Is Immunotherapy a 1st Line Treatment in NSCLC? Case Against

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Disclosures

Honoraria for advisory board work or speaker bureau activites from Pfizer, Roche, AZD, BI, BMS, Lilly, MSD

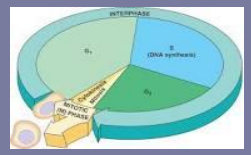
Key Messages

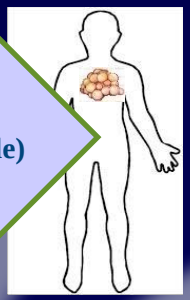
- Chemotherapy remains the cornerstone of 1st line patient care in advanced NSCLC
- Targeted therapies required rigorous evaluation before replacing established first line regimens
  - EGFR TKIs and ALK inhibitors of value in ~20% patients with non-squamous NSCLC (higher in East Asia)
- The results of Immune Checkpoint therapies show limited, albeit encouraging, activity relative to the enthusiasm surrounding their efficacy
  - Phase III data needed to establish their role in 1st line therapy of NSCLC

Evolution of Approaches to Drug Improvements in NSCLC

HISTORICAL

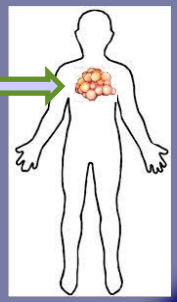
CYTOTOXIC CHEMOTHERAPY
Targets rapidly dividing cells (cell cycle)
Systemic effects





1990's

KINASE INHIBITION
Targets tumor itself; acquired resistance



Today

RATIONAL USE OF MULTIPLE MODALITIES

Leverage strengths of each approach

Overcome weaknesses

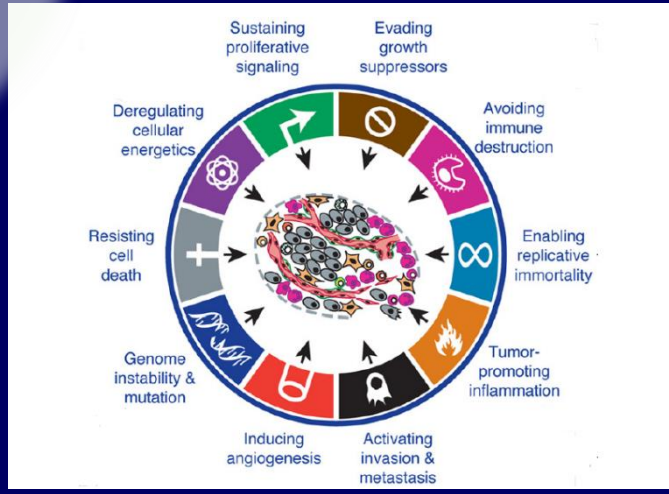


Image adapted with permission from Hanahan D, Weinberg RA. *Cell*. 2011;144(5):646-674.

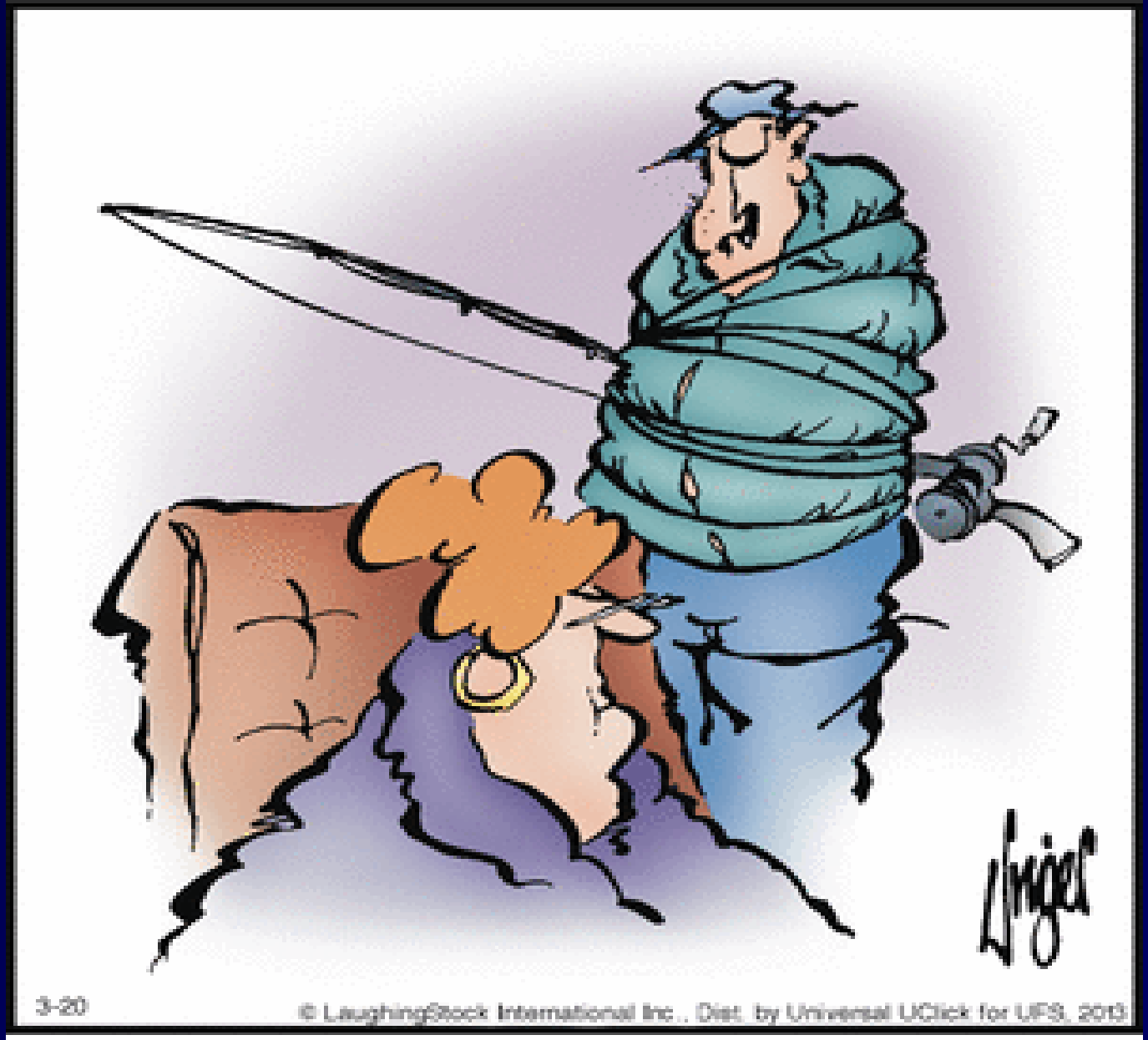
1. Hanahan D, Weinberg RA. *Cell*. 2011;144(5):646-674.

Immune Therapy

Optimism

vs

Scientific Method, Reality



"I hooked a real big one but it kept swimming around the boat."

