Opportunities and risk related to companion diagnostics: *The MET biomarker story*

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EFSPI Meeting Basel, Oct 2017

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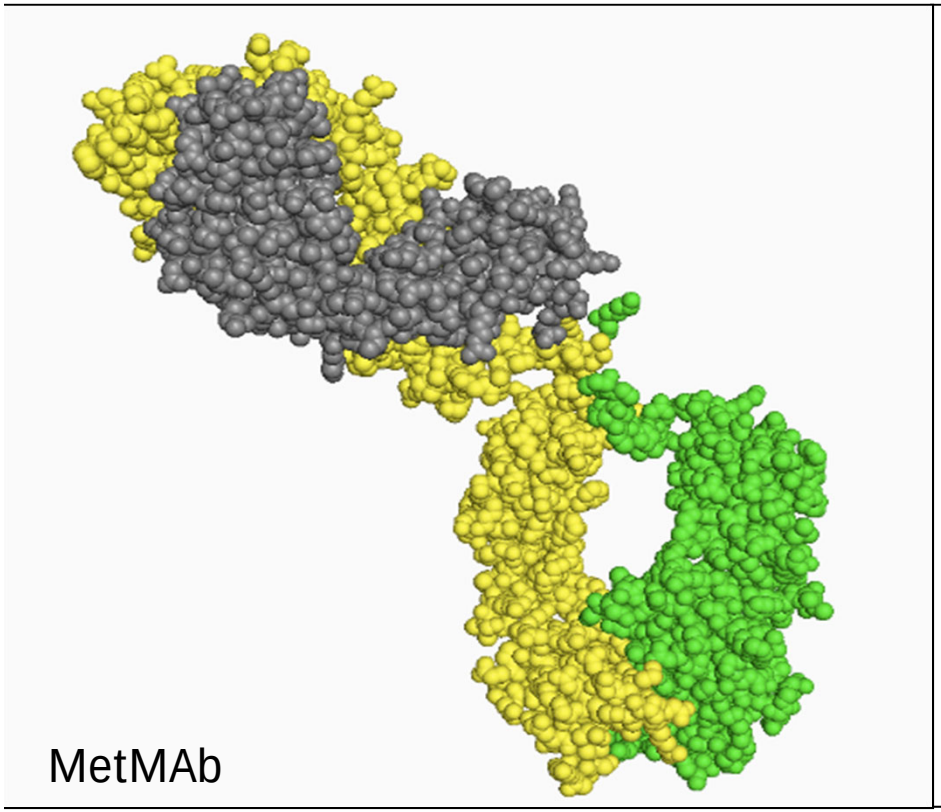
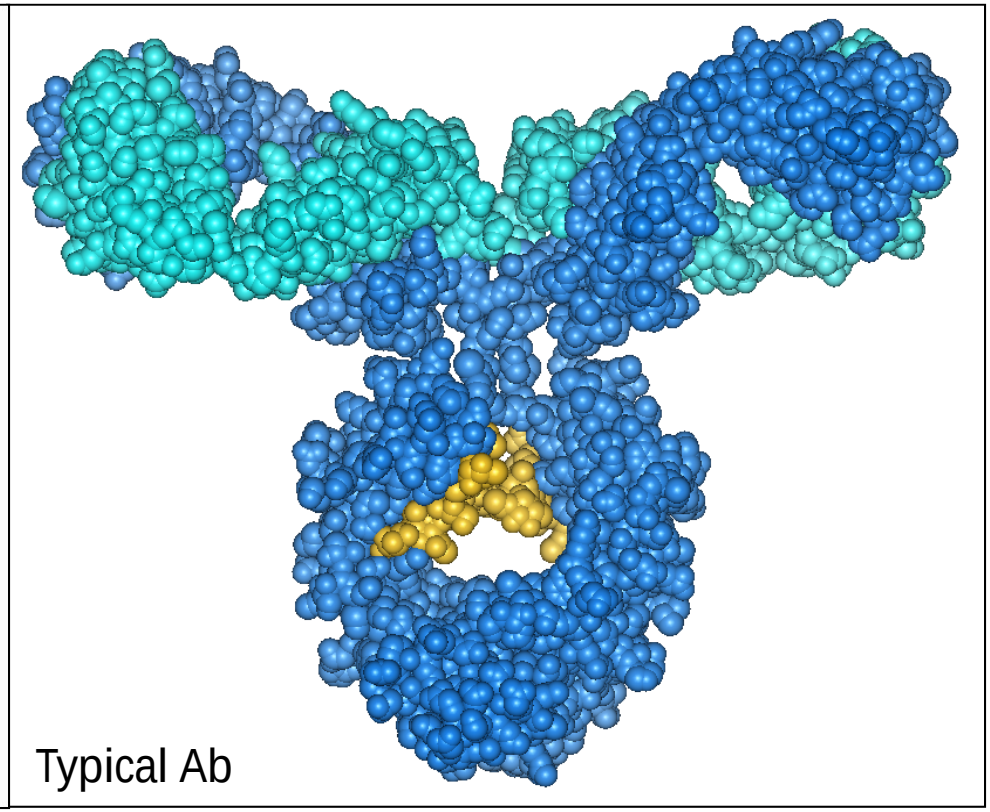
MET pathway: Promising target for anti-cancer drug development?

