Overall Response Rate, Progression-Free Survival, and Overall Survival with Targeted and Standard Therapies in Advanced Non–Small-Cell Lung Cancer

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Outline

- Background
- Purpose
- Trial Selection
- Statistical Approach
- Results
- Conclusion

Background

- Lung cancer: Leading cause for cancer-related death
  - 224,390 new cases, 158,080 deaths in US in 2016
  - 85%-90% are Non-small Cell Lung Cancer (NSCLC)
- Majority of patients diagnosed at advanced stage
- New therapies needed to cure, prolong survival, delay progression, or improve symptoms

Paradigm Shift in Lung Cancer

- Traditionally classified based on histology
  - Small cell vs. non small cell, adenocarcinoma vs. squamous, etc.
- Increasingly classified by underlying oncogenic driver mutation subset due to improved genomic technologies and molecular profiling
- Targeted therapy developed to inhibit oncogenic pathways
  - EGFR, ALK inhibitors: high and durable overall response rate (ORR)

Approval for treatment of advanced NSCLC

- Regular approval based on improvement in symptoms, functions, overall survival (OS), or progression-free survival (PFS) of large magnitude

- Accelerated approval based on surrogate endpoint reasonably likely to predict clinical benefit, e.g. high and durable ORR
  - Advantage of ORR: tumor response directly attributed to therapy
  - More than 30-years experience of response criteria enables comparisons with historic controls

Purpose

- Relationship between ORR and PFS or ORR and OS in advanced NSCLC not established
- Meta-analysis using advanced NSCLC trials to evaluate the relationship between ORR and PFS/OS

Trial Selection

- New Drug or Biologics License Applications submitted for treatment of advanced NSCLC between 2003-2013
- Randomized, multicenter, active-controlled trials with at least 150 patients
- Identified 14 trials with 15 comparisons
  - 8 head-to-head trials (Drug A vs. Drug C)
    6 add-on trials (Drug A+B vs. Drug A)
  - 3 targeted trials (2 EGFR mutation positive, 1 ALK positive)

Outcome Measures

- ORR: proportion of patients who achieved a complete or partial response
- PFS: Time from randomization to progression or death
- OS: Time from randomization to death

Statistical approach

Buyse's criteria (2000)

- "trial-level" association: treatment effect on the surrogate tightly correlated with the treatment effect on the true endpoint at trial level

- "individual-level" association: surrogate tightly correlated with the true endpoint at patient level

Trial-level association

- Treatment effect estimates
  - PFS: hazard ratio (HR) from Cox regression model
  - OS: HR from Cox regression model
  - ORR: odds ratio from logistic regression model

- Weighted linear regression model performed on log-transformed effects
  - weights equal to number of patients
  - R^2 used to quantify the proportion of variance explained by the regression

Individual-level association

Patient-level responder analysis performed to compare PFS and OS between responders and non-responders, irrespective of treatment assignment using the pooled dataset

- Hazard ratios of PFS and OS estimated from Cox model stratified by study
- Kaplan-Meier estimates of PFS and OS by response status
- Multivariable analyses using Cox regression models including baseline factors (age, race, smoking status, histology, performance status, and number of prior lines of therapy) and response status

Individual-level association (Cont'd)

- Individual-level association estimated by θ , the consistent odds ratio for surviving beyond any time t in responders versus non-responders (Burzykowski, 2004)

- Supportive analysis: Landmark method to eliminate possible length-bias

Summary of Trials

Drug	Control Arm	Design	N	Patient Population	Primary Endpoint
Crizotinib	Pem (or doc)	H-H	347	2L ALK+	PFS (IRC)
Afatinib	Cis + pem	H-H	345	1L EGFRm	PFS (IRC)
Erlotinib	Cis (car) + doc (gem)	H-H	174	1L EGFRm	PFS (INV)
Nab-pac + car	Car + pac	H-H	1,052	1L	ORR (IRC)
Cetuximab	Car + tax	A-O	676	1L	PFS (IRC)
Cetuximab	Cis + vin	A-O	1,125	1L	OS
Vandetanib	Erl	H-H	1,240	2L+	PFS (INV)
Vandetanib	Pem	A-O	534	2L+	PFS (INV)
Vandetanib	Doc	A-O	1,391	2L+	PFS (INV)
Gefitinib	Doc	H-H	1,466	2L+	OS (NI)
Bevacizumab	Cis + gem	A-O	692	1L NSq	PFS (INV)
Bevacizumab	Cis + gem	A-O	698	1L NSq	PFS (INV)
Pemetrexed + cis	Cis + gem	H-H	1,725	1L	OS (NI)
Bevacizumab	Car + pac	A-O	878	1L NSq	OS
Pemetrexed	Doc	H-H	571	2L	OS (NI)