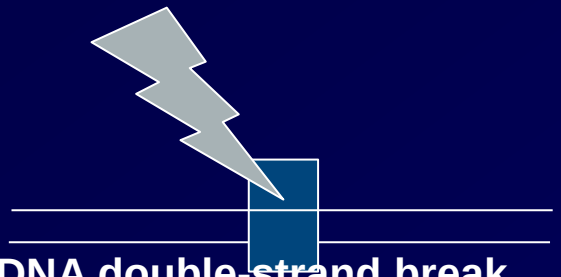
Fueling the Optimism

- Academic enthusiasm
- Modern science
  - Increased understanding of immune biology in malignant disease
  - Technology to rapidly interrogate a target: we're learning how to do things better
  - Media links: we have all become immuno-oncologists overnight
- Huge investment by pharma and biotech companies
  - Multiple agents for same target/pathway
  - Multiple targets

Immune privilege

DNA instability

Ionising irradiation
Chemotherapeutic agents
Products of normal cellular metabolism



DNA double-strand break

Repair defect/Age

Genomic instability

Cancer

Deregulation of DNA repair pathways

Tumor genetic heterogeneity

Environmental adaptation

Invasion

Metastisis

Resistance

Genome stability and cancer

BRCA1, BRCA2, Homologous recombination: Breast and ovarian cancers

ATM, Homologous recombination: Breast, leukemia and lymphoma

NBS1, Homologous recombination: Lymphoid malignancies

MREII, Homologous recombination: Breast cancer

BLM, Homologous recombination: Leukemia, lymphomas, colon, breast, skin, tongue, lung, stomache…

WRN, Homologous and non homologous recombination: sarcomas, skin, thyroid and pancreatic cancers

RECQ4, Homologous recombination: Rothmund-Thomas syndrome, Rapadilino syndrome and Baller Gerold syndrome

FANC1, FANCB, FANCC, FANCD1, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FANCN, Homologous recombination and translesion synthesis: leukemia, liver and many solid cancers.

XPC, XPE, Nucleotide excision repair: skin cancer and melanoma.

XPA, XPB, XPD, XPF, XPG, Nucleotide excision repair: skin cancer, melanoma, central nervous system cancers.

XPV, translesion synthesis: Skin cancer and melanoma

hMSH2, hMSH6, hMLH1, hPMS2, Miss match repair: colorectal, endometrial and ovarian cancers.

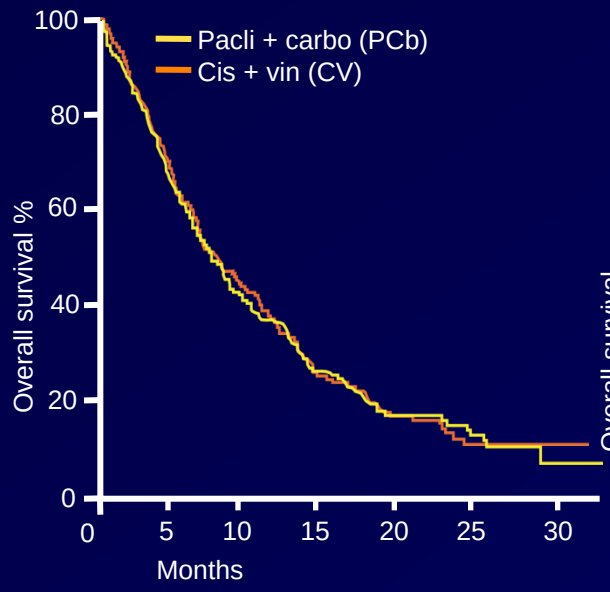
MUTYH, base excision repair, and miss match repair: colon cancer.

***Nature Reviews Cancer* 3, 952-959 (December 2003)**

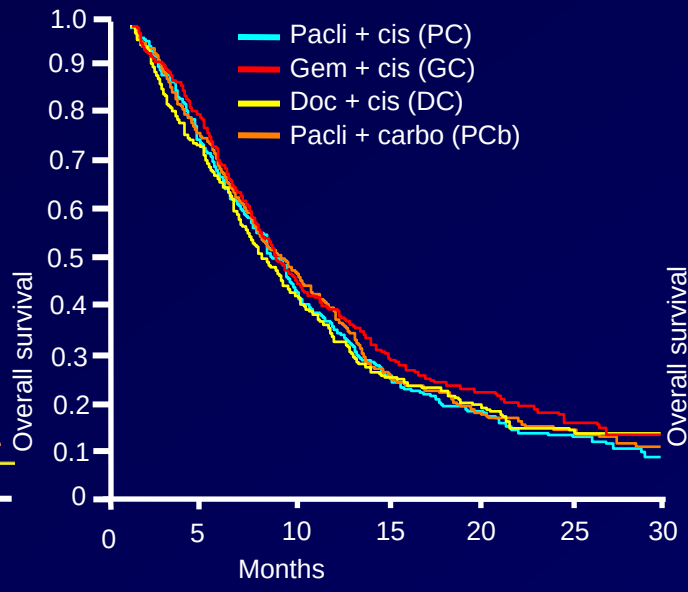
Efficacy of Chemotherapy
1st Line:

What we know

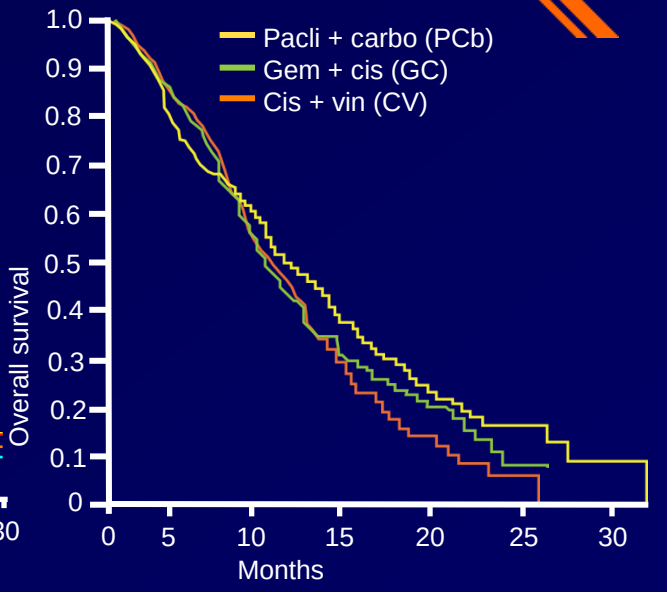
1st-line platinum-based CT: Efficacy plateau



Study arm	OS (mo)	1 year (%)
PCb	8.6	38
CV	8.1	36



Study arm	OS (mo)	1 year (%)
PC	7.8	31
GC	8.1	36
DC	7.4	31
PCb	8.1	34



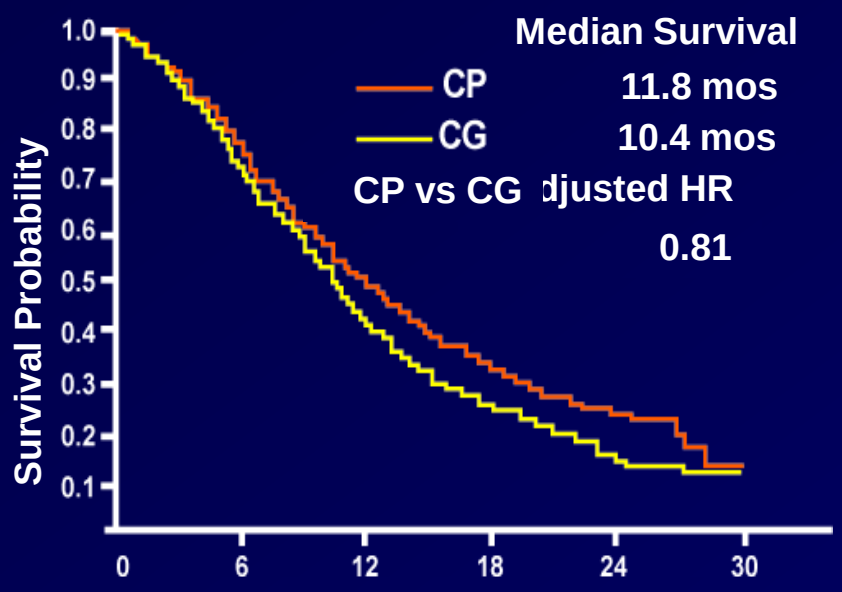
Study arm	OS (mo)	1 year (%)
PCb	9.9	43
GC	9.8	37
CV	9.5	37