- Upon binding and activation by HGF (hepatocyte growth factor) , **MET** (mesenchymal-epithelial transition factor) **elicits cell signaling that results in cell proliferation and survival, and can promote metastasis in tumors**
- MET pathway can be dysregulated by MET receptor mutations or amplification, and overexpression of its ligand HGF
- High levels of MET and/or HGF have been associated with poor prognosis in multiple cancer settings

- MetMAb (Onartuzumab) was the first anti-MET antibody to reach late stage clinical development
- First one-armed antibody to be tested in a global series of studies

MetMAb (Onartuzumab)





- Monovalent: does not dimerize Met*
- Non-glycosylated (No ADCC**)

- Bivalent: Potential for Met dimerization*
- Glycosylated antibody (ADCC*)

*Targeting MET with bivalent antibodies can mimic HGF agonism via receptor dimerization
**No ADCC: No antibody dependent cellular cytotoxicity against normal MET-expressing cells

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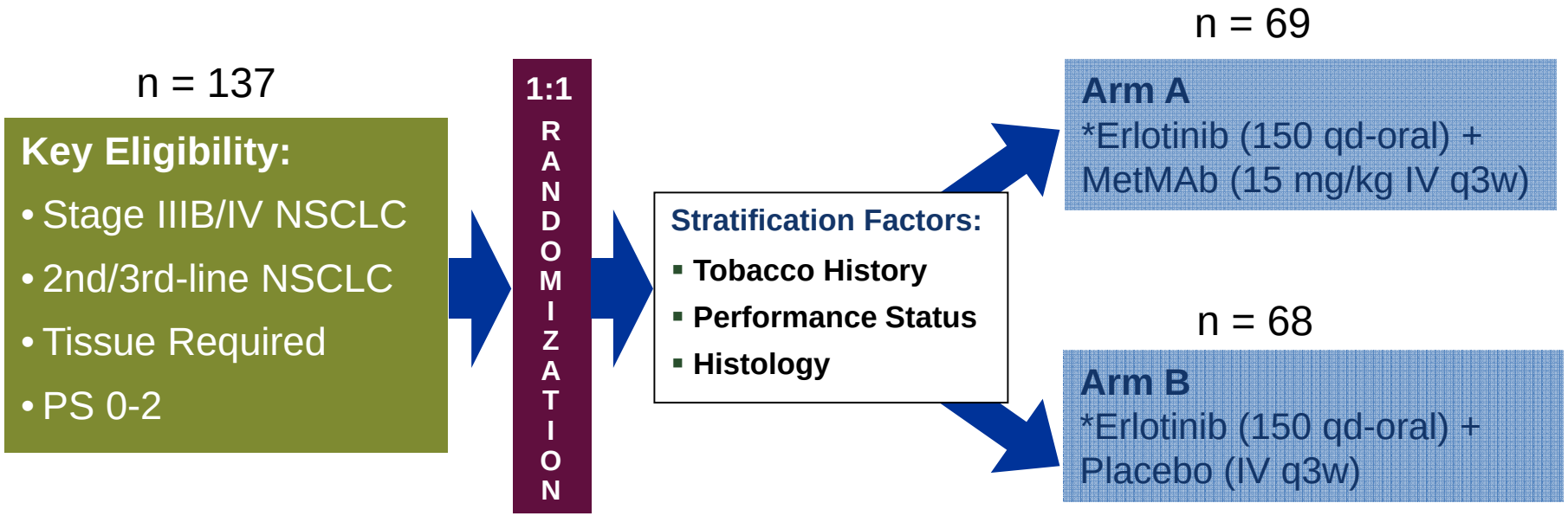
PoC Phase II** Study Design (OAM4558g)



Co-Primary Objectives:

- **PFS in "Met High" patients**
- PFS in overall ITT population

Other Key Objectives:

- **OS in "Met high" patients**
- OS in Overall ITT patients
- Overall Response Rate
- Safety/Tolerability

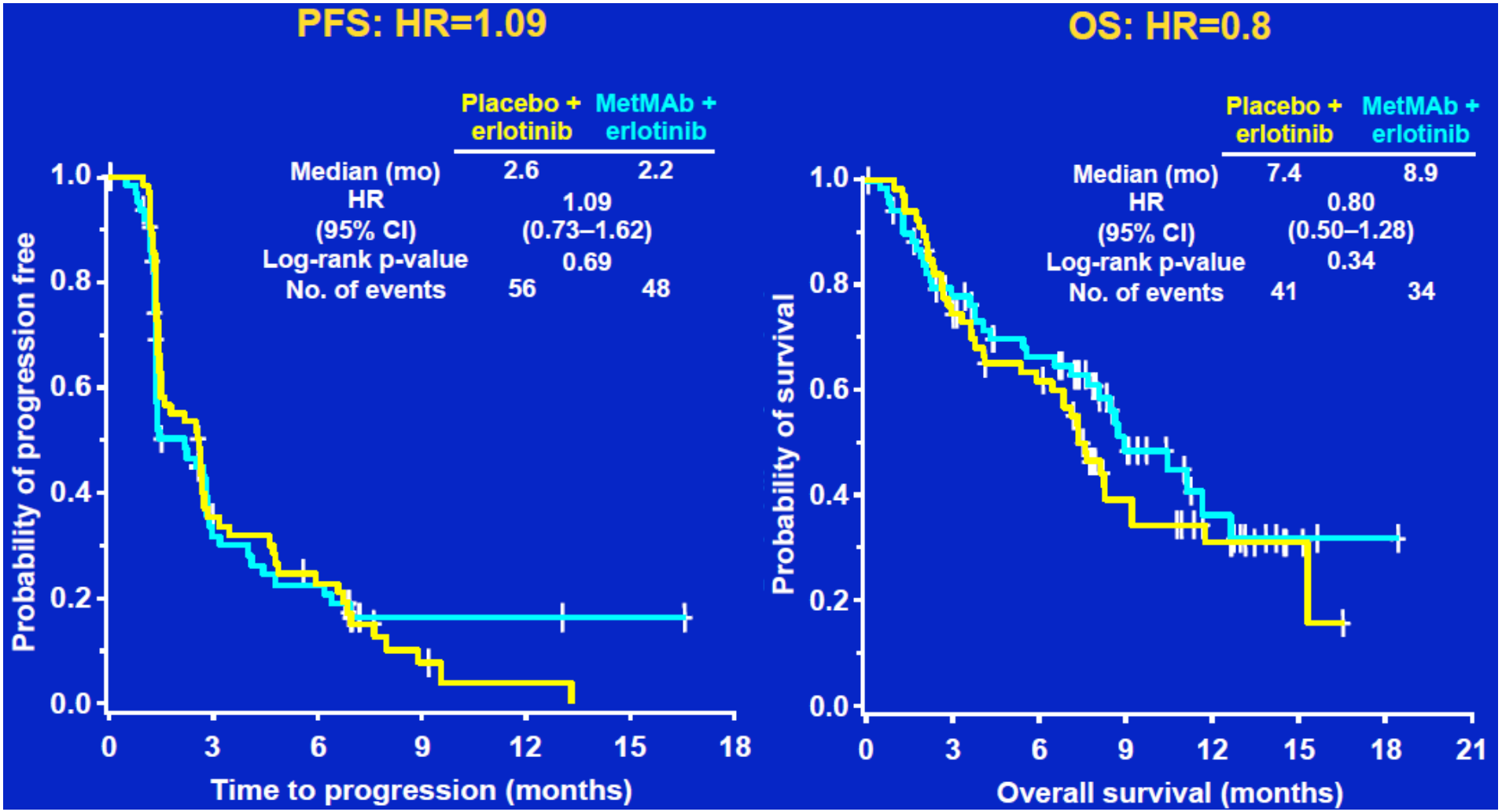
Met as stratification factor: Met diagnostic status was assessed after randomization and prior to unblinding

