable safety profile and significantly improved PFS and TTDS compared with PPC
  - Crizotinib should be considered as first-line standard-of-care in these patients

PPC, pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2 or carboplatin AUC 5–6; all IV q3w for ≤6 cycles

Solomon et al. Ann Oncol 2014; 25 (suppl 4): abstr 1225O

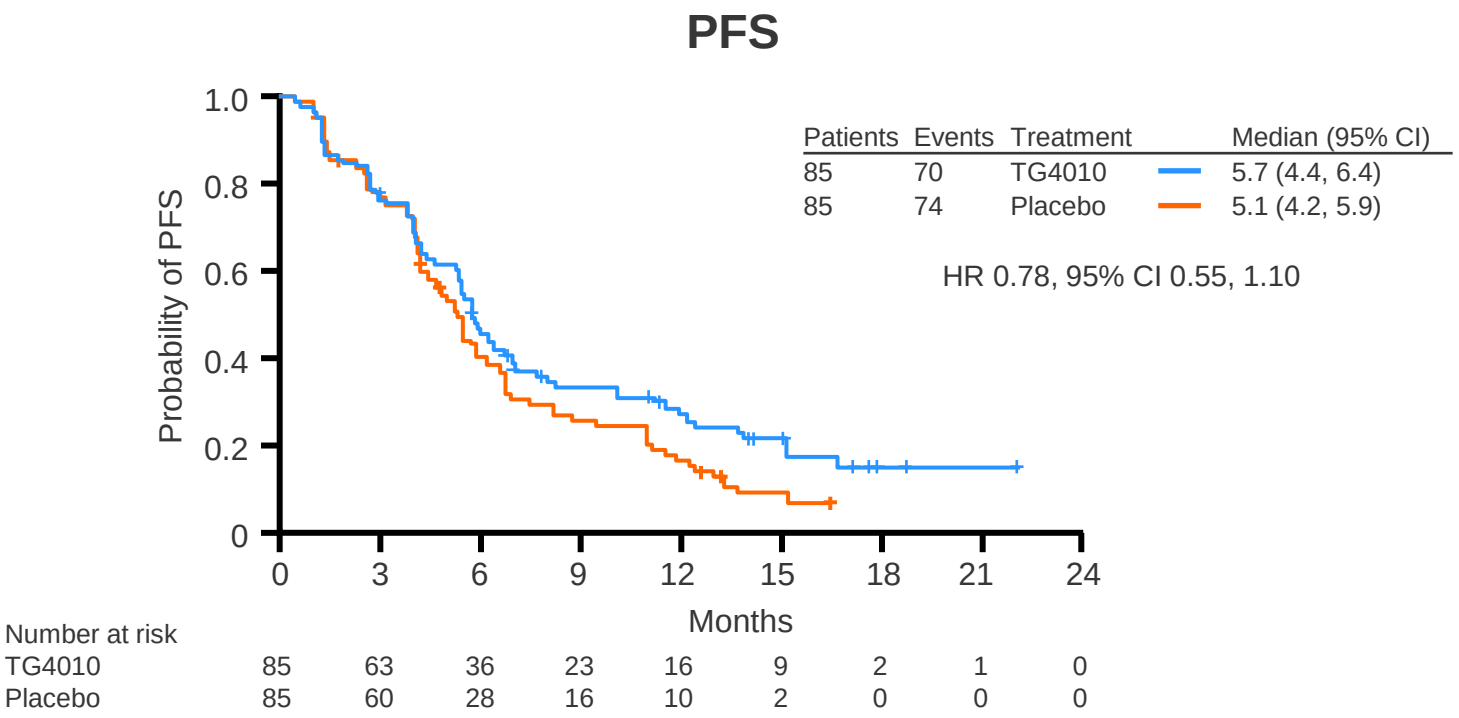
1055PD: TIME, a phase 2b/3 study evaluating TG4010 in combination with first line therapy in advanced non small cell lung cancer (NSCLC). Phase 2b results – Quoix E et al

- **Study objective**
  - To validate baseline level of triple positive activated lymphocytes (TrPAL) as a predictive biomarker of response to TG4010 in patients with NSCLC
- **Study design**
  - Double-blind, phase IIb/III trial comparing the efficacy of TG4010 and placebo when given in combination with first-line treatment in patients with stage IV MUC1+ NSCLC
  - Primary endpoint: PFS
  - Secondary endpoints: ORR, safety, OS and response by subgroup
- **Key results**
  - Of 221 enrolled patients, 170 had a normal TrPAL level; after 144 PD events the HR for PFS was 0.78 (95% CI 0.55, 1.10) (see next slide)
  - Subgroup analyses identified significantly improved PFS in TG4010-treated patients with non-squamous tumours (n=195; HR 0.71, 95% CI 0.51, 0.97) and those in with low TrPAL levels (n=131; HR 0.60, 95% CI 0.41, 0.88)

Quoix et al. Ann Oncol 2014; 25 (suppl 4): abstr 1055PD

1055PD: TIME, a phase 2b/3 study evaluating TG4010 in combination with first line therapy in advanced non small cell lung cancer (NSCLC). Phase 2b results – Quoix E et al

- **Key results (cont.)**

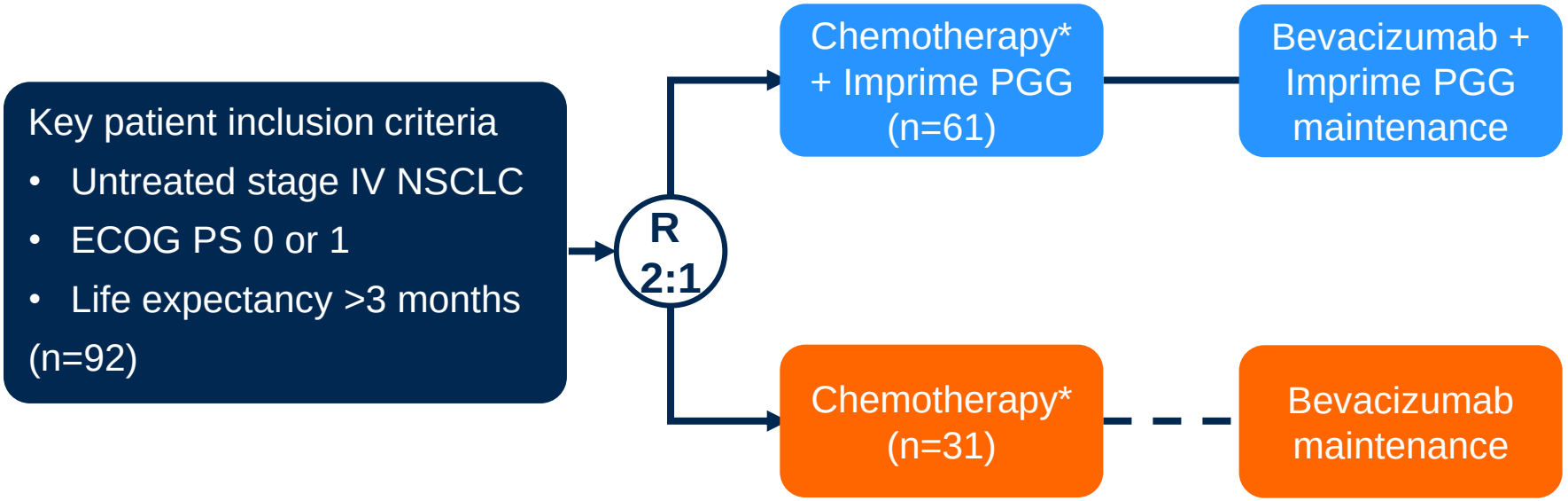


- **Conclusions**
  - TrPAL is a predictive biomarker of response to TG4010
  - TG4010 has efficacy and acceptable safety profile in patients with stage IV NSCLC, particularly in the non-squamous population

Quoix et al. Ann Oncol 2014; 25 (suppl 4): abstr 1055PD

LBA32: Imprime PGG, a novel immune modulator, in the 1st-line treatment of stage IV NSCLC: Results from a randomized, controlled, multicenter phase 2 study – Engel-Riedel et al

- **Study objective**
  - To determine if addition of Imprime PGG to standard of care chemotherapy will improve ORR in patients with advanced NSCLC



Primary endpoint

- ORR

Secondary endpoints

- Duration of response, TTP, PFS, OS
- Safety

*Standard of care chemotherapy (carboplatin AUC6, paclitaxel 200 mg/m^2 IV D2 q3w + bevacizumab 15 mg/kg IV D1, D8 and D15)
TTP, time to progression

Engel-Riedel et al. Ann Oncol 2014; 25 (suppl 4): abstr LBA32

LBA32: Imprime PGG, a novel immune modulator, in the 1st-line treatment of stage IV NSCLC: Results from a randomized, controlled, multicenter phase 2 study – Engel-Riedel et al

- **Key results**
  - Imprime PGG increased ORR by approximately 16.9% and increased the duration of response by 4.7 months

	Imprime PGG (n=48)		Control (n=23)		p value
	N	% [95% CI]	N	% [95% CI]	
ORR	29	60.4 [45.3, 74.2]	10	43.5 [23.2, 65.5]	0.2096
Complete response	1	2.1	0	0.0	
Partial response	28	58.3	10	43.5	
Stable disease	16	33.3	11	47.8	
Progressive disease	3	6.3	2	8.7	

  - Although the study was not powered for time-to-event endpoints, there was a trend towards improved PFS and OS, with an increase in median survival of 4.5 months and a 34% reduction in the risk of death
- **Conclusion**
  - In combination with standard of care chemotherapy, Imprime PGG improved ORR and duration of response in patients with non-squamous NSCLC