OS, overall survival

Kelly et al. JCO 2001; Schiller et al. NEJM2002; Scagliotti et al. JCO 2002

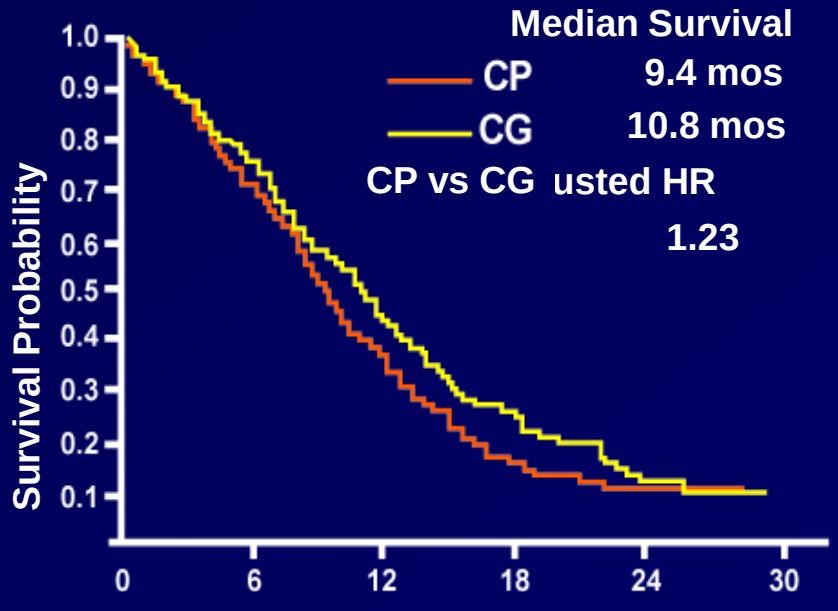
Cisplatin/Pemetrexed vs Cisplatin/ Gemcitabine in Advanced NSCLC: Results