Met diagnostic positive (Dx+) defined as ≥50% of tumour cells with 2+/3+ staining

*Combination or Erlotinib & MetMAb showed promising efficacy in xenograph models

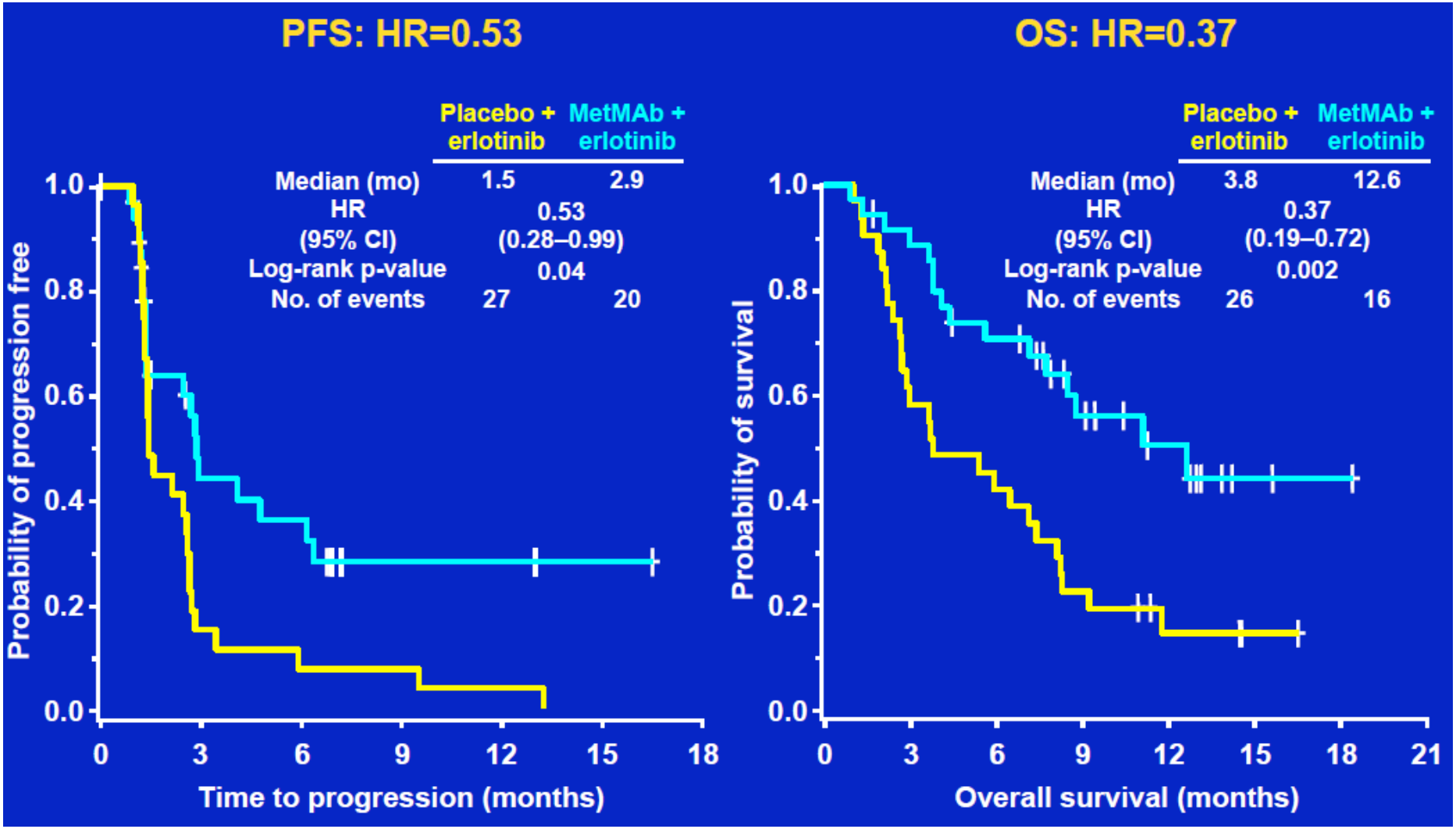
** Spigel, Ervin et al, JCO 2013, "Randomized Phase II Trial of Onartuzumab in Combination With Erlotinib in Patients With Advanced Non–Small-Cell Lung Cancer"