Engel-Riedel et al. Ann Oncol 2014; 25 (suppl 4): abstr LBA32

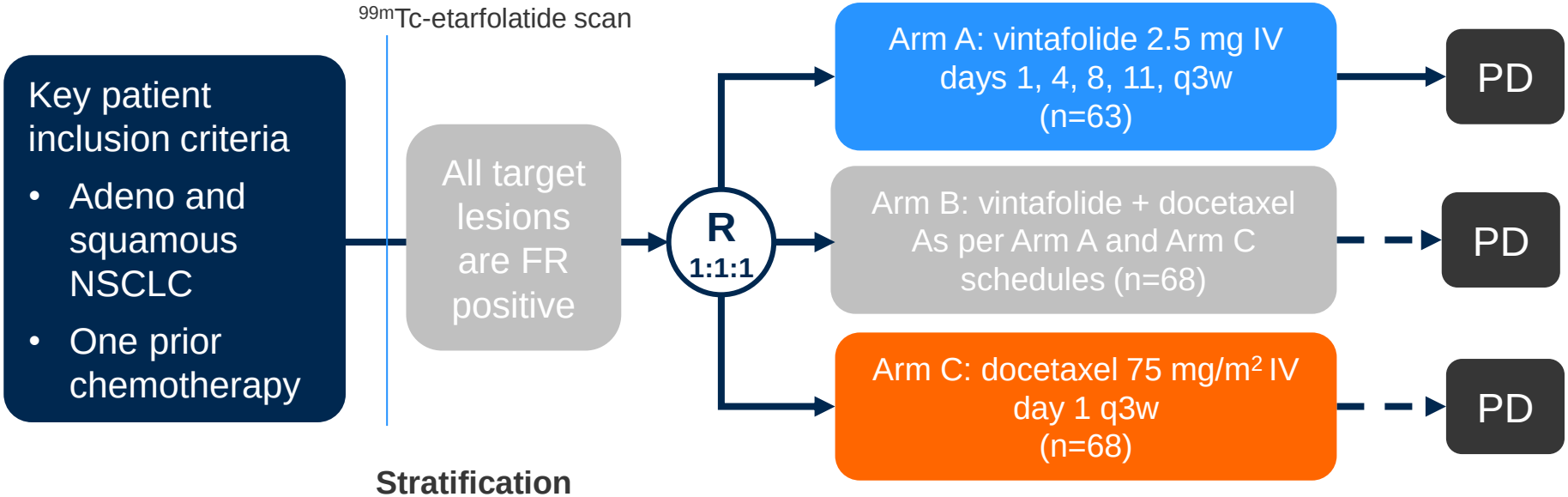
Advanced NSCLC

Not radically treatable stage III and stage IV

Later lines

LBA40_PR: TARGET: A randomized, phase II trial comparing vintafolide versus vintafolide plus docetaxel, versus docetaxel alone in second-line treatment of folate-receptor-positive non-small cell lung cancer (NSCLC) patients – Hanna N et al

- **Study objective**
  - To compare vintafolide with vintafolide + docetaxel and docetaxel alone as second-line treatment in patients with folate-receptor-positive NSCLC



Stratification

- Time since last chemotherapy (<3 vs. ≥3 months); best response to chemotherapy; stage IIIB vs. IV; prior EGFR inhibitor treatment (yes vs. no)

Primary endpoint

- PFS

Secondary endpoints

- ORR, DCR, OS

Hanna et al. Ann Oncol 2014; 25 (suppl 4): abstr LBA40_PR

LBA40_PR: TARGET: A randomized, phase II trial comparing vintafolide versus vintafolide plus docetaxel, versus docetaxel alone in second-line treatment of folate-receptor-positive non-small cell lung cancer (NSCLC) patients – Hanna N et al

- **Key results**

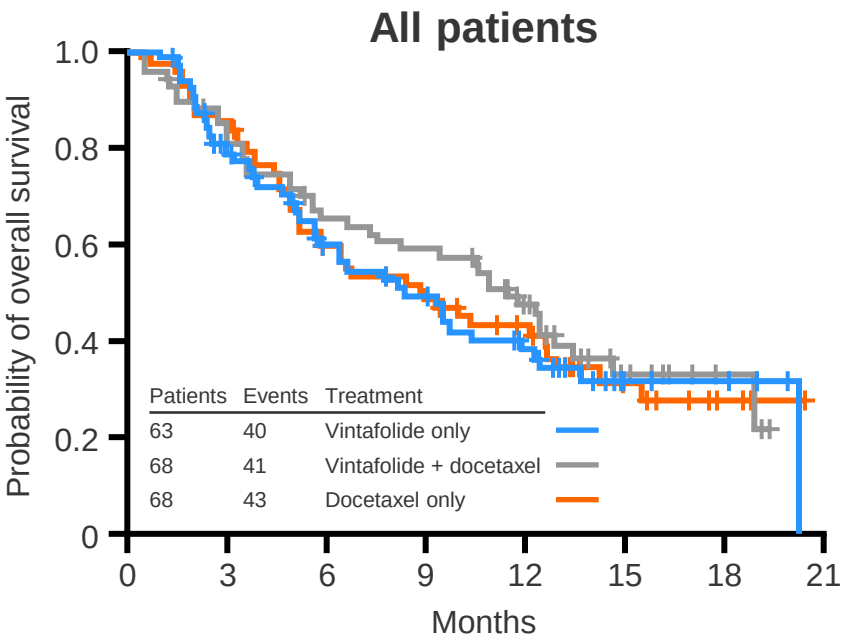
	Vintafolide (n=63)	Vintafolide + docetaxel (n=68)	Docetaxel (n=68)
All patients			
Median (95% CI) PFS, months	1.6 (1.4, 3.2)	4.2 (2.8, 5.4)	3.3 (1.7, 4.2)
PFS HR (95% CI; vs. docetaxel)*; p value†	1.35 (0.92, 1.96); 0.9421	0.75 (0.52, 1.09); 0.0696	
Median (95% CI) OS, months	8.4 (5.6, 12.3)	11.5 (7.3, 13.4)	8.8 (5.4, 12.6)
OS HR (95% CI; vs. docetaxel)*; p value†	1.05 (0.68, 1.61); 0.5818	0.88 (0.58, 1.36); 0.2874	
Stratified analysis			
All patients	n=63	n=68	
PFS HR (95% CI; vs. docetaxel); p value†	1.35 (0.89, 2.04); 0.9266	0.78 (0.52, 1.17); 0.1175	
OS HR (95% CI; vs. docetaxel); p value†	0.96 (0.62, 1.50); 0.4396	0.75 (0.48, 1.18); 0.1066	
Adenocarcinoma	n=41	n=43	
PFS HR (95% CI; vs. docetaxel); p value†	1.32 (0.79, 2.21); 0.8590	0.68 (0.41, 1.14); 0.0732	
OS HR (95% CI; vs. docetaxel); p value†	0.88 (0.51, 1.52); 0.3274	0.51 (0.28, 0.94); 0.0147	

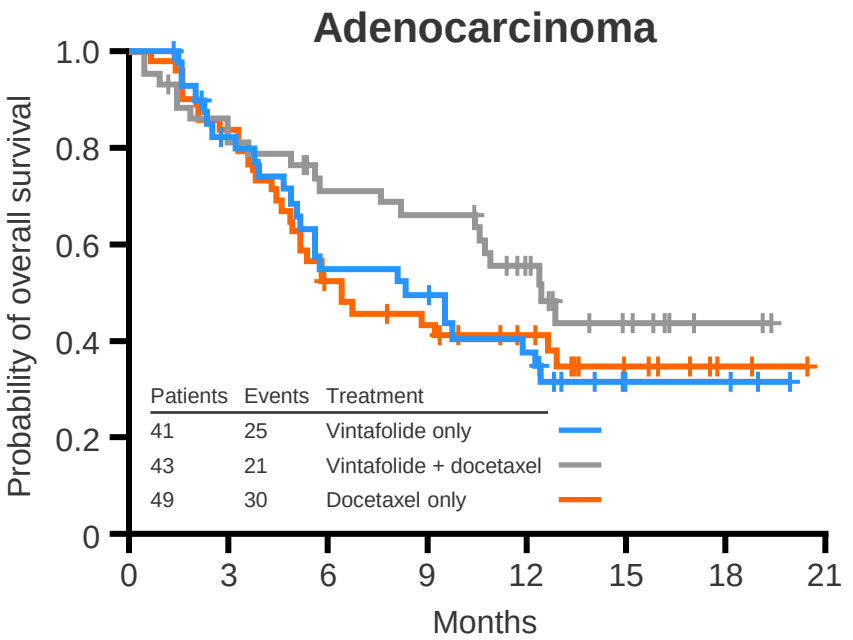
*Unstratified log-rank; †1-sided

Hanna et al. Ann Oncol 2014; 25 (suppl 4): abstr LBA40_PR

LBA40_PR: TARGET: A randomized, phase II trial comparing vintafolide versus vintafolide plus docetaxel, versus docetaxel alone in second-line treatment of folate-receptor-positive non-small cell lung cancer (NSCLC) patients – Hanna N et al