Nonsquamous



Survival Time (months) in Patients With Nonsquamous Histology

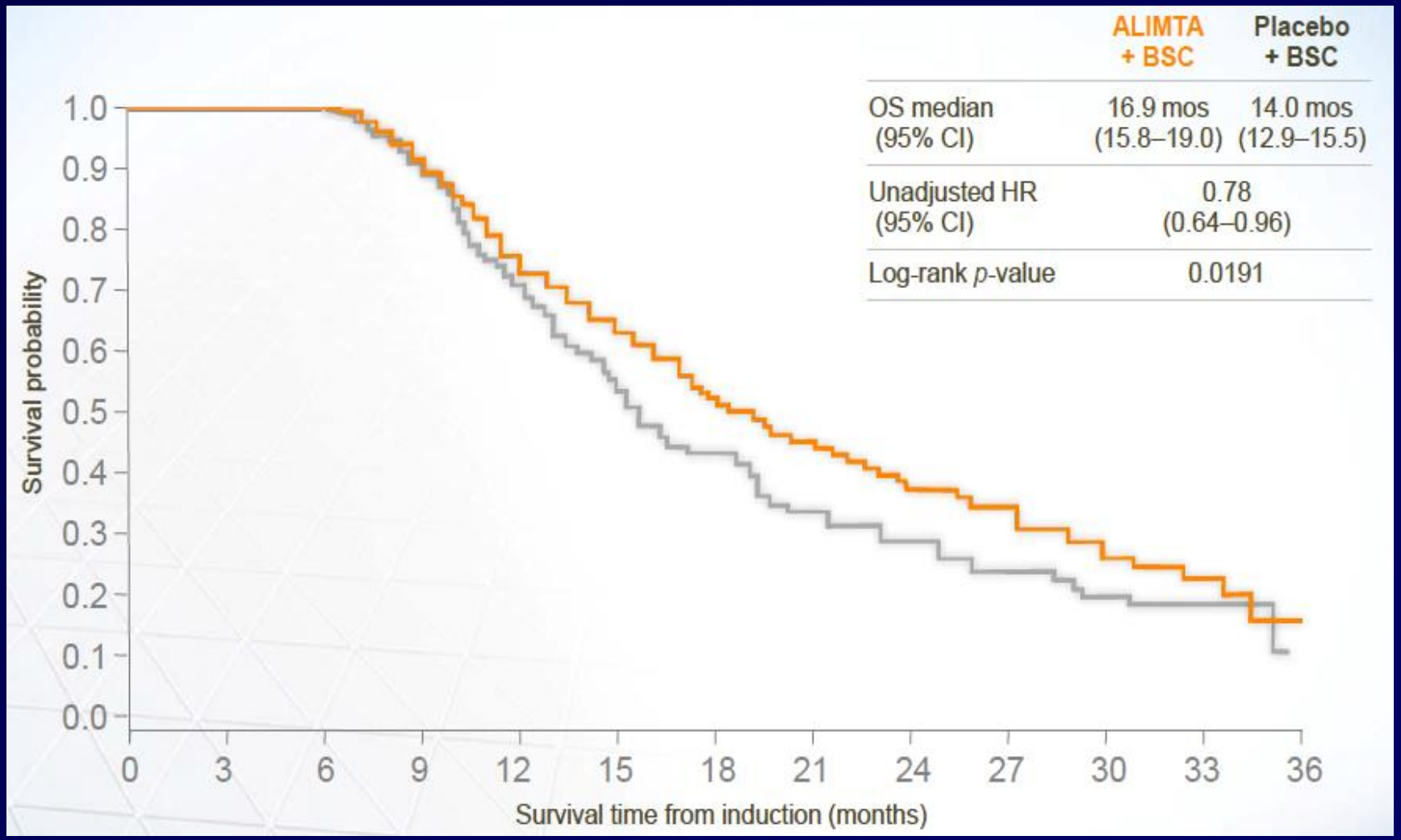
Squamous



Survival Time (months) in Patients With SCC

Scagliotti, G. *J Clin Oncol. 2008*

Maintenance Therapy: Paramount Overall Survival Data



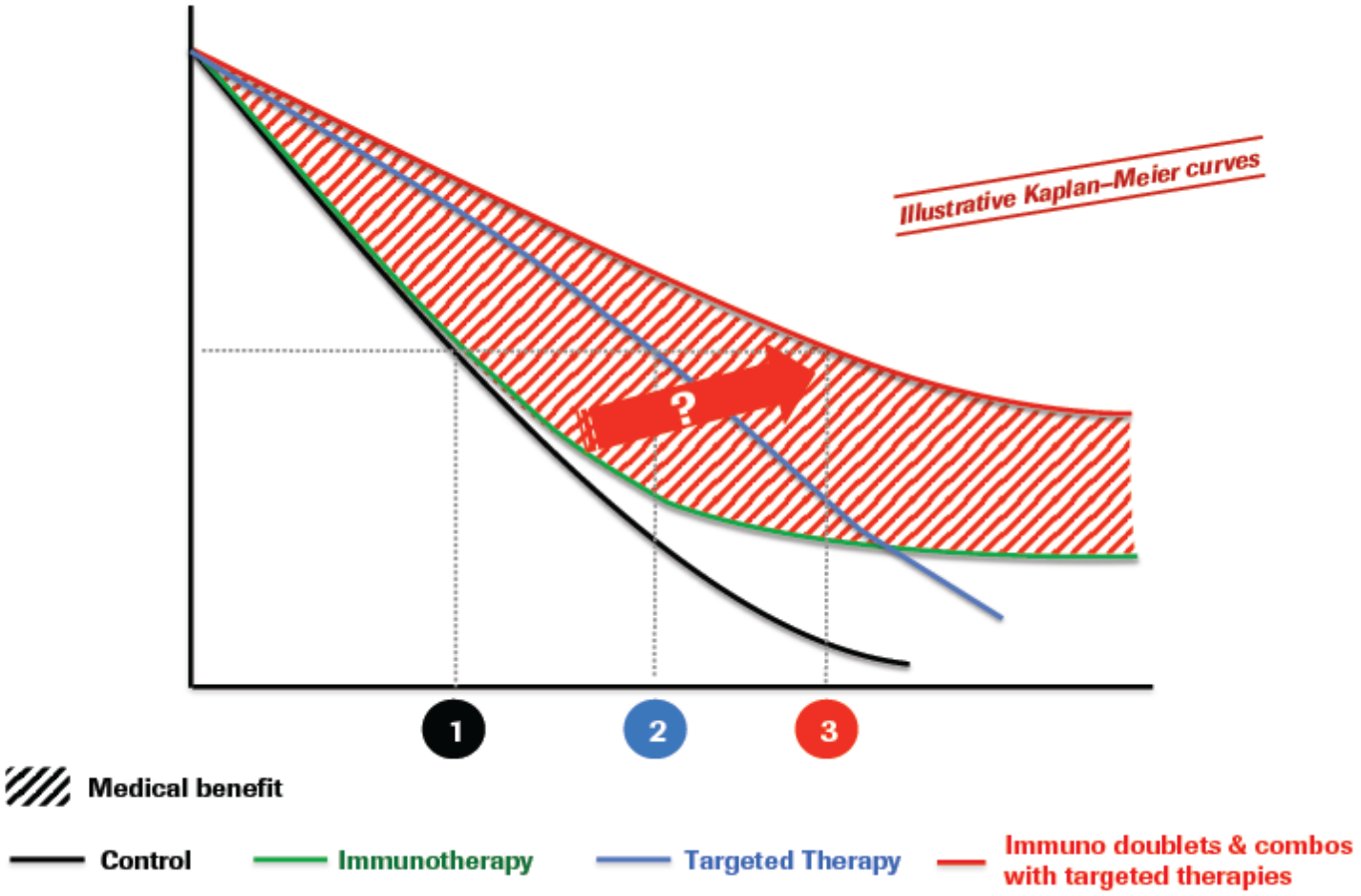
Paz Ares L et al, J Clin Oncol 2013; 31(23): 2895-902

Efficacy of Immune Checkpoint chemotherapy 1st Line:

What we know

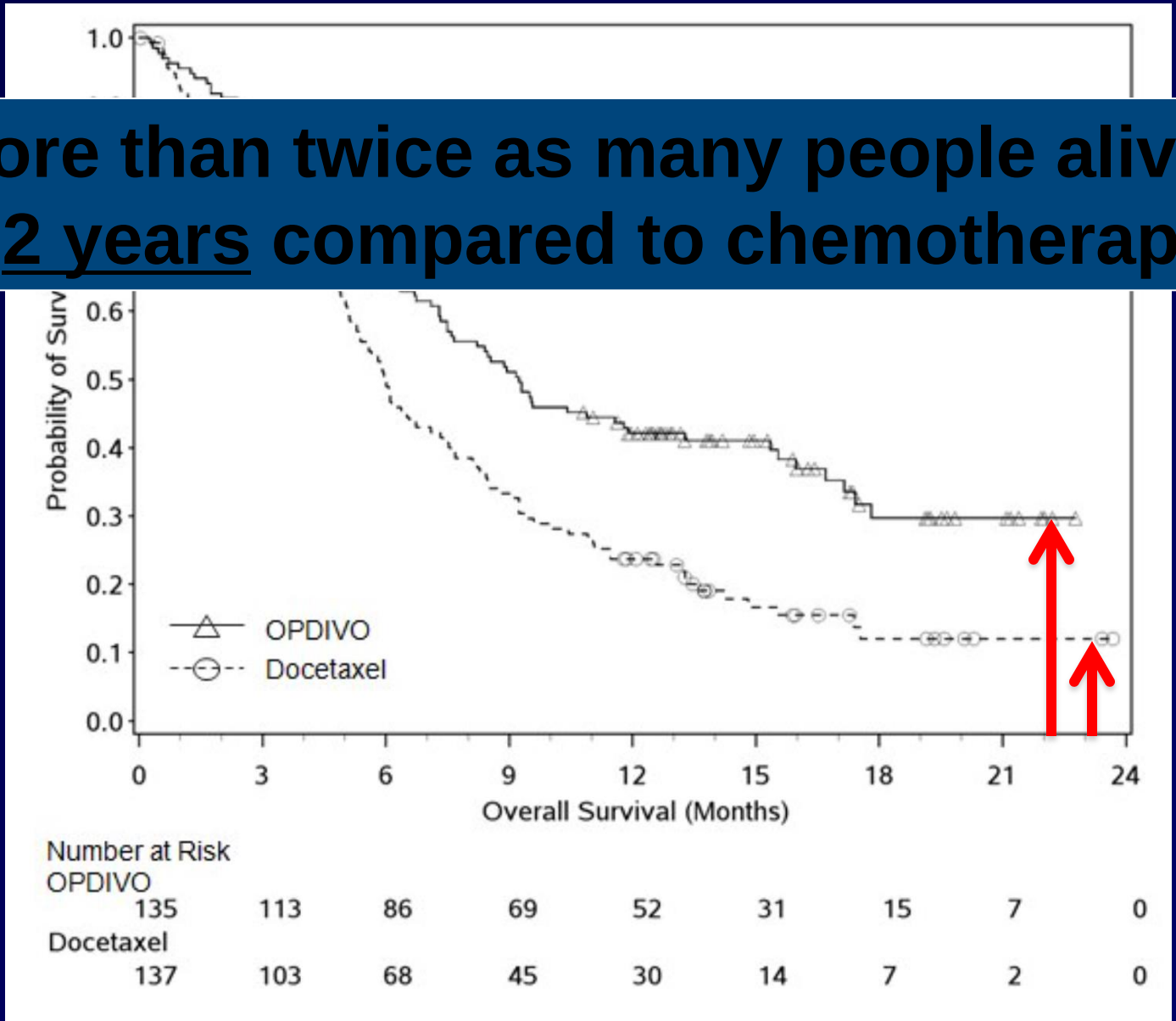
Cancer immunotherapy in the future

Better patient selection, combinations, broader use?