Summary of Trials (Cont'd)

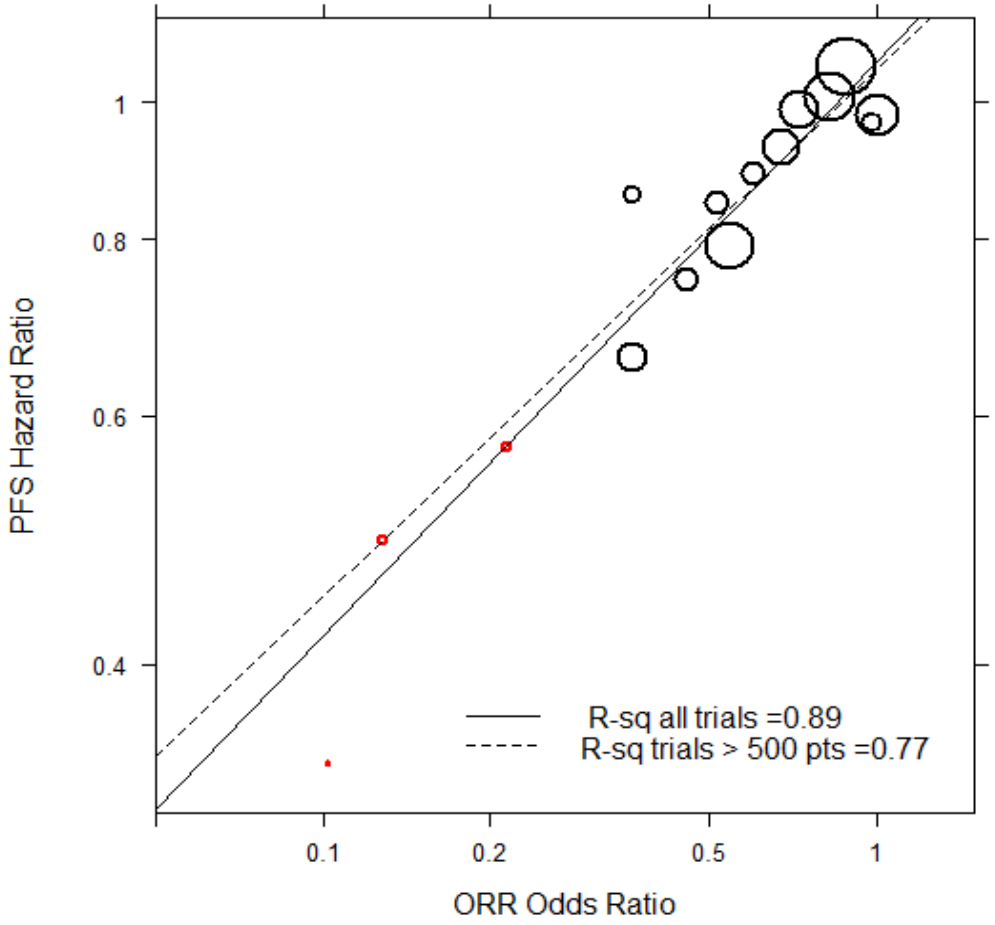
Drug	Control (design)	N	ORR OR	ORR (%)	PFS HR	Median PFS	OS HR	Median OS
Crizotinib	Pem (or doc) (HH)	347	0.13	65 v. 20	0.49	7.7 v. 3	1.04	20.3 v. 22.8
Afatinib	Cis + pem (HH)	345	0.21	56 v. 23	0.58	11.1 v. 6.9	0.91	28.1 v. 28.2
Erlotinib	Cis (car) + doc (gem) (HH)	174	0.10	65 v. 16	0.34	10.4 v. 5.2	0.93	22.9 v. 19.5
Nab-pac + car	Car + pac (HH)	1,052	0.68	33 v. 25	0.93	6.3 v. 5.8	0.93	12.1 v. 11.2
Cetuximab	Cis + tax (AO)	676	0.60	26 v. 17	0.89	4.4 v. 4.2	0.95	9.7 v. 8.4
Cetuximab	Cis + vin (AO)	1,125	0.72	36 v. 29	0.99	4.7 v. 4.9	0.90	11.3 v. 10.1
Vandetanib	Erl (HH)	1,240	1.00	12 v. 12	0.98	2.6 v. 2.1	1.01	6.9 v. 7.8
Vandetanib	Pem (AO)	534	0.36	19 v. 8	0.86	4.0 v. 2.7	0.86	10.5 v. 9.2
Vandetanib	Doc (AO)	1,391	0.54	17 v. 10	0.79	4.0 v. 3.2	0.91	10.6 v. 10
Gefitinib	Doc (HH)	1,466	0.82	8 v. 7	1.01	2.2 v. 2.7	1.02	8.4 v. 7.5
Bevacizumab	Cis + gem (AO)	692	0.45	37 v. 22	0.75	6.7 v. 6.1	0.93	13.6 v. 13.1
Bevacizumab	Cis + gem (AO)	698	0.52	34 v. 22	0.85	6.5 v. 6.1	1.03	13.4 v. 13.1
Pemetrexed + cis	Cis + gem (HH)	1,725	0.88	27 v. 25	1.06	4.8 v. 5.1	0.93	10.3 v. 10.3
Bevacizumab	Car + pac (AO)	878	0.37	27 v. 12	0.66	6.2 v. 4.5	0.80	12.3 v. 10.3
Pemetrexed	Doc (HH)	571	0.98	9 v. 8	0.97	2.9 v. 2.9	0.99	8.3 v. 7.9