- **Key results (cont.)**
  - **OS**



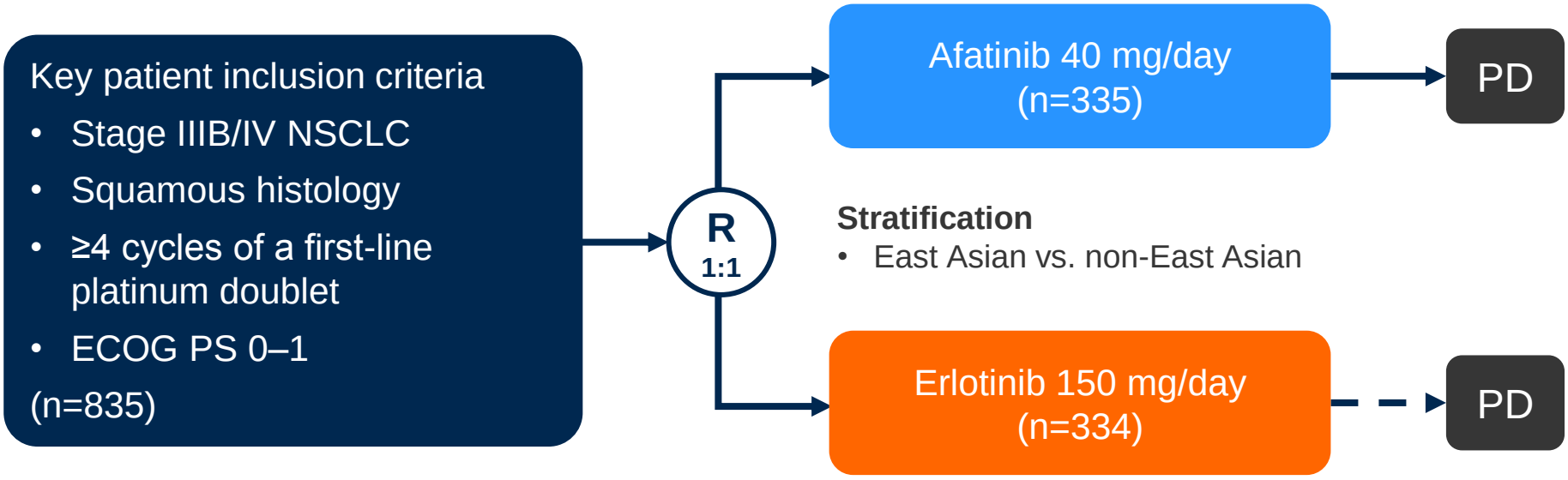


- **Conclusions**
  - Compared with docetaxel alone, vintafolide + docetaxel provided a non-significant trend in PFS and OS outcomes
    - Outcomes were better in patients with adenocarcinoma

Hanna et al. Ann Oncol 2014; 25 (suppl 4): abstr LBA40_PR

1222O: A randomized, open-label, phase III trial of afatinib (A) vs erlotinib (E) as second-line treatment of patients (pts) with advanced squamous cell carcinoma (SCC) of the lung following first-line platinum-based chemotherapy: LUX-Lung 8 (LL8) – Goss G et al

- **Study objective**
  - To compare afatinib with erlotinib in patients with squamous cell carcinoma (SCC) of the lung following failure of first-line chemotherapy



Primary endpoint

- PFS

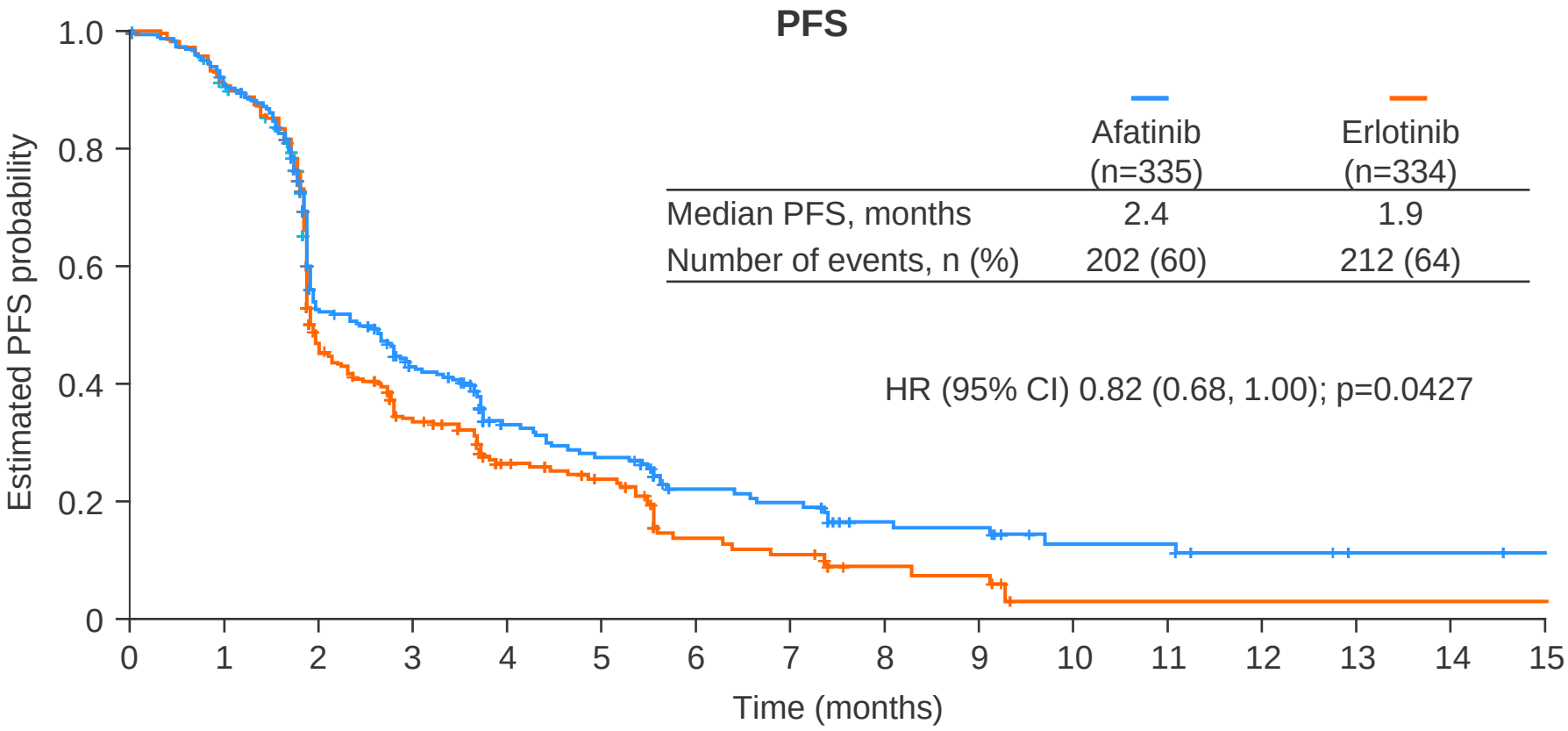
Secondary endpoints

- OS, ORR, DCR, tumour shrinkage
- Safety, health-related QoL

Goss et al. Ann Oncol 2014; 25 (suppl 4): abstr 1222O

1222O: A randomized, open-label, phase III trial of afatinib (A) vs erlotinib (E) as second-line treatment of patients (pts) with advanced squamous cell carcinoma (SCC) of the lung following first-line platinum-based chemotherapy: LUX-Lung 8 (LL8) – Goss G et al

- **Key results**



Goss et al. Ann Oncol 2014; 25 (suppl 4): abstr 1222O

1222O: A randomized, open-label, phase III trial of afatinib (A) vs erlotinib (E) as second-line treatment of patients (pts) with advanced squamous cell carcinoma (SCC) of the lung following first-line platinum-based chemotherapy: LUX-Lung 8 (LL8) – Goss G et al

- **Key results (cont.)**
  - ORR and DCR were higher with afatinib than erlotinib (4.8% vs. 3.0%; p=0.233 and 45.7% vs. 36.8%; p=0.020, respectively)
  - The AE profiles between afatinib and erlotinib were comparable
    - The proportion of patients with grade ≥3 AEs were 50.2% and 49.1%, respectively
    - The incidence of drug-related grade ≥3 diarrhoea (9.7% vs. 2.4%) and grade 3 stomatitis (3.3% vs. 0.0%) was higher with afatinib, while grade 3 rash/acne was higher with erlotinib (5.5% vs. 9.0%)

- **Conclusions**
  - Afatinib was associated with better PFS and DCR than erlotinib in patients with advanced SSC of the lung
    - The AE profile of both treatments were similar
    - Clinical significance of such benefit might be questioned

Goss et al. Ann Oncol 2014; 25 (suppl 4): abstr 1222O

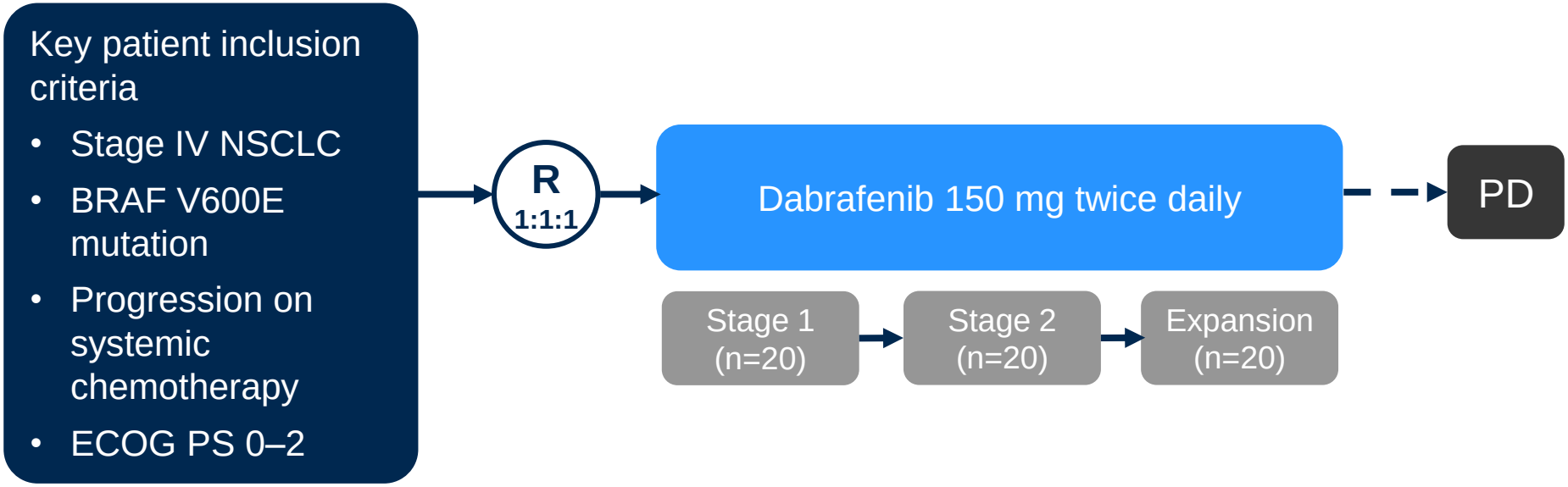
1224O: Anti-tumor activity of alectinib in crizotinib pre-treated ALK-rearranged NSCLC in JP28927 study – Seto T et al