Survival in patients with previously treated squamous cancer

More than twice as many people alive at ~2 years compared to chemotherapy!!



Nivolumab monotherapy as 1st-line treatment: study design

Chemotherapy-naïve patients with stage IIIB or IV NSCLC
Non-squamous or squamous histology

↓

Nivolumab 3 mg/kg IV Q2W until disease progression or unacceptable toxicity[a]

↓

Primary objective: safety and tolerability

Secondary objectives:
ORR and PFS rate at 24 weeks

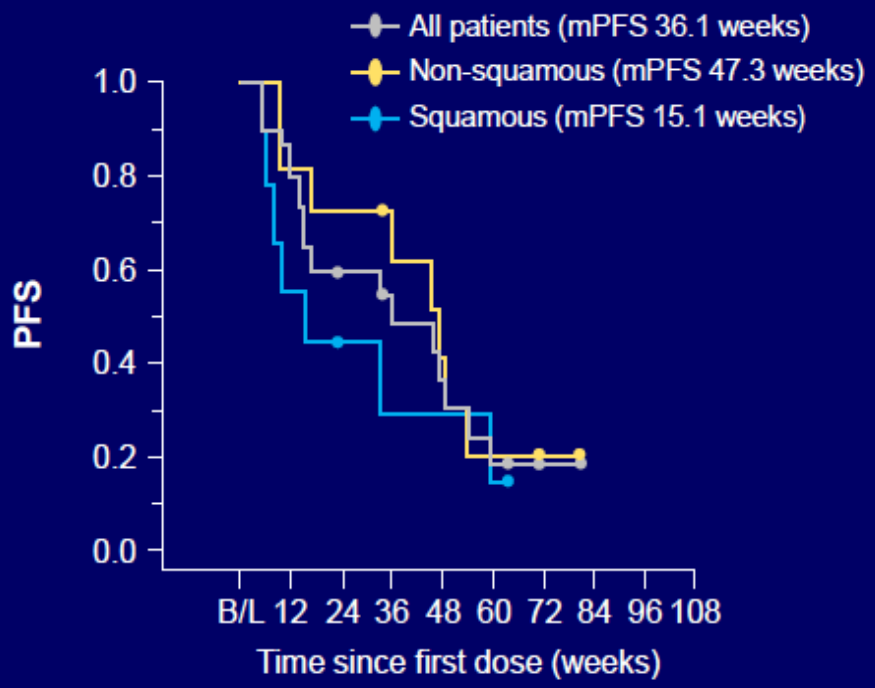
Key eligibility criteria

- ≥18 years of age
- Stage IIIb/IV NSCLC
- ECOG PS ≤1
- Chemotherapy naïve; prior use of EGFR TKI is acceptable
- No symptomatic brain metastasis, autoimmune disease, grade ≥2 neuropathy, significant cardiac disease, interstitial lung disease
- Collection of tumour tissue (archival or recent)

Start date: December 2011
Estimated study completion date: September 2017
Estimated primary completion date: September 2016
Status: Recruiting

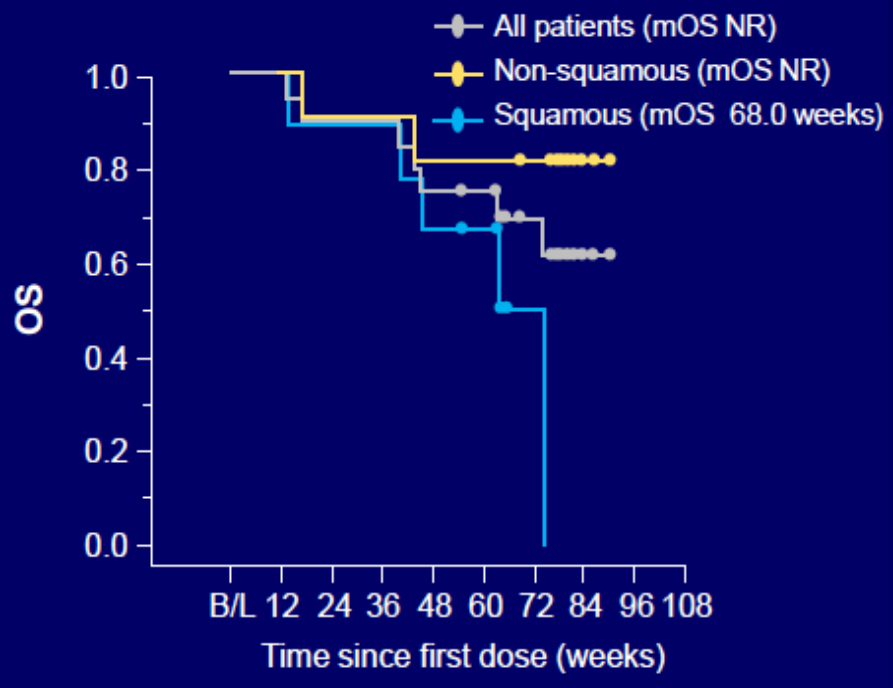
Gettinger SN, et al. Poster 38 presented at ASCO 2014 (Abstract 8024).

Nivolumab as 1st-line treatment: PFS and OS



Number of Patients at Risk

All patients	20	14	11	9	6	3	1	0	0	0
Non-squamous	11	9	8	7	4	2	1	0	0	0
Squamous	9	5	3	2	2	1	0	0	0	0



Number of Patients at Risk

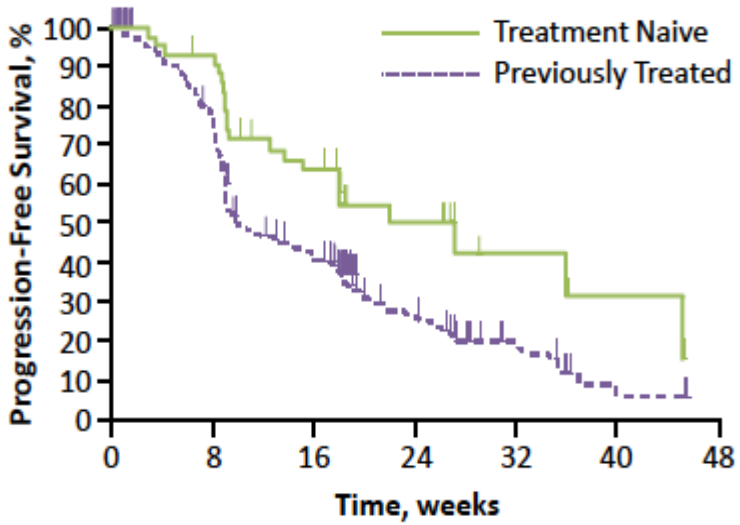
All patients	20	20	18	18	15	14	9	2	0	0
Non-squamous	11	11	10	10	9	9	8	2	0	0
Squamous	9	9	8	8	6	5	1	0	0	0