PFS and OS: ITT Population



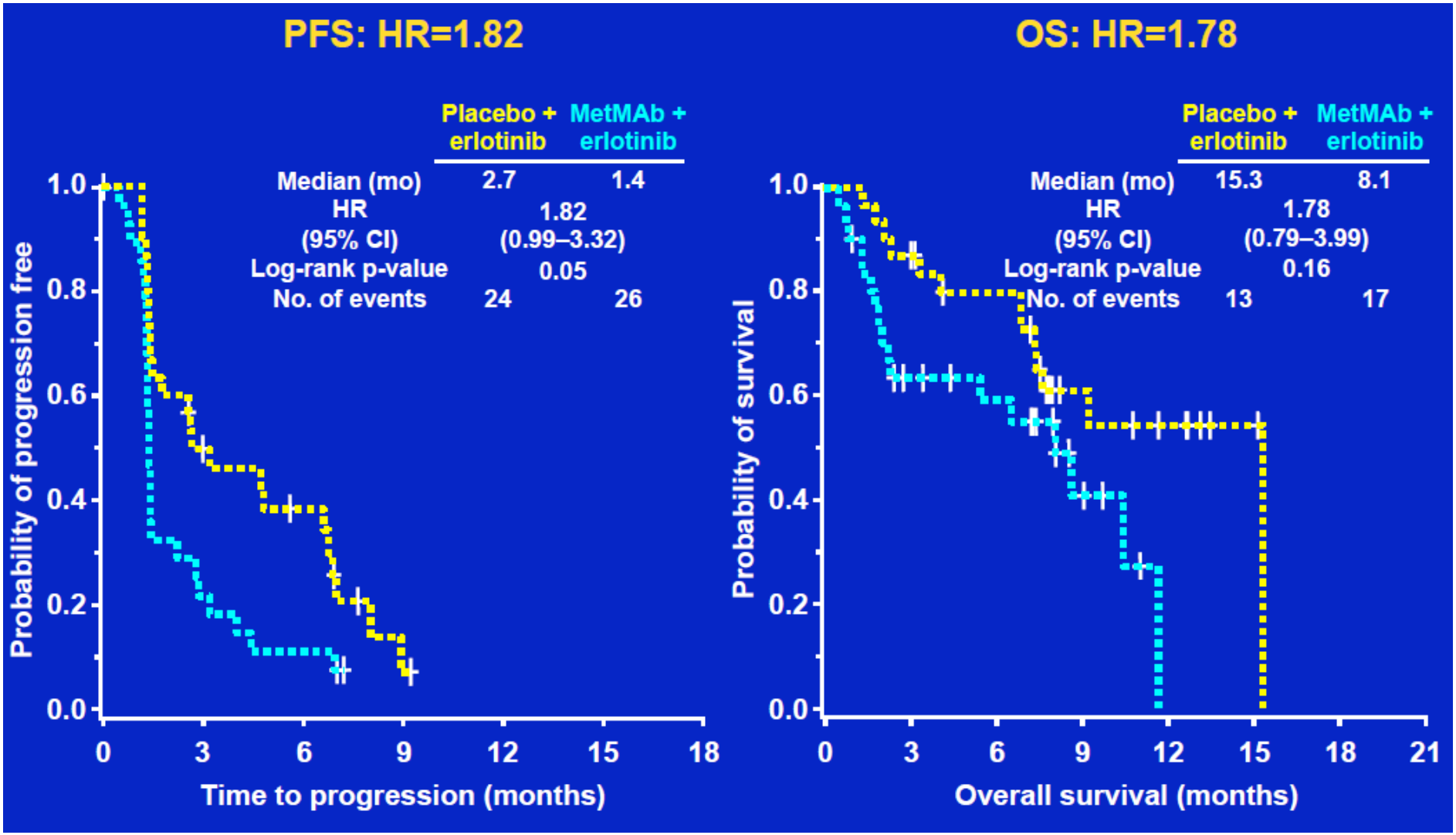
REF: Spigel, Ervin et al, JCO 2013, "Randomized Phase II Trial of Onartuzumab in Combination With Erlotinib in Patients With Advanced Non–Small-Cell Lung Cancer"

PFS and OS: Met High (Dx+) Patients



REF: Spigel, Ervin et al, JCO 2013, "Randomized Phase II Trial of Onartuzumab in Combination With Erlotinib in Patients With Advanced Non–Small-Cell Lung Cancer"

PFS and OS: Met Low (Dx-) Patients

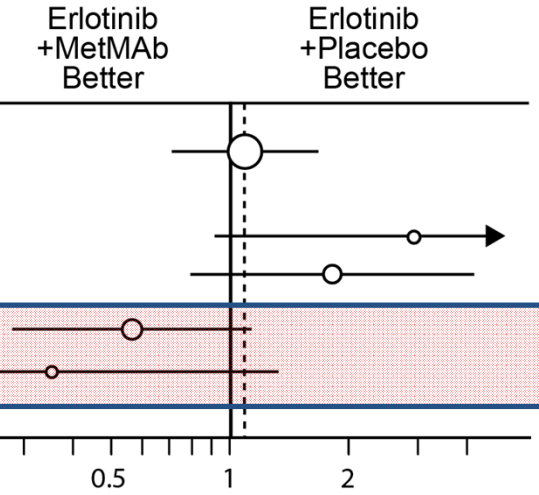


REF: Spigel, Ervin et al, JCO 2013, "Randomized Phase II Trial of Onartuzumab in Combination With Erlotinib in Patients With Advanced Non–Small-Cell Lung Cancer"