- **Study objective**
  - To examine the bioequivalence of different alectinib doses and effect of food in patients with ALK-rearranged NSCLC
- **Study design**
  - Updated efficacy and safety in 28 crizotinib pretreated patients who received alectinib 300 mg bid until lack of clinical benefit as assessed by the investigator
- **Key results**
  - After a median follow-up of 141 days, 21 patients continued treatment without PD
  - Tumour shrinkage of ≥30% was observed in 18 of 24 patients with target lesions
  - Response rate was 58.3% (95% CI 36.6, 77.9) and DCR was 83.3% (95% CI 62.6, 95.3)
  - Of the 19 patients with brain metastases at baseline (from 28 patients) 13 were still on alectinib without PD
  - Alectinib had a favourable safety profile consistent with previous reports and no patients discontinued treatment for safety reasons
- **Conclusion**
  - In patients with ALK-rearranged NSCLC pre-treated with crizotinib, alectinib had a good tolerability profile and demonstrated positive efficacy

Seto et al. Ann Oncol 2014; 25 (suppl 4): abstr 1224O

LBA38_PR: Dabrafenib in patients with BRAF V600E-mutant advanced non-small cell lung cancer (NSCLC): A multicenter, open-label, phase II trial (BRF113928) – Planchard B et al

- **Study objective**
  - To investigate efficacy of dabrafenib in patients with BRAF V600E-mutant advanced NSCLC



Primary endpoint

- ORR

Secondary endpoints

- PFS, duration of response, OS
- Safety, tolerability
- Population pharmacokinetics

Planchard et al. Ann Oncol 2014; 25 (suppl 4): abstr LBA38_PR

LBA38_PR: Dabrafenib in patients with BRAF V600E-mutant advanced non-small cell lung cancer (NSCLC): A multicenter, open-label, phase II trial (BRF113928) – Planchard B et al

- **Key results**
  - Dabrafenib was associated with ORR of 32% and DCR of 56%

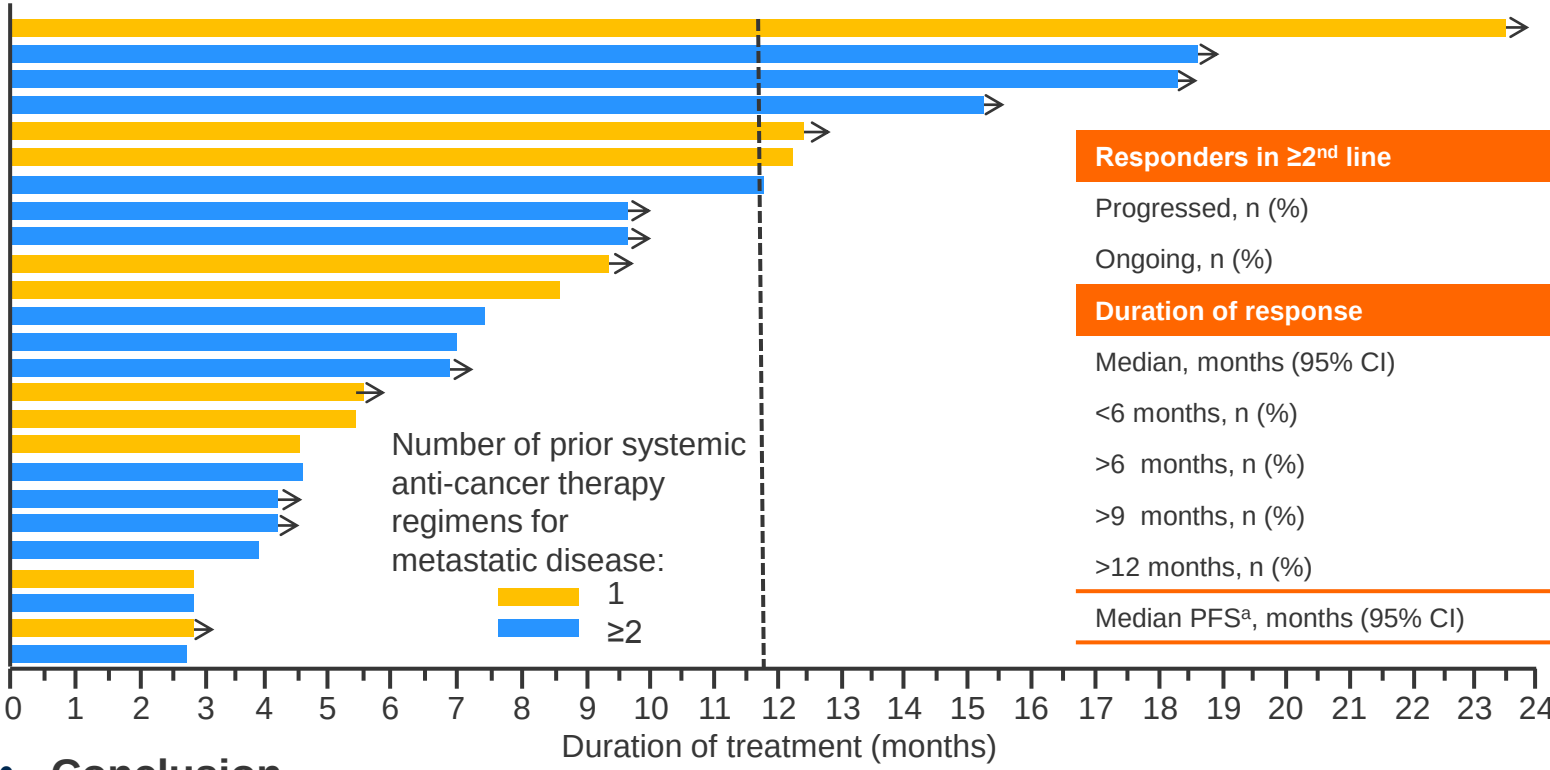
	≥ 2nd line (n=78)
PR, n (%)	25 (32)
SD*, n (%)	19 (24)
PD, n (%)	23 (29)
Not evaluable, n (%)	11 (14)
Response rate, i.e. confirmed CR + PR (95% CI), %	32 (21.9, 43.6)
Disease control rate, i.e. confirmed CR + PR + SD (95% CI), %	56 (44.7, 67.6)

*SD is defined as meeting SD ≥12 weeks (planned time for the second post-baseline disease assessment)

Planchard et al. Ann Oncol 2014; 25 (suppl 4): abstr LBA38_PR

LBA38_PR: Dabrafenib in patients with BRAF V600E-mutant advanced non-small cell lung cancer (NSCLC): A multicenter, open-label, phase II trial (BRF113928) – Planchard B et al

- **Key results (cont.)**
  - Median duration of response: 11.8 months with 48% responders progressed
  - Median PFS: 5.5 months with 62% patients progressed or died



Responders in ≥2nd line	N=25
Progressed, n (%)	12 (48)
Ongoing, n (%)	13 (52)
Duration of response	
Median, months (95% CI)	11.8 (5.4, NR)
<6 months, n (%)	11 (44), 4 ongoing
>6 months, n (%)	14 (56), 9 ongoing
>9 months, n (%)	10 (40), 8 ongoing
>12 months, n (%)	6 (24), 4 ongoing
Median PFS[a], months (95% CI)	5.5, (2.8, 7.3)

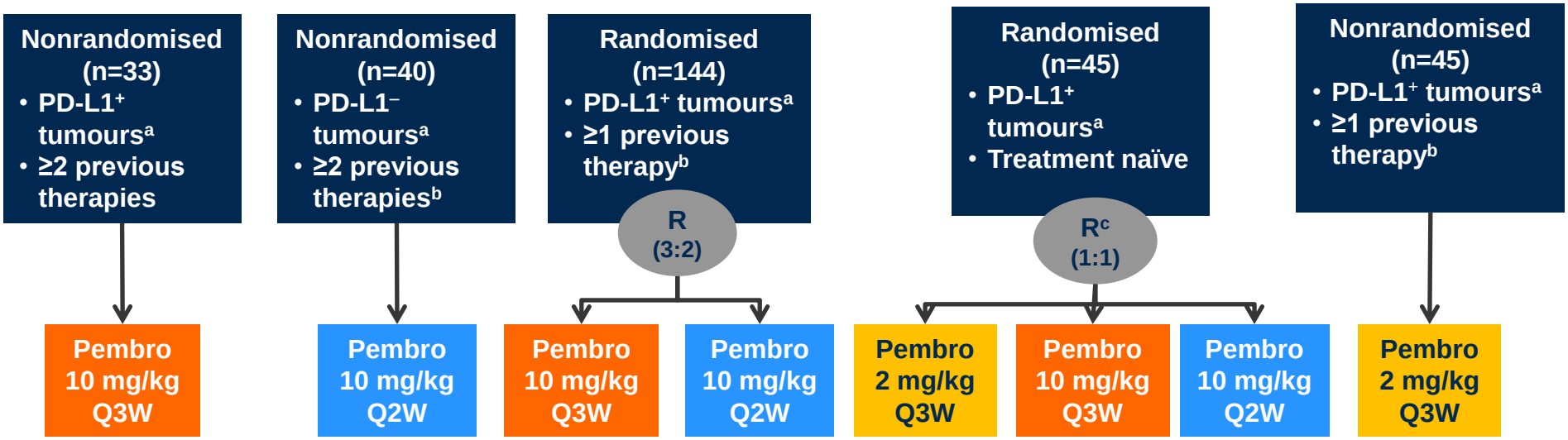
- **Conclusion**
  - Dabrafenib showed clinically meaningful antitumour activity with durable objective responses in BRAF V600E mutated NSCLC