- **PFS rate at 24 weeks was 60% and 1-year OS rate was 75%**

Pembrolizumab OS Data

Kaplan-Meier Estimates of Survival

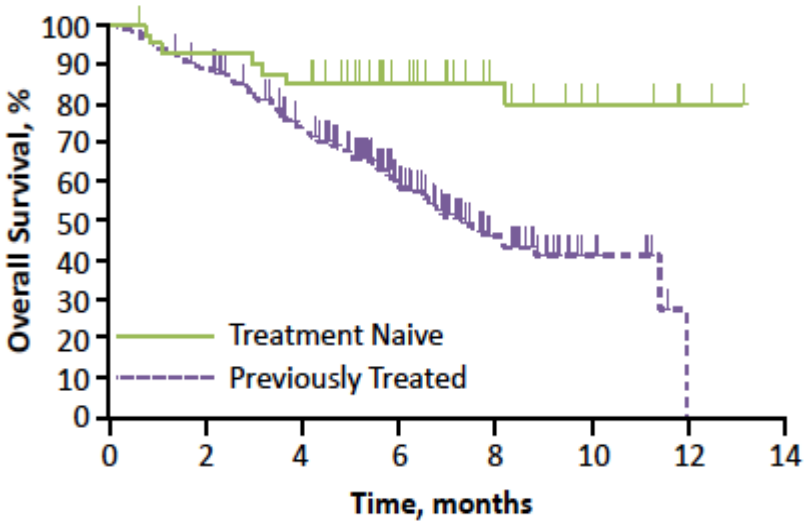
PFS (RECIST v1.1, Central Review)



n at risk							
Treatment Naive	45	39	25	11	4	2	0
Previously Treated	217	159	81	33	13	2	0

- Treatment naive
  - Median PFS: 27 weeks (95% CI, 14-45)
  - 24-week PFS: 51%
- Previously treated
  - Median PFS: 10 weeks (9.1-15.3)
  - 24-week PFS: 26%

OS



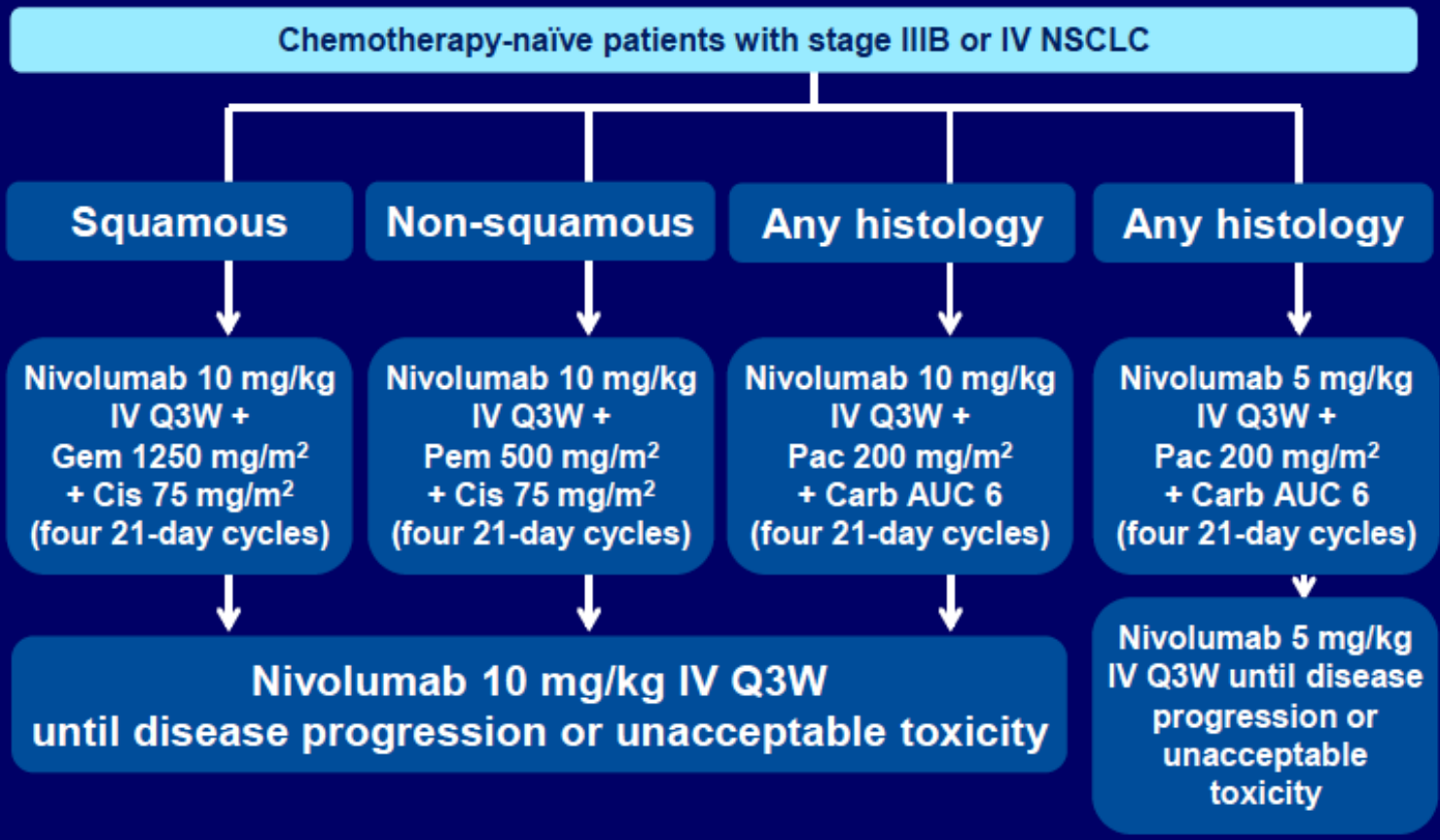
45	41	38	24	13	7	2	0
217	192	146	77	33	8	0	0

- Treatment naive
  - Median OS: NR (95% CI, NE-NE)
  - 6-month OS: 86%
- Previously treated
  - Median OS: 8.2 months (7.3-NR)
  - 6-month OS: 59%