IHC Met Cut-off

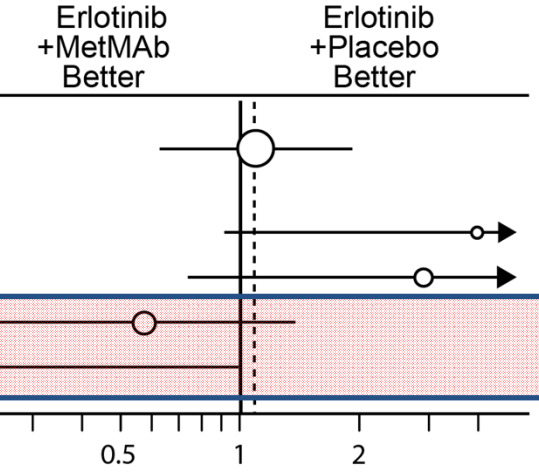
PFS by MET IHC Score (ITT)

Baseline Risk Factor	Erlotinib +Placebo Median (wk)	Erlotinib +MetMAb Median (wk)	Hazard Ratio	(95% CI)	p-Value
All Subjects (n=128)	11.1	9.6	1.09	(0.71–1.67)	0.699
Met IHC Scheme II Score					
0 (n=18)	8.8	5.9	2.94	(0.92–9.40)	0.058
1 (n=38)	11.4	6.1	1.82	(0.79–4.18)	0.151
2 (n=51)	6.4	12.9	0.57	(0.28–1.14)	0.105
3 (n=14)	6.3	11.6	0.36	(0.09–1.33)	0.108



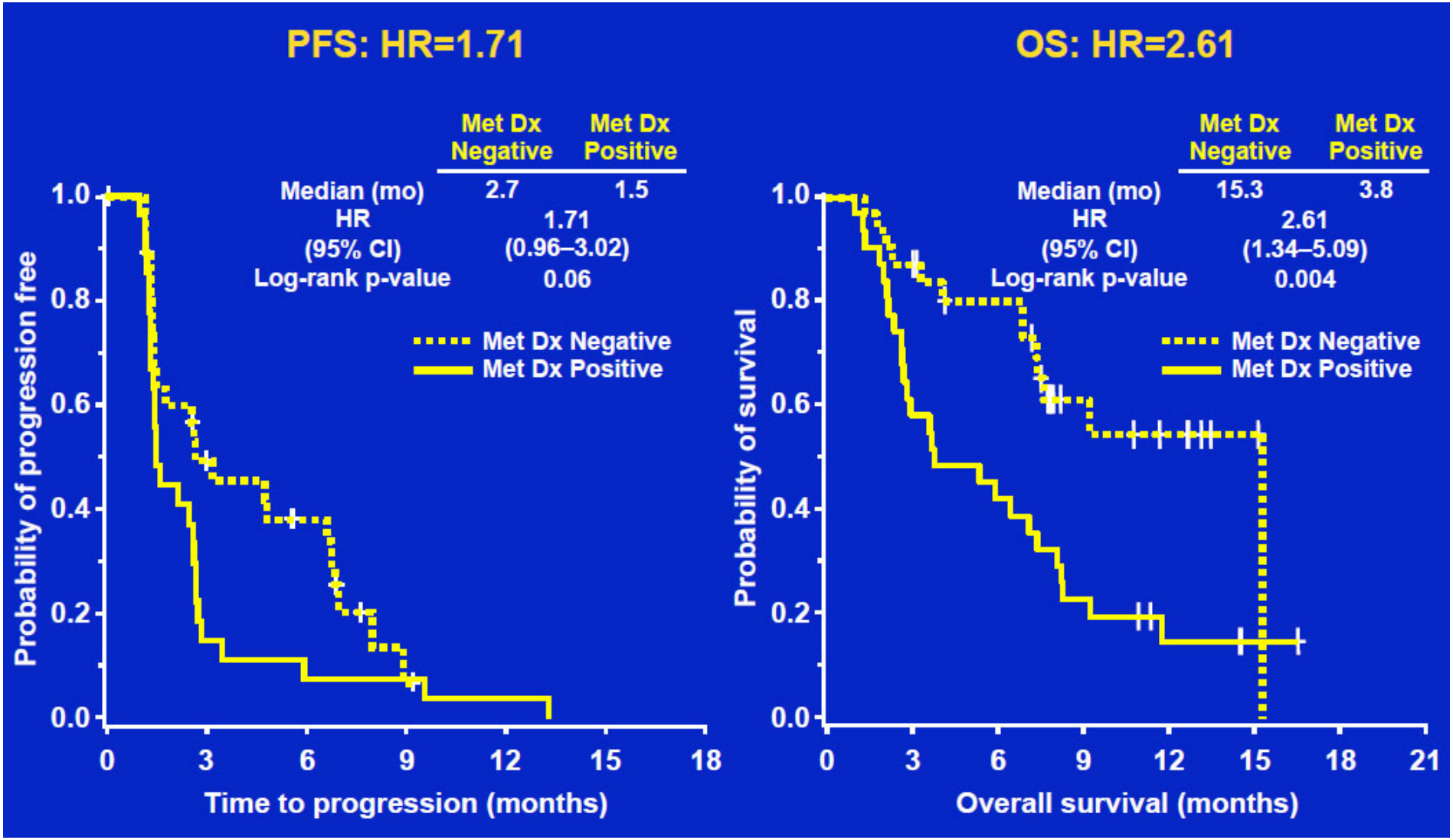
OS by MET IHC Score (ITT)