*62% of patients progressed or died

Planchard et al. Ann Oncol 2014; 25 (suppl 4): abstr LBA38_PR

LBA43: Antitumor activity of pembrolizumab (Pembro; MK-3475) and correlation with programmed death ligand 1 (PD-L1) expression in a pooled analysis of patients (pts) with advanced non-small cell lung carcinoma (NSCLC) – Garon E et al

- **Study objective**
  - To evaluate the efficacy and safety of pembrolizumab among a number of cohorts of patients with EGFR+ or ALK+ advanced NSCLC



Primary endpoint

- ORR

Secondary endpoints

- Immune-related response criteria

[a]Tumour PD-L1 expression was determined by a prototype assay to inform enrolment. Samples were independently reanalysed using a clinical trial IHC assay

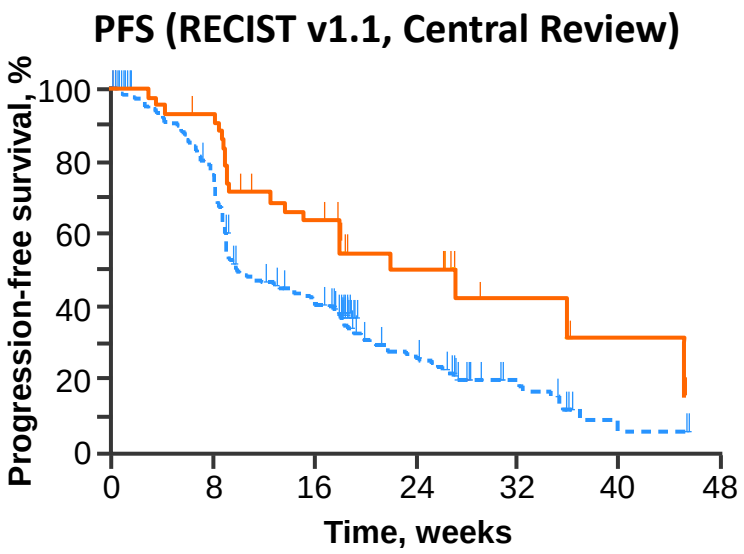
[b]Including ≥1 therapy platinum-containing doublet. [c]First 11 patients randomised to 2 mg/kg q3w and 10 mg/kg q3w. The remaining 34 patients were randomised to 10 mg/kg q2w and 10 mg/kg q3w.

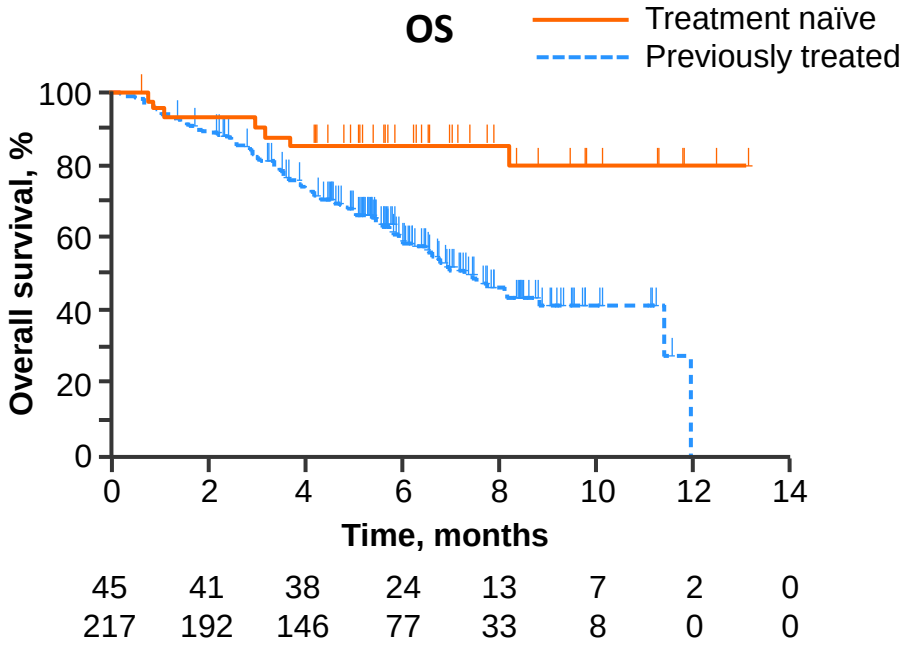
Analysis cut-off date is September 11, 2014 for the nonrandomised cohort of 45 patients treated at 2 mg/kg q3w

Garon et al. Ann Oncol 2014; 25 (suppl 4): abstr LBA43

LBA43: Antitumor activity of pembrolizumab (Pembro; MK-3475) and correlation with programmed death ligand 1 (PD-L1) expression in a pooled analysis of patients (pts) with advanced non-small cell lung carcinoma (NSCLC) – Garon E et al

- **Key results**
  - Robust antitumour activity was observed in both treatment-naïve and previously treated advanced NSCLC observed for all doses and schedules assessed





Treatment naïve
- Median PFS: 27 weeks (95% CI 14, 45)
- 24-week PFS: 51%

Previously treated
- Median PFS: 10 weeks (95% CI 9.1, 15.3)
- 24-week PFS: 26%

Treatment naive
- Median OS: NR (95% CI NE, NE)
- 6-month OS: 86%

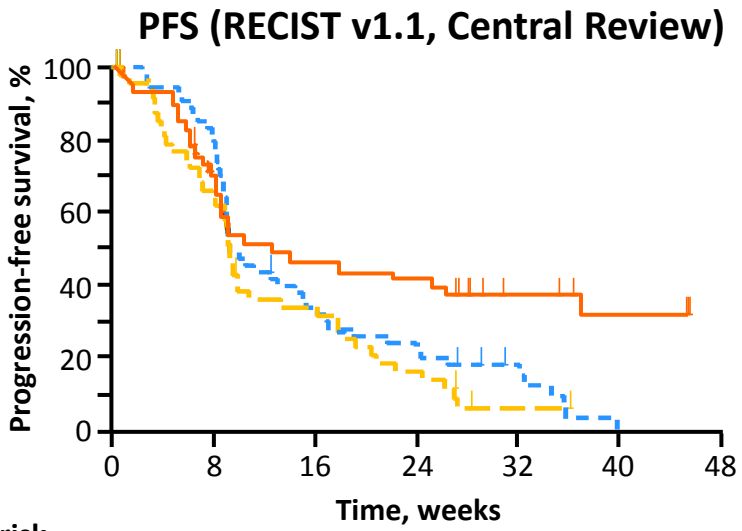
Previously treated
- Median OS: 8.2 months (95% CI 7.3, NR)
- 6-month OS: 59%

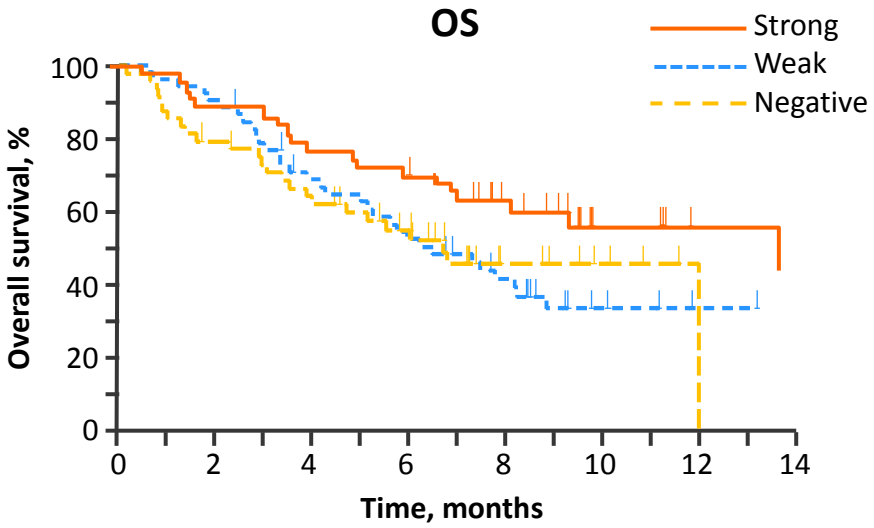
Garon et al. Ann Oncol 2014; 25 (suppl 4): abstr LBA43

Analysis cutoff date: March 3, 2014

LBA43: Antitumor activity of pembrolizumab (Pembro; MK-3475) and correlation with programmed death ligand 1 (PD-L1) expression in a pooled analysis of patients (pts) with advanced non-small cell lung carcinoma (NSCLC) – Garon E et al

- **Key results (cont.)**
  - Strong PD-L1 tumour expression correlated with improved response, PFS and OS





n at risk							
Strong	44	28	18	17	9	6	3
Weak	53	43	17	12	6	0	0
Negative	49	30	15	7	1	0	0

Strong	44	43	38	38	34	32	30	27	21	18	9	8	5	5	4
Weak	53	51	48	40	34	31	26	22	18	11	8	7	5	5	4
Negative	49	42	38	34	29	26	21	14	8	6	4	2	0	0	0