Garon EB et al, ESMO, 2014

Immune Checkpoint Therapy and Chemotherapy

Nivolumab plus platinum-based chemotherapy: Study Design



Primary endpoints

- Safety and tolerability

Secondary endpoints

- ORR at 24 weeks
- PFS rate at 24 weeks

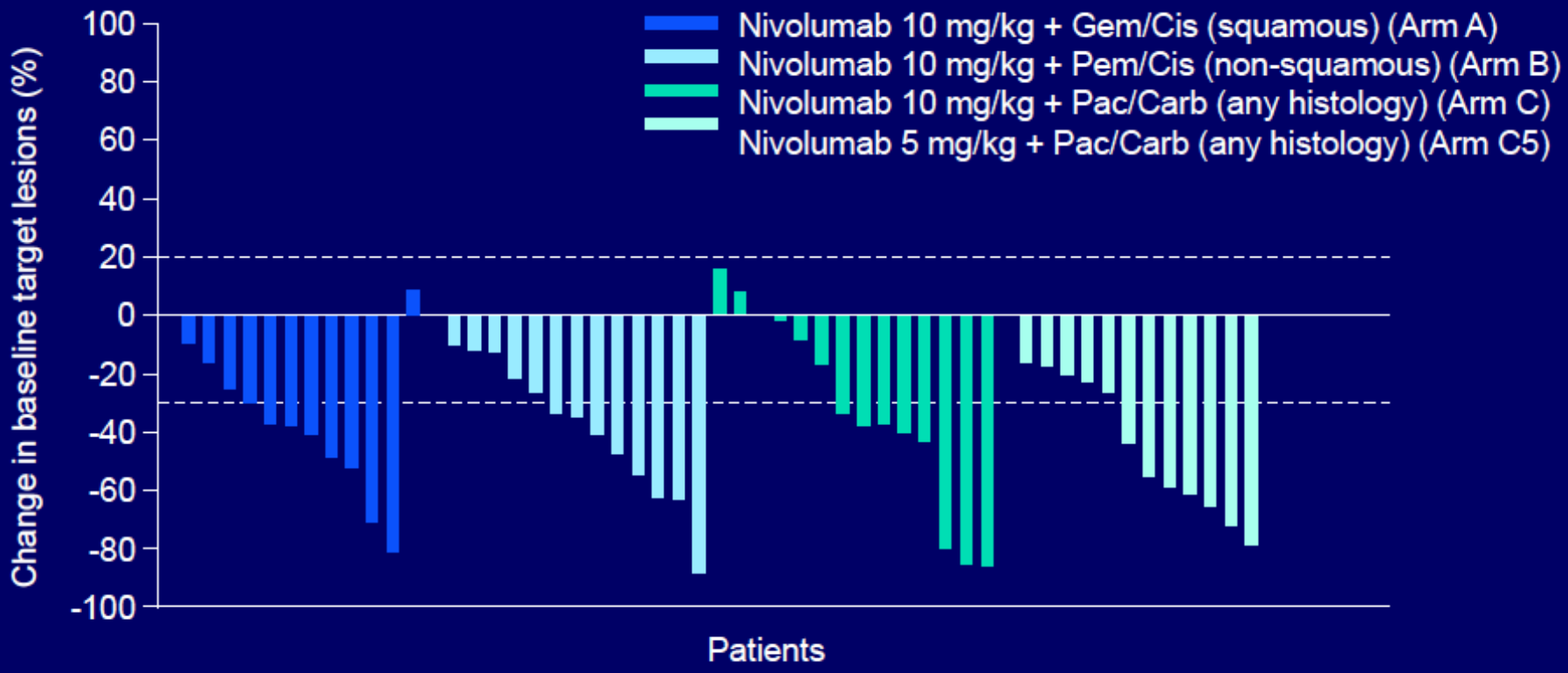
Key eligibility criteria

- ≥18 years of age
- Stage IIIb/IV NSCLC
- ECOG PS ≤1
- Chemotherapy naive; prior use of EGFR TKI is acceptable
- No symptomatic brain metastasis, autoimmune disease, grade ≥2 neuropathy, significant cardiac disease, interstitial lung disease
- Collection of tumour tissue (archival or recent)

Start date: December 2011
Estimated study completion date: September 2017
Estimated primary completion date: September 2016
Status: Recruiting

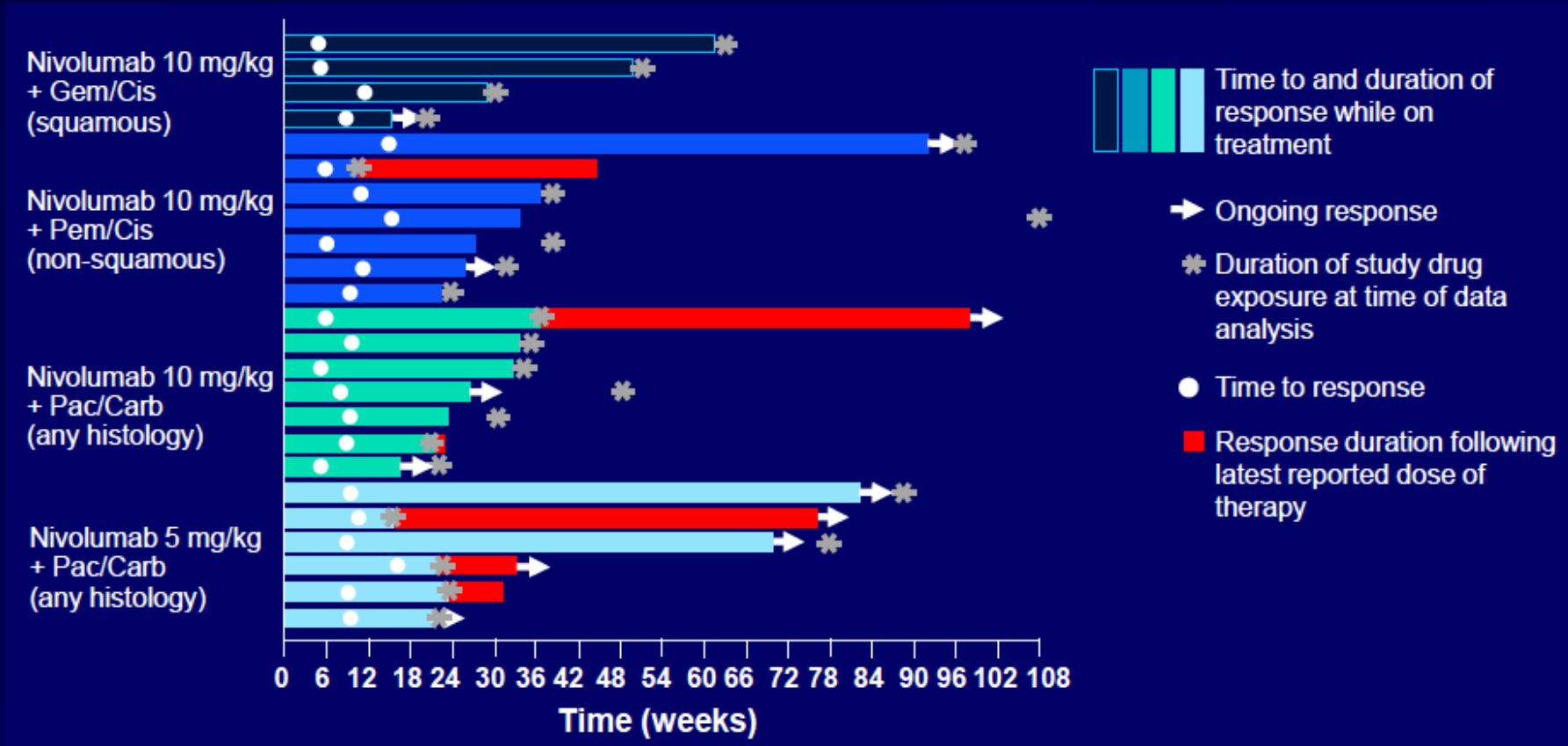
Antonia SJ, et al. Poster 294 presented at ASCO 2014 (Abstract 8113)

Nivolumab plus platinum-based chemotherapy: Percentage change in tumour burden from baseline