Demographics and Disease Characteristics

Variable	Result
Median age (range)	60 (18-92)
Gender	Male: 64% Female: 36%
Race	White: 76% Black: 2% Asian: 20% Other: 2%
Region	US: 20% Non-US: 80%

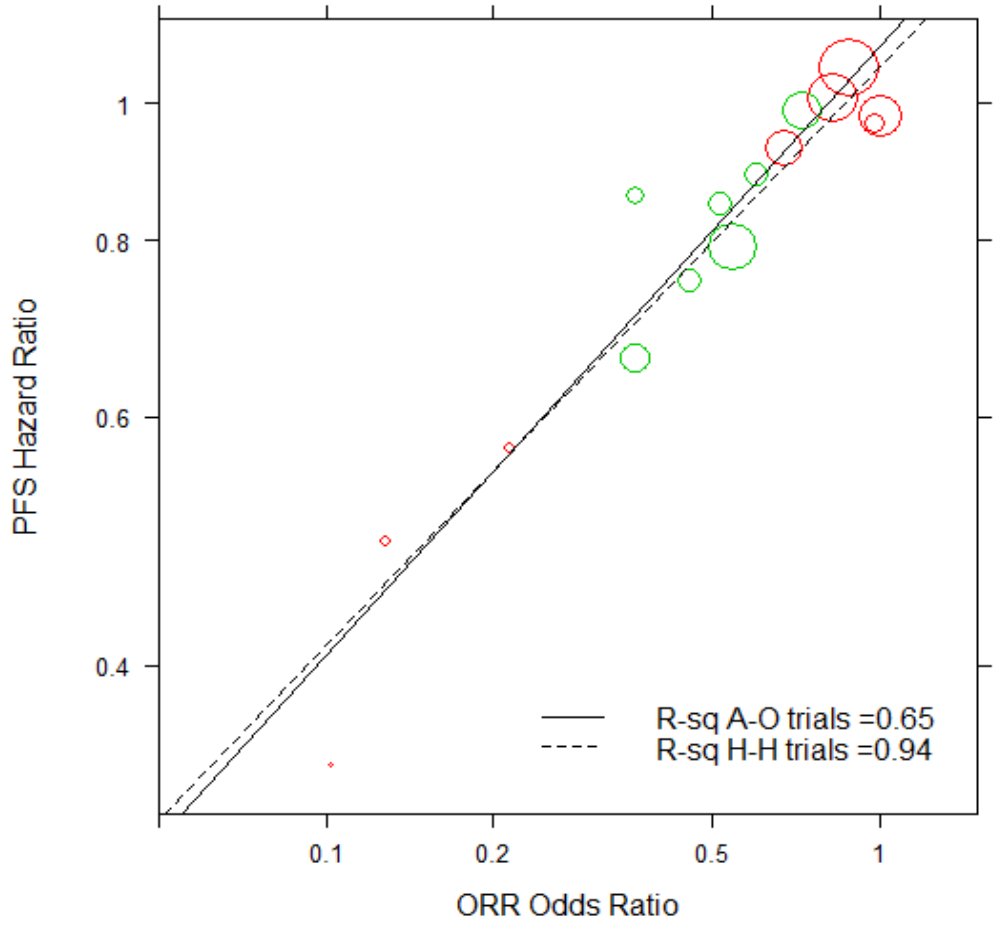
Variable	Result
Smoking status	Never: 25% Former/Current: 75%
Histology	Squamous: 21% Nonsquamous: 79%
Performance status	0: 32% 1: 63% 2: 5%
Prior lines of therapy	0: 56% 1: 38% 2: 6%