Conclusions

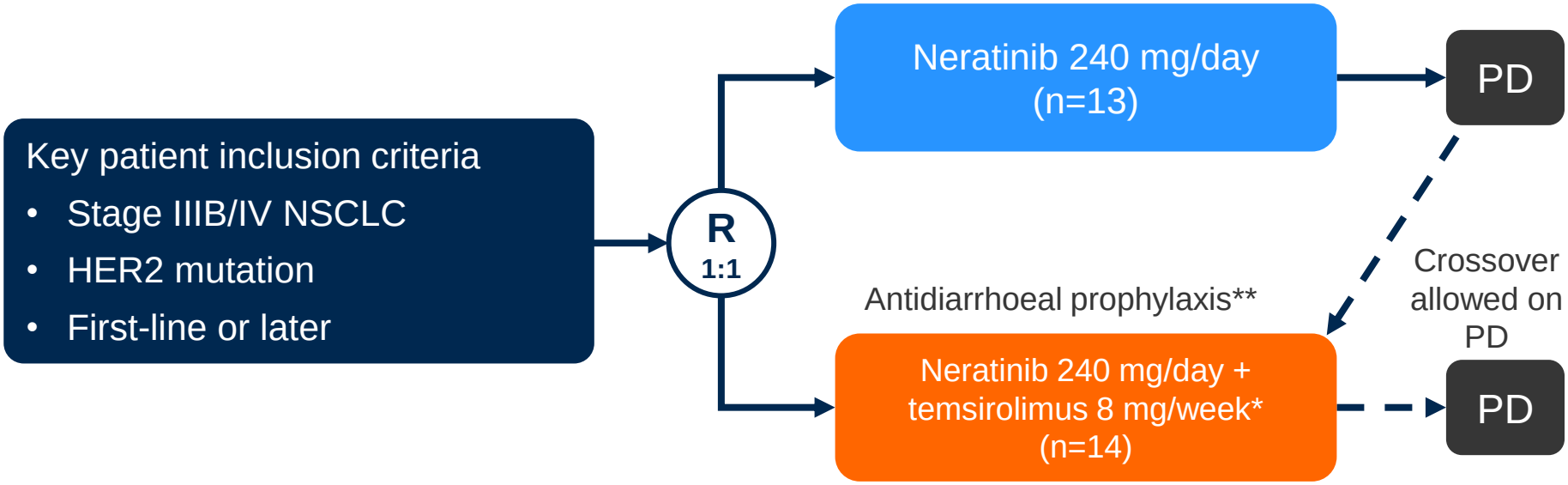
- Pembrolizumab was effective in patients with treatment-naïve or previously treated advanced NSCLC
  - In particular, patients with strong PD-L1 tumour expression may benefit from this treatment

Strong PD-L1 positivity defined as staining in ≥50% of tumour cells, and weak PD-L1 positivity as staining in 1–49% of tumour cells. Negative staining is no PD-L1 staining in tumour cells. Data cutoff: March 3, 2014.

Garon et al. Ann Oncol 2014; 25 (suppl 4): abstr LBA43

LBA39_PR: Neratinib (N) with or without temsirolimus (TEM) in patients (pts) with non-small cell lung cancer (NSCLC) carrying HER2 somatic mutations: An international randomized phase II study – Besse B et al

- **Study objective**
  - To investigate neratinib alone or in combination with temsirolimus in patients with HER2+ NSCLC



Primary endpoint

- ORR

Secondary endpoints

- Clinical benefit rate, duration of response, PFS, OS
- Safety, health outcomes

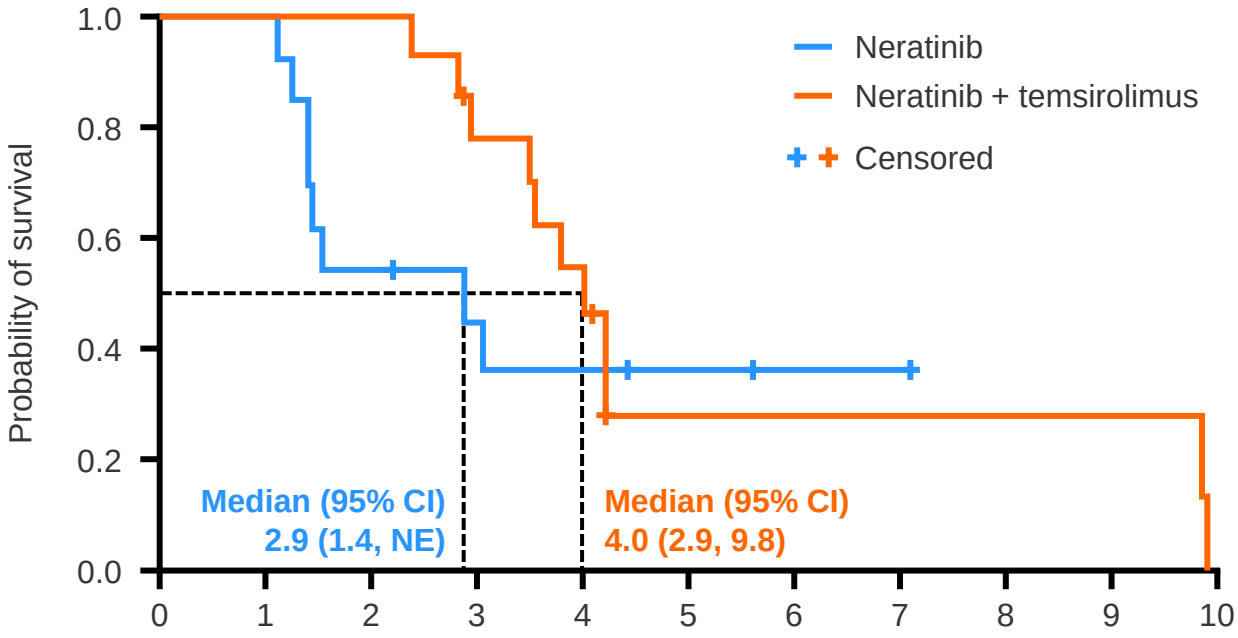
*Temsirolimus dose escalated to 15 mg IV weekly after 1st cycle if tolerated

**Mandatory primary antidiarrhoeal prophylaxis with a 21-day regimen of high-dose loperamide

Besse et al. Ann Oncol 2014; 25 (suppl 4): abstr LBA39_PR

LBA39_PR: Neratinib (N) with or without temsirolimus (TEM) in patients (pts) with non-small cell lung cancer (NSCLC) carrying HER2 somatic mutations: An international randomized phase II study – Besse B et al

- **Key results**
  - A median PFS of 4 months was observed with neratinib plus temsirolimus



No. of patients										
Neratinib	13	13	7	5	4	3	2	2	0	
Neratinib + temsirolimus	14	14	14	10	7	2	2	2	2	0

Besse et al. Ann Oncol 2014; 25 (suppl 4): abstr LBA39_PR

LBA39_PR: Neratinib (N) with or without temsirolimus (TEM) in patients (pts) with non-small cell lung cancer (NSCLC) carrying HER2 somatic mutations: An international randomized phase II study – Besse B et al

- **Key results (cont.)**
  - An ORR of 21% was observed with neratinib plus temsirolimus

	Neratinib (n=13)	Neratinib + temsirolimus (n=14)
Best overall response, n (%)		
Partial response	0 (0)	3 (21)*
Stable disease	7 (54)	11 (79)
Progressive disease	6 (46)	0 (0)

  - No apparent correlation was observed between HER2 mutation type and response

*2 of 3 responses were confirmed

Besse et al. Ann Oncol 2014; 25 (suppl 4): abstr LBA39_PR

LBA39_PR: Neratinib (N) with or without temsirolimus (TEM) in patients (pts) with non-small cell lung cancer (NSCLC) carrying HER2 somatic mutations: An international randomized phase II study – Besse B et al

- **Key results (cont.)**

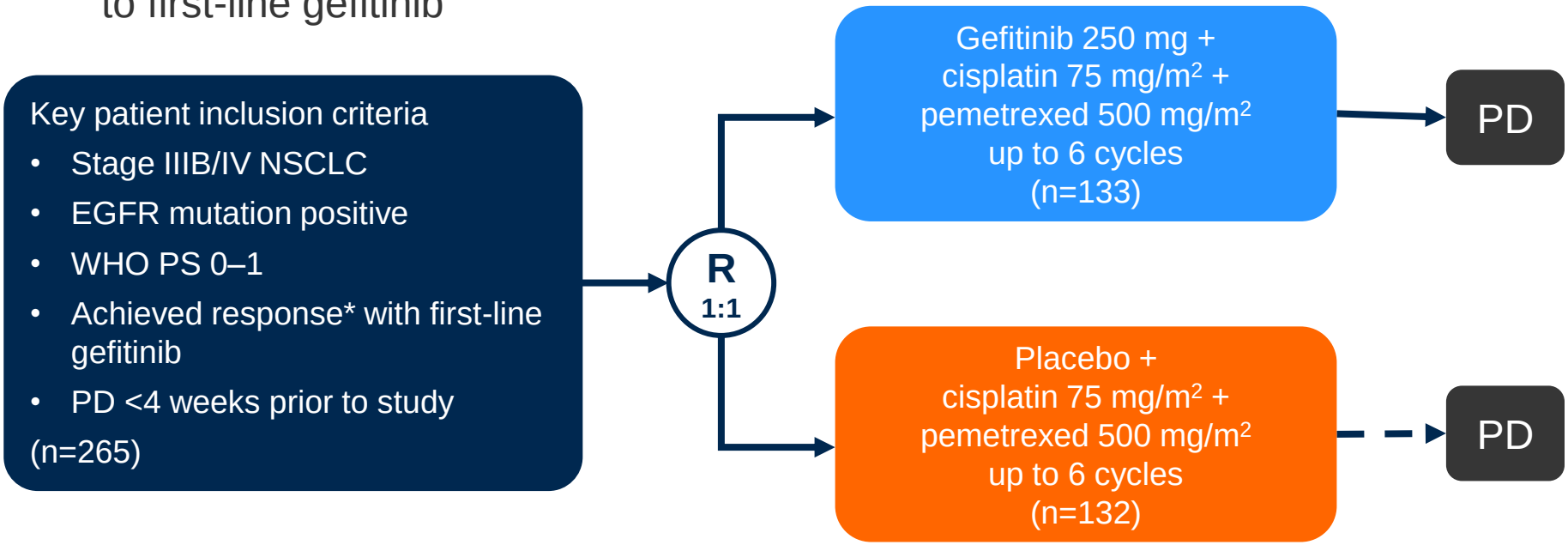
AEs occurring in >40% in either group, n (%)	Neratinib (n=13)	Neratinib + temsirolimus (n=14)
Diarrhoea	10 (77)	14 (100)
Asthenia	6 (46)	5 (36)
Nausea	6 (46)	7 (50)
Constipation	5 (38)	8 (57)
Dyspnoea	4 (31)	7 (50)
Vomiting	3 (23)	8 (57)
Anaemia	3 (23)	6 (43)
Decreased appetite	3 (23)	6 (43)