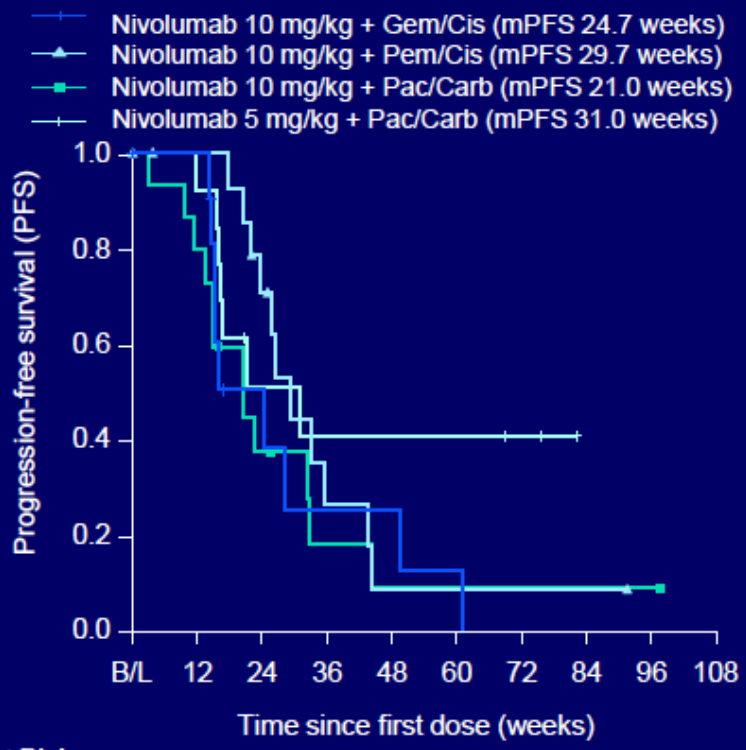
- The majority of patients across arms experienced a decrease in tumour burden (47/56, 84%)
- By week 18, one patient in the nivolumab 10 mg/kg + Pem/Cis arm and one patient in the nivolumab 10 mg/kg + Pac/Carb arm had a tumour burden reduction of >80%

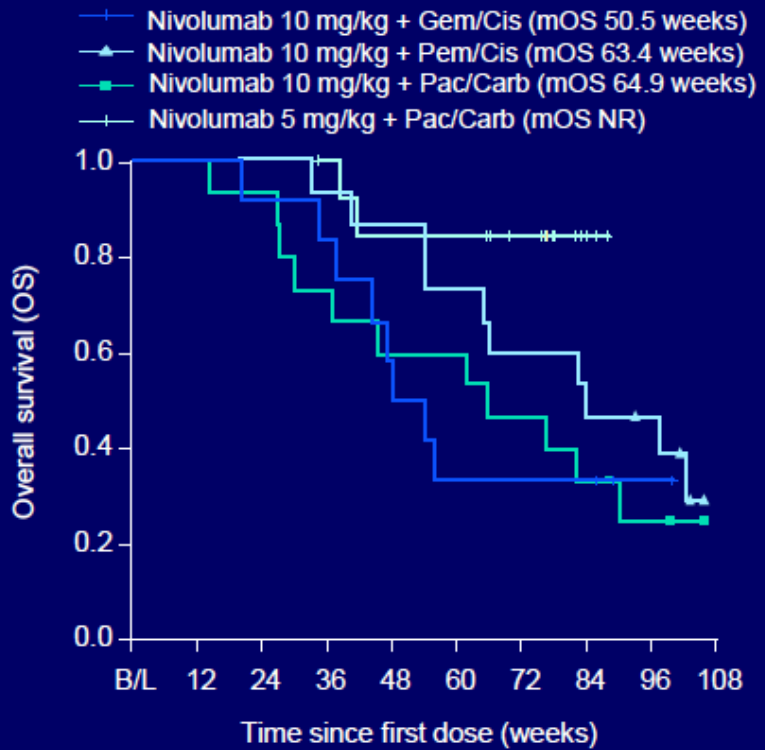
Nivolumab plus platinum-based chemotherapy: Characteristics of response by treatment arm



- Across arms, responses were ongoing in 11 of 24 responders at the time of analysis
- 5 of the 11 patients with ongoing response were still alive and had not started subsequent therapy at the time of this analysis

Nivolumab plus platinum-based chemotherapy: PFS and OS





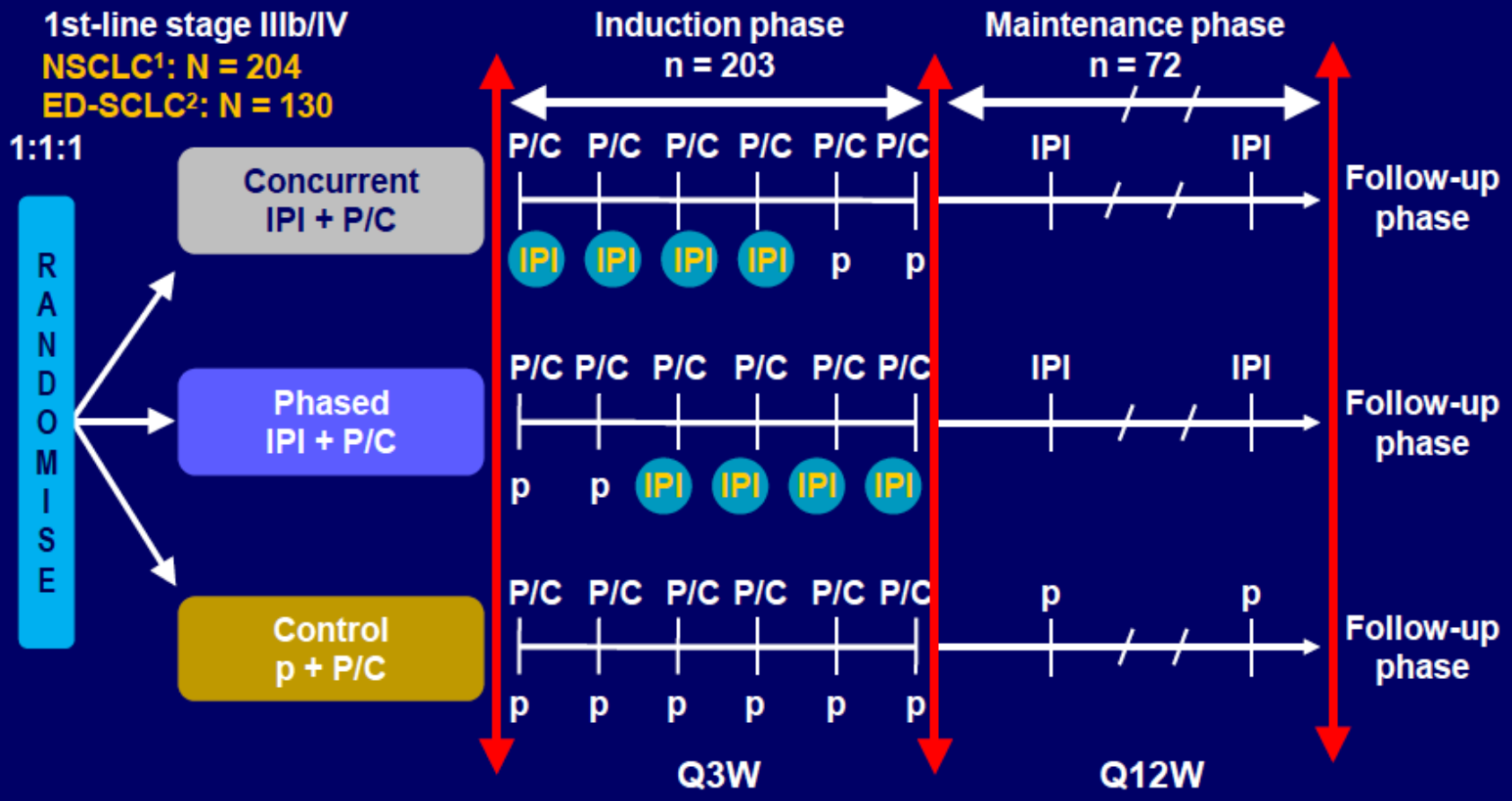
Number