Trial-level association results: PFS vs. ORR



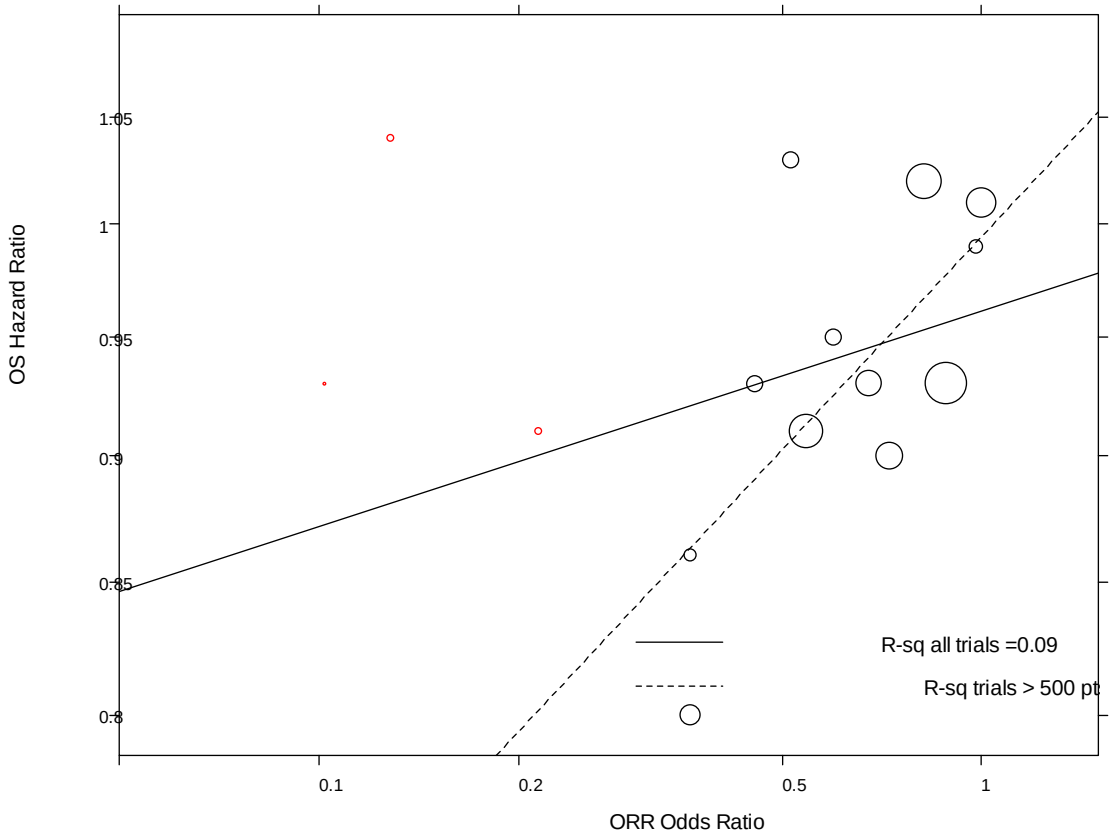
- trials <= 500 pts

Trial-level association results: PFS vs. ORR by trial type



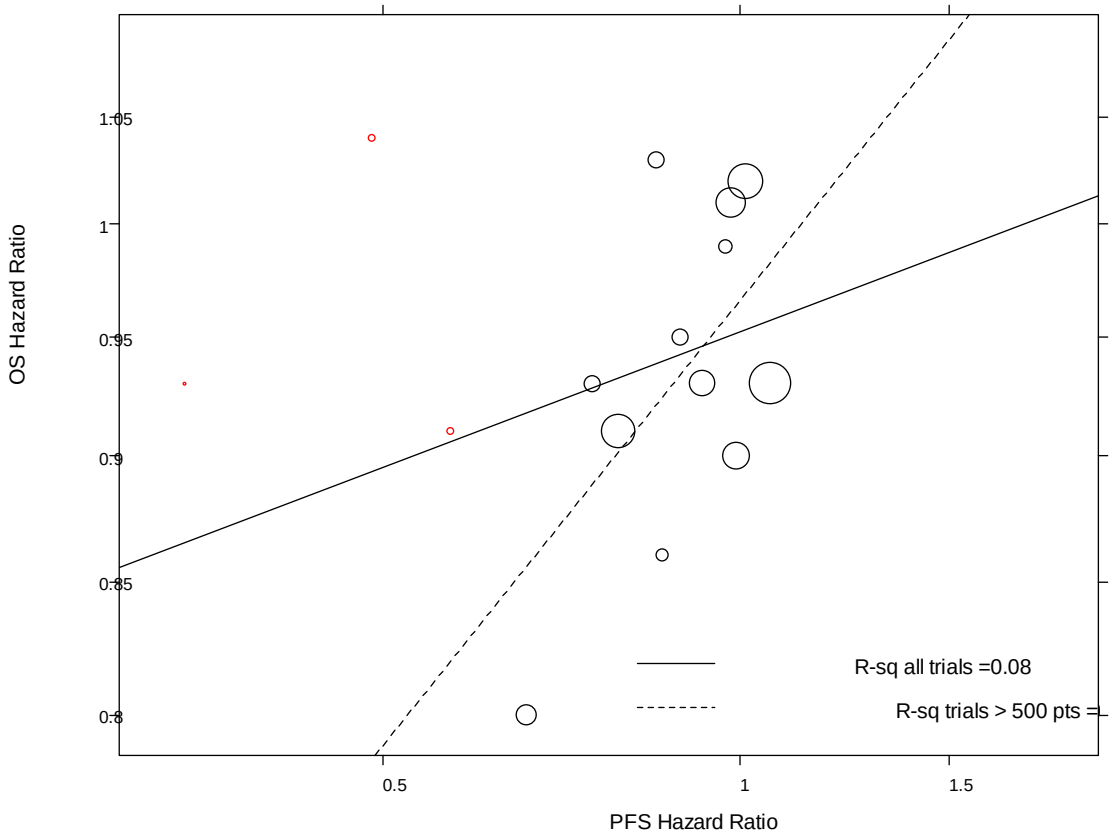
- Add-on trials
- Head-to-head trials

Trial-level association results: OS vs. ORR



- trials <= 500 pts

Trial-level association results: OS vs. PFS

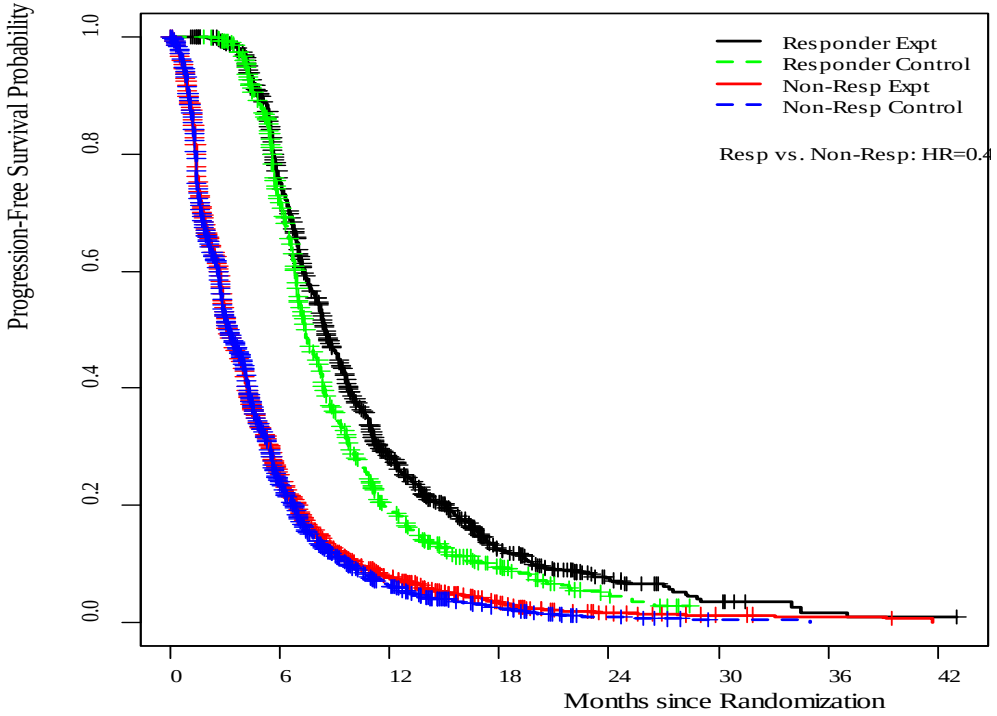


- trials <= 500 pts

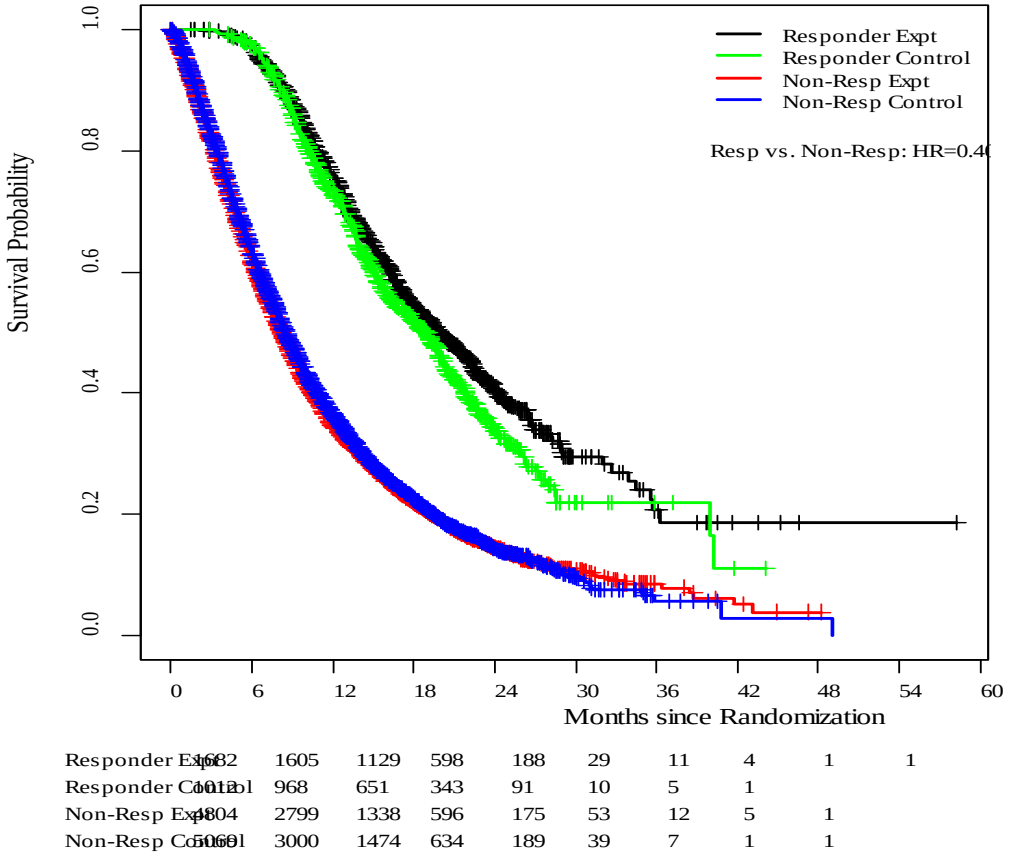
Individual-level association results irrespective of treatment received

- Responders were associated with better PFS (HR=0.40, 95% CI: 0.38, 0.42) compared with non-responders
- Responders were associated with better OS (HR=0.40, 95% CI: 0.38, 0.43) compared with non-responders
- Multivariable Cox model adjusted by baseline factors (age, race, smoking status, histology, performance status, and number of prior lines of therapy) shows consistent association

KM estimates of PFS between responders and nonresponders



KM estimates of OS between responders and nonresponders



Individual-level association results (Cont'd)

- Association between PFS and ORR: $\theta = 7.11$ (95% CI: 6.52, 7.70)
- Association between OS and ORR: $\theta = 4.66$ (95% CI: 4.27, 5.06)
- Supportive analyses using a landmark at different time points (2.5, 3, 4, and 5 months) show an individual association between PFS and ORR and between OS and ORR

Conclusion

- Strong patient-level association between ORR and PFS, and ORR and OS
- Strong trial-level association between ORR and PFS
- Weak or no correlation between either ORR and OS or PFS and OS
  - Possible explanation: no relationship (not a surrogate) or high cross-over, subsequent therapies, and long post-progression survival confound analysis

Conclusion (Cont'd)

A drug with a large magnitude of effect on ORR in patients with advanced NSCLC may have a large effect on PFS.