Baseline Risk Factor	Erlotinib +Placebo Median (mo)	Erlotinib +MetMAb Median (mo)	Hazard Ratio	(95% CI)	p-Value
All Subjects (n=128)	8.2	7.1	1.09	(0.62–1.91)	0.764
Met IHC Scheme II Score					
0 (n=18)	na	2.3	3.98	(0.92–17.23)	0.049
1 (n=38)	9.2	6.5	2.91	(0.74–11.43)	0.110
2 (n=51)	7.4	na	0.57	(0.24–1.39)	0.211
3 (n=14)	3.8	7.1	0.10	(0.01–1.00)	0.018



Met biomarker prognostic

Analysis of patients treated with erlotinib + placebo



REF: Spigel, Ervin et al, JCO 2013, "Randomized Phase II Trial of Onartuzumab in Combination With Erlotinib in Patients With Advanced Non–Small-Cell Lung Cancer"

Summary Phase II PoC study

- Met expression by IHC correlated inversely with prognosis
- MetMab + erlotinib led to improved outcomes in both PFS and OS in Met Diagnostic Positive patients
  - Effect was not driven by key subpopulations or imbalances in baseline characteristics
- Outcomes in the diagnostic subpopulation highlighted the importance of diagnostic development

- **Next steps:** A Phase III study testing Metmab+ erlotinib in Met Dx+ patients was anticipated to start enrolling soon after the previous results became available

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Large investment

- NSCLC and TNBC were planned to be investigated in 2010
- In 2014, program was much larger consisting among others of trials in NSCLC, TNBC, gastric, CRC, GMB etc.

Phase III trial replicated Phase II with only minor changes in design and conduct

Design changes

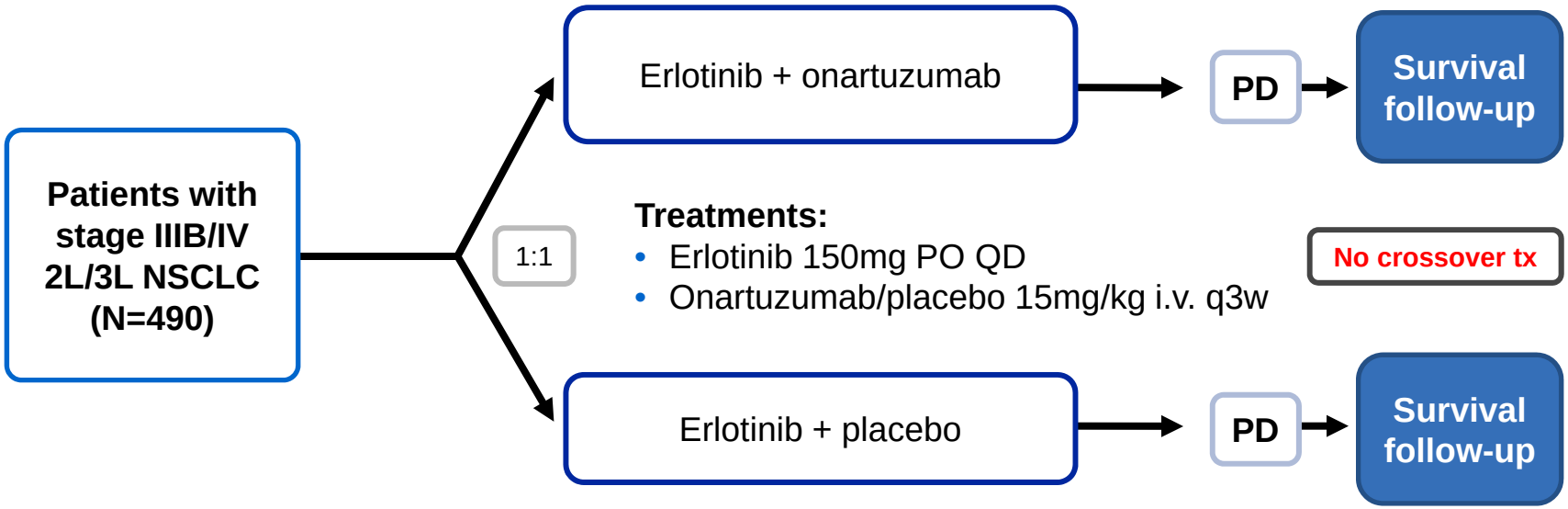
- Treatment schema unchanged
- Same target patient population but selected by MET status
- Primary endpoint of OS rather than PFS

Conduct changes

- Asian and South American sites added, though as in phase 2 majority of enrollment came from North America and Europe

MetLung trial (OAM4971g) design based on Phase II design (OAM4558g)

Minor changes from Phase II design are highlighted in red



Stratification criteria
- EGFR mut vs wt
- MET 2+ vs 3+
- Number of prior treatments
- Histology

Key eligibility criteria
- MET-positive (2+ or 3+)
- 1 prior Pt-based treatment
- ECOG PS 0–1
- Central testing for
  - MET IHC status
  - EGFR mutation status

Primary endpoint
- OS

Secondary endpoints
- PFS
- ORR
- QoL
- Safety
- PK

*MetLung (OAM4971g, NCT01456325); EGFR = epidermal growth factor receptor; ECOG PS = Eastern Cooperative Oncology Group performance status; IHC = immunohistochemistry; i.v. = intravenous; NSCLC = non-small-cell lung cancer; ORR = overall response rate; OS = overall survival; PD = progression of disease; p.o. = by mouth; PFS = progression-free survival; Pt = platinum; QoL = quality of life; q3w = every 3 weeks