- **Conclusions**
  - Inhibition of both HER2 and PI3K pathways appeared to be superior to HER2 pathway blockade alone
  - With upfront management, diarrhoea was not a limiting toxicity

Besse et al. Ann Oncol 2014; 25 (suppl 4): abstr LBA39_PR

LBA2_PR: Gefitinib/chemotherapy vs chemotherapy in epidermal growth factor receptor (EGFR) mutation-positive non-small-cell lung cancer (NSCLC) after progression on first-line gefitinib: The phase III, randomised IMPRESS study – Mok T et al

- **Study objective**
  - To compare continuation treatment with gefitinib + chemotherapy versus chemotherapy alone in patients with advanced NSCLC and acquired resistance to first-line gefitinib



Primary endpoint

- PFS

Secondary endpoints

- OS, ORR, DCR
- Safety and tolerability, health-related QoL

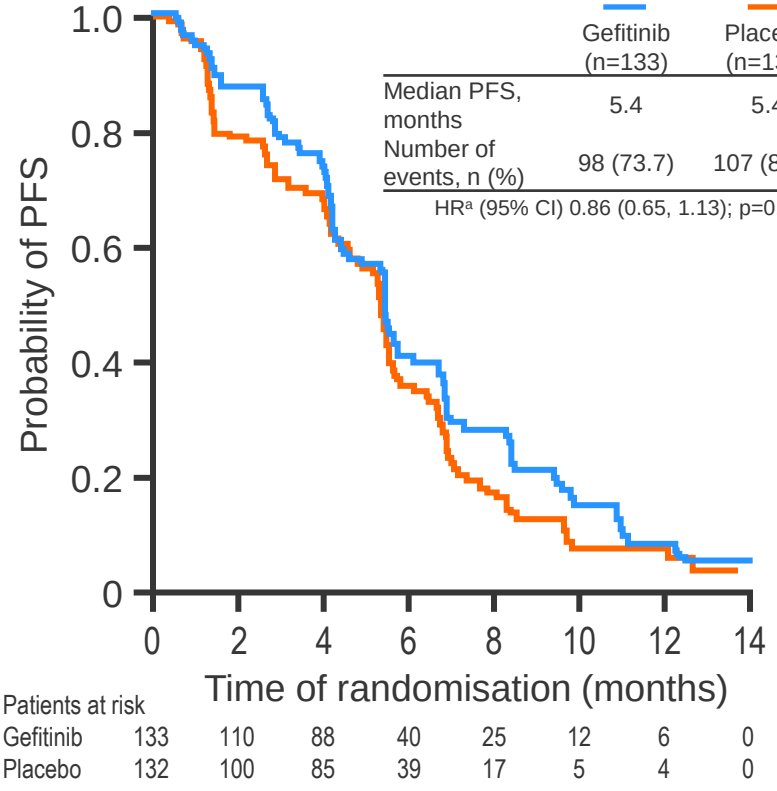
*CR/PR ≥4 months or SD >6 months

Mok et al. Ann Oncol 2014; 25 (suppl 4): abstr LBA2_PR

LBA2_PR: Gefitinib/chemotherapy vs chemotherapy in epidermal growth factor receptor (EGFR) mutation-positive non-small-cell lung cancer (NSCLC) after progression on first-line gefitinib: The phase III, randomised IMPRESS study – Mok T et al

- **Key results**
  - No statistically significant improvement in PFS with continuation of gefitinib; OS in favour of placebo arm but analysis was immature

PFS

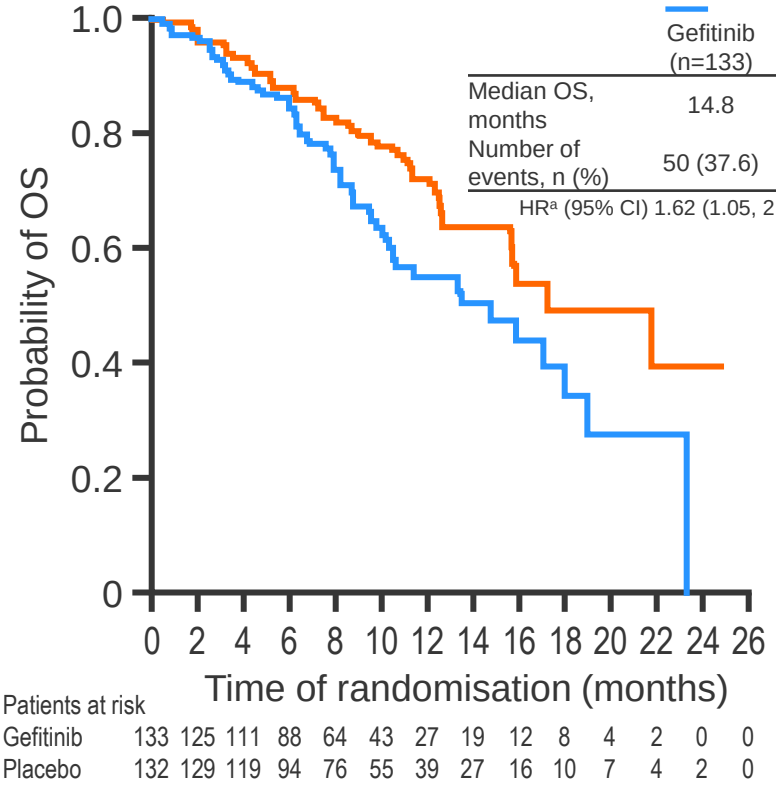


	Gefitinib (n=133)	Placebo (n=132)
Median PFS, months	5.4	5.4
Number of events, n (%)	98 (73.7)	107 (81.1)

HR[a] (95% CI) 0.86 (0.65, 1.13); p=0.273

Patients at risk								
Gefitinib	133	110	88	40	25	12	6	0
Placebo	132	100	85	39	17	5	4	0

OS (33% of events)



	Gefitinib (n=133)	Placebo (n=132)
Median OS, months	14.8	17.2
Number of events, n (%)	50 (37.6)	37 (28.0)

HR[a] (95% CI) 1.62 (1.05, 2.52); p=0.029

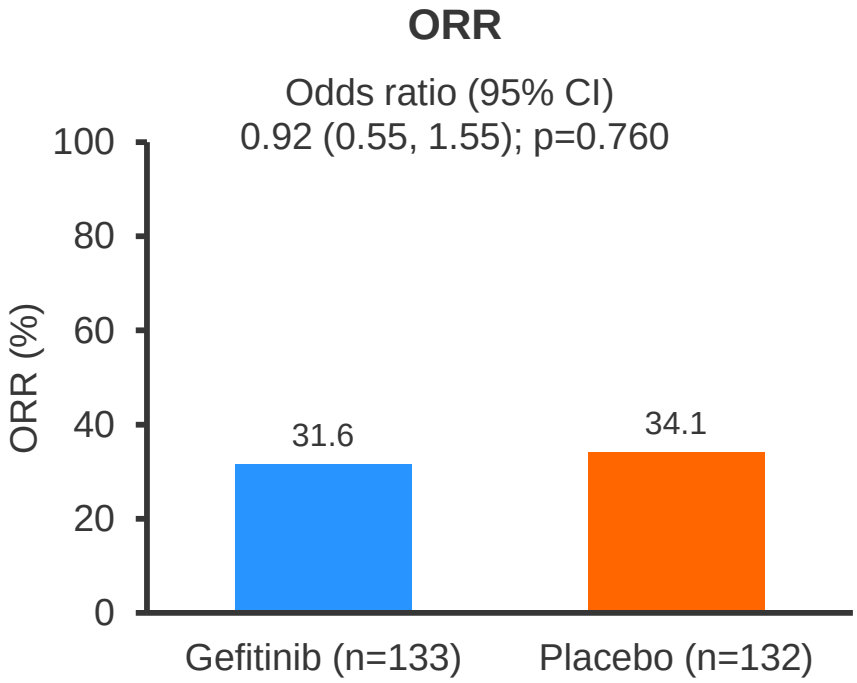
Patients at risk														
Gefitinib	133	125	111	88	64	43	27	19	12	8	4	2	0	0
Placebo	132	129	119	94	76	55	39	27	16	10	7	4	2	0