*Spigel, Edelmann, JCO 2017, "Results From the Phase III Randomized Trial of Onartuzumab Plus Erlotinib Versus Erlotinib in Previously Treated Stage IIIB or IV Non–Small-Cell Lung Cancer: METLung"

MetLung recruited patient population similar to Ph II:

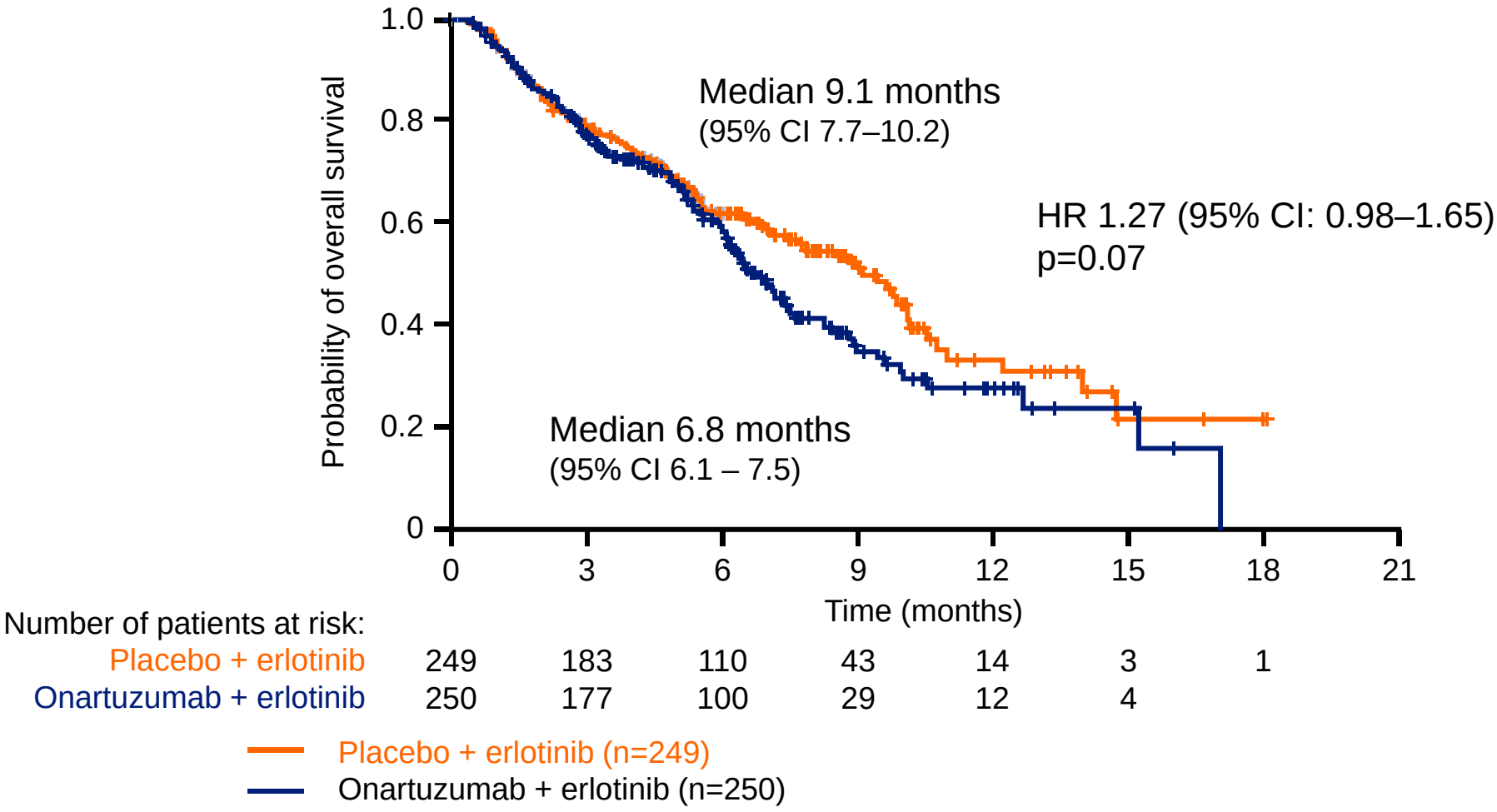
Comparison of demographics/disease characteristics

	MetLung (Ph 3)		OAM4558g Ph 2 (MET+)	
	Pcbo + Erl N=249	Onar + Erl N=250	Pcbo + Erl N=31	Onar + Erl N=35
Age, median yrs	63	62	64	66
Gender (M%/F%)	56/44	56/44	65/35	51/49
White/Asian (%)	72 / 15	73 / 14	90 / 3	91 / 3
Non-Squam/ Sq (%)	88 / 12	84 / 16	84 / 16	86 / 14
EGFR Mut+ (%)	11.6	11.2	8	23
MET IHC 2+/3+ (%)	78 / 22	79 / 21	81 / 19	74 / 26
2L/3L (%)	63 /37	64 /36	71 / 29	63 / 37
ECOG 0-1 / 2 (%)	99.2 / 0.4	98.4 / 1.6	94 / 6	97 / 3
Time from Ca Dx→ Randomization (months, range)	12.7 (1.9-97.3)	11.7 (1.1-90.7)	10.6 (3-96)	12.6 (3-42)

*Spigel, Edelmann, JCO 2017, "Results From the Phase III Randomized Trial of Onartuzumab Plus Erlotinib Versus Erlotinib in Previously Treated Stage IIIB or IV Non–Small-Cell Lung Cancer: METLung"

Spigel, Ervin et al, JCO 2013, "Randomized Phase II Trial of Onartuzumab in Combination With Erlotinib in Patients With Advanced Non–Small-Cell Lung Cancer"

MetLung Phase III did not reproduce benefit observed in Phase II in MET+ patients



Trial terminated early for crossing futility boundary at recommendation of IDMC at 244/364 OS events

No treatment effect seen in any efficacy endpoint in MetLung trial

	MetLung (Phase 3)		OAM4558g (Phase 2)			
			ITT		MET+	
	Pcbo + Erl (n=249)	Onar + Erl (n=250)	Pcbo+ Erl (n=68)	Onar + Erl (n=69)	Pcbo+ Erl (n=31)	Onar + Erl (n=35)
OS median months (95%CI)	9.1 (7.7 – 10.2)	6.8 (6.1-7.5)	7.4 (5.9-9.2)	8.9 (7.1-12.7)	3.8 (2.7-7.4)	12.6 (7.1-NE)
HR (95% CI, p value) stratified	1.27 (0.98-1.65, p=0.07)		0.80 (0.50,1.28, p=0.34)		0.37 (0.19,0.72,p=0.002)	
PFS median months (95%CI)	2.6 (1.5-2.8)	2.7 (2.4-2.9)	2.6 (1.5-2.8)	2.2 (1.4-2.9)	1.5 (1.4-2.6)	2.9 (1.4-6.2)
HR (95% CI, p value) stratified	0.99 (0.81,1.20, p=0.92)		1.09 (0.73,1.62,p=0.69)		0.53 (0.28,0.99, p=0.04)	
Confirmed ORR (%)	8.8	6.4	4.4	5.8	3.2	8.6

*Spigel, Edelmann, JCO 2017, "Results From the Phase III Randomized Trial of Onartuzumab Plus Erlotinib Versus Erlotinib in Previously Treated Stage IIIB or IV Non–Small-Cell Lung Cancer: METLung"

Spigel, Ervin et al, JCO 2013, "Randomized Phase II Trial of Onartuzumab in Combination With Erlotinib in Patients With Advanced Non–Small-Cell Lung Cancer"

Final analyses from other trials: Clinical benefit observed only in PoC study

Indication	Treatment	PFS (ITT)	PFS (MET+)	OS (ITT)	OS (MET+)
OAM4558g **2L/3L NSCLC**	Erlotinib +/- Onartuzumab	1.09	0.53	0.80	0.37
OAM4861g **1L/2L TNBC**	Pac +/- Onartuzumab	1.74	*	1.92	*
	Pac + Bev +/- Onartuzumab	1.08	*	1.36	*
GO27821 **1L NSCLC Nsq**	Pt + Pac + Bev +/- Onartuzumab	1.24	1.71	1.34	2.00
	Pt + Pem +/- Onartuzumab	1.23	1.25	1.15	1.17
GO27820 **1L NSCLC Sq**	Pt + Pac +/- Onartuzumab	0.95	1.27	0.90	0.81
GO278219 **rGBM**	Bev +/- Onartuzumab	1.06	*	1.45	*
GO27827 **1L mCRC**	FOLFOX + Bev +/- Onartuzumab	0.75	1.03	0.96	1.24
YO28252 **1L Her2- GC**	FOLFOX +/- Onartuzumab	1.08	1.38	1.06	1.12

*Insufficient sample size to evaluate MET 2+/3+ population

REFERENCES: All published studies

Any other reasons for discrepancy?

1) Robustness of PFS and OS results meant that the Phase II sample size was not an issue

- Because of the strength of results, increasing sample size unlikely to have changed outcome/decision
- Extensive simulations & modeling done

2) Absence of single agent activity in the clinic

3) MET IHC measured only one part of the MET pathway, but did not account for other variables (i.e. level of local ligand HGF)

- Uncovered potential role of HGF as biomarker only later (due to technical advancements)

4) Negative prognostic effect not definitively proven despite results from Phase II

  - Evaluation from prior NSCLC studies inconclusive
  - Prospective data at that time was weighted stronger than retrospective data
  - Subsequent NSCLC trials of MetMAb did not confirm negative prognostic effect of Met

Met biomarker outcomes beyond the MetMAb program

- **Correlated risk beyond a single company?**
- **Negative study data have been published for**
  - Rilotumumab (example **REF:** Cunningham & Tebbutt et al. Phase III, randomized, double-blind, multicenter, placebo (P)-controlled trial of rilotumumab (R) plus epirubicin, cisplatin and capecitabine (ECX) as first-line therapy in patients (pts) with advanced MET-positive (pos) gastric or gastroesophageal junction (G/GEJ) cancer: RILOMET-1 study. *J Clin Oncol*. 2015;33)
  - Ficlatuzumab (example **REF**: Mok & Geater et al. A Randomized Phase 2 Study Comparing the Combination of Ficlatuzumab and Gefitinib with Gefitinib Alone in Asian Patients with Advanced Stage Pulmonary Adenocarcinoma J Thorac Oncol. 2016)
  - both of which are biologics and block hepatocyte growth factor (HGF) binding to MET receptor

Summary

- The Ph III METLung Study was a well-conducted, well-balanced study with a patient population that was consistent with the Phase II study population.
- The MET IHC companion diagnostic performed well.
- No clinical variable were identified that accounts for the large discrepancy in outcomes between the Ph II & III
- “Conclusion”: Phase II study was an outlier, in which PFS and OS appeared to correlate with increasing MET expression (IHC 0 through 3+), a pre-specified biomarker-defined subset, leading to the false conclusion that MET expression was a clear predictive marker for MetMAb activity.

Key Lessons

- When a biomarker hypothesis is evaluated in a trial, its association with outcome should be treated cautiously until confirmed in a second study.
- For broad programs there is a correlated risk that should be assessed to fully understand potential risk-adjusted value of a program

Doing now what patients need next