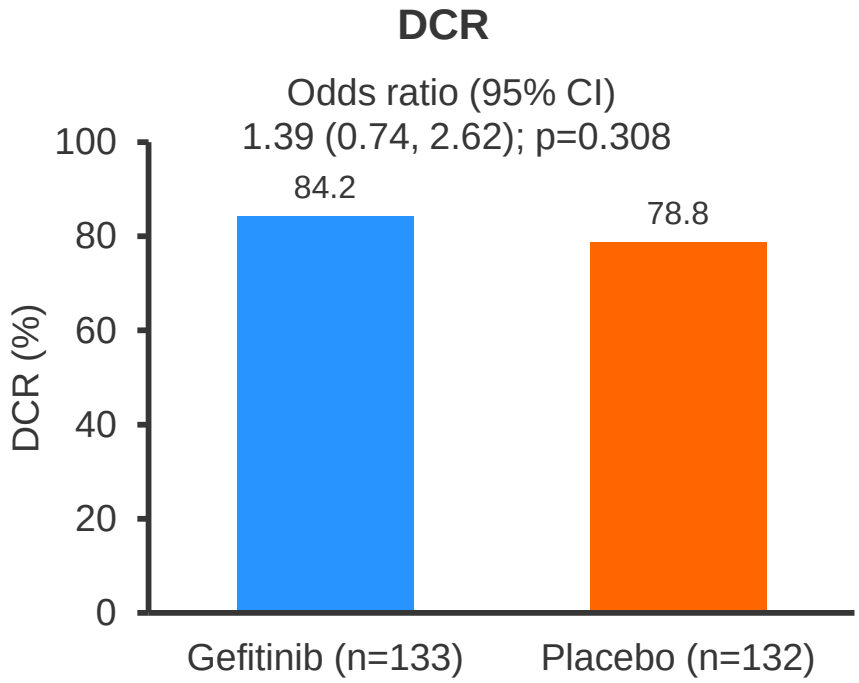
[a]Primary Cox analysis with covariates

Mok et al. Ann Oncol 2014; 25 (suppl 4): abstr LBA2_PR

LBA2_PR: Gefitinib/chemotherapy vs chemotherapy in epidermal growth factor receptor (EGFR) mutation-positive non-small-cell lung cancer (NSCLC) after progression on first-line gefitinib: The phase III, randomised IMPRESS study – Mok T et al

- **Key results (cont.)**
  - No treatment differences were observed for ORR or DCR





- **Conclusion**
  - IMPRESS results do not support continuation of gefitinib after PD when platinum-based doublet chemotherapy is used as second-line treatment

Mok et al. Ann Oncol 2014; 25 (suppl 4): abstr LBA2_PR

1229PD: Smoking history and response to nivolumab in patients with advanced NSCLCs – Hellman MD et al

- **Study objective**
  - To determine the influence of smoking on response to nivolumab in patients with NSCLC
- **Study design**
  - Retrospective analysis of 89 of 129 pretreated patients with advanced NSCLC who had been treated with nivolumab (NCT00730639)
  - Patients were categorised by smoking history (never/minimal [≤5 pack-years] or former/current [>5 pack-years])
- **Key results**
  - ORR was significantly higher in former/current smokers (30% [95% CI 20, 43]) vs. never/minimal smokers (0% [95% CI 0, 23]; p=0.018)
  - There was no association between response and time-since-quitting in smokers (current smokers ORR 27%; quit 1–5 years ago 46%; quit 6–15 years ago 17%, quit >15 years ago 26%; p=0.12)
  - PFS was significantly longer in former/current smokers than never/minimal smokers (2.2 vs. 1.7 months; HR 0.41; p=0.003), but there was no difference in OS (10.1 vs. 13.7 months; HR 1.34; p=0.44)
- **Conclusions**
  - Compared with never/minimal smokers, response to nivolumab in advanced NSCLC was significantly higher in former/current smokers
  - The findings suggest that smoking history might be used as a stratification factor in trials of PD-1 pathway inhibitors
  - Correlation between smoking and PD-L1 expression needs to be explored

Hellman et al. Ann Oncol 2014; 25 (suppl 4): abstr 1229PD

Other malignancies

SCLC and mesothelioma

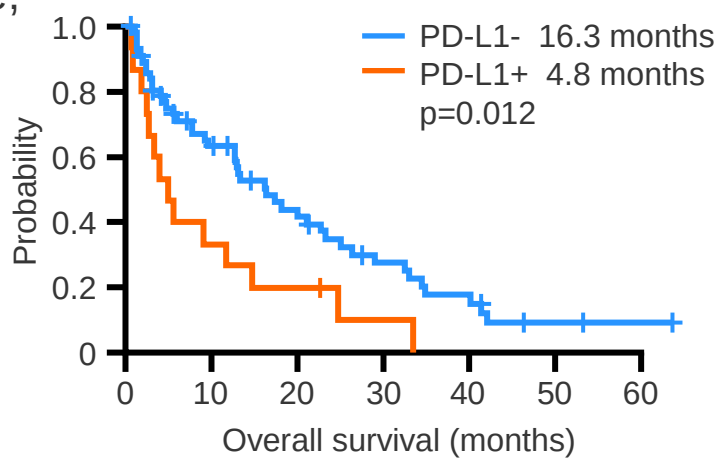
1463O: Prospective molecular evaluation of small cell lung cancer (SCLC) utilizing the comprehensive Mutation Analysis Program (MAP) at Memorial Sloan Kettering Cancer Center (MSKCC) – Krug LM et al

- **Study objective**
  - To examine comprehensive mutation analysis in patients with advanced SCLC
- **Study design**
  - This ongoing study is examining biopsies from patients with advanced SCLC who are receiving active treatment; analyses include FISH, point mutation genotyping by mass spectrometry based assay (Sequenom) and next-generation sequencing
  - A feasibility analysis was performed in patients with SCLC identified retrospectively
- **Key results**
  - Of 21 patients involved in the feasibility analysis, adequate material for next-generation sequencing was available for 10 patients
    - Using as little as 15 ng of DNA, recurrent mutations in RB1, TP53 and amplification of FGFR1 and MET were detected
  - Samples from 36 actively treated patients have been tested
    - Sequenom identified an AKT1 E17 and PIK3CA E542K mutation
    - Next-generation sequencing detected loss of RB1; mutations in TP53, MLL3 and EPHA 5; amplifications of CDKN2C, MYCL1, SOX2 and FGFR1 (the latter confirmed by FISH)
- **Conclusion**
  - Comprehensive molecular evaluation of SCLC can be performed on clinical specimens

Krug et al. Ann Oncol 2014; 25 (suppl 4): abstr 1463O

1556O_PR: Analysis of expression of programmed cell death 1 ligand 1 (PD-L1) in malignant pleural mesothelioma (MPM) – Cedres S et al

- **Study objective**
  - To evaluate PD-L1 expression in patients with malignant pleural mesothelioma (MPM)
- **Study design**
  - From 2000 to 2014, consecutive patients were recruited and a PD-L1 rabbit monoclonal antibody was used to confirm expression
- **Key results**
  - Of 119 patients, 77 tumour samples were available; of these 16 (20.8%) were positive for PD-L1
  - OS was 13.8 months and significantly longer in:
    - Patients with PS score 0–1 vs. 2–3 (20 vs. 2.4 months; p<0.001)
    - Epithelioid vs. non-epithelioid histology (16.4 vs. 5.5 months; p<0.001)
    - PR or SD vs. PD (26.2, 17.5 vs. 7.8 months; p=0.003)



  - PD-L1 was a significant prognostic factor* (HR 2.08, 95% CI 1.12, 3.88; p=0.021)
- **Conclusion**
  - In patients with MPM, being PD-L1 positive is a negative prognostic factor

*After adjusting for performance status, histology and response to chemotherapy

Cedres et al. Ann Oncol 2014; 25 (suppl 4): abstr 15560_PR

LBA37_PR: Neoadjuvant chemotherapy and extrapleural pneumonectomy (EPP) of malignant pleural mesothelioma (MPM) with or without hemithoracic radiotherapy: Final results of the randomized multicenter phase II trial SAKK17/04 – Stahel R et al

- **Study objective**
  - To examine the short-term outcomes of neoadjuvant chemotherapy and extrapleural pneumonectomy (EPP) followed by long-term outcomes with or without hemithoracic radiotherapy in patients with malignant pleural mesothelioma (MPM)
- **Study design**
  - Part 1: Prospective phase II study in which patients received neoadjuvant chemotherapy (3 cycles of cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2 q3w, 3 cycles) followed by restaging and EPP with RFS as primary endpoint
  - Part 2: Patients who achieved complete macroscopic resection were randomised to control arm or radiotherapy arm (56 Gy in 2 Gy fractions) with RFS as primary endpoint
- **Key results**
  - Of 153 patients who entered the trial, 99 achieved complete resection and 54 were randomised to control (n=27) or radiotherapy (n=27)
  - Median RFS after initial CT and surgery of part 1 was 8.8 months (95% CI 7.3, 10.7)
  - Radiotherapy in part 2 did not significantly prolong RFS compared with no radiotherapy (9.4 months [95% CI 6.5, 11.9] vs. 7.6 months [95% CI 4.5, 10.7])
- **Conclusion**
  - Routine use of hemithoracic radiotherapy after neoadjuvant chemotherapy and EPP is not supported by this trial

RFS, relapse-free survival

Stahel et al. Ann Oncol 2014; 25 (suppl 4): abstr LBA37_PR

Other malignancies

Rare tumours

1557PD: GTF2I mutations are frequent in thymic epithelial tumors – Petrini I et al

- **Study objective**
  - To investigate gene expression in thymic epithelial tumours
- **Study design**
  - Tumour and blood samples from 28 patients with thymic epithelial tumours were examined with exome capture and then sequenced and screened for mutations
- **Key results**
  - The number of mutations was significantly higher in thymic carcinomas vs. thymomas (43.5 vs. 17.4, respectively; p=0.001)
  - Thymic carcinomas had recurrent mutations in TP53, CYLD, BAP1, CDKN2A and PBRM1
  - A single nucleotide mutation of GTF2I (chr7:74146970T/A) was observed in 42% of thymomas; this was a missense mutation (leucine to histidine), not previously described in cancer or as a polymorphism in the dbSNP137 database and was predicted to alter the structure and, therefore, function of the protein
    - In an extended cohort analysis, GTF21 mutation was present in 82% of A, 74% of AB, 32% of B1, 22% of B2 and 21% of B3 thymomas, and 8% of thymic carcinomas
- **Conclusion**
  - Mutation in GTF21 occurs frequently in thymic epithelial tumours (particularly A-AB histotypes) and is associated with better outcomes

Petrini et al. Ann Oncol 2014; 25 (suppl 4): abstr 1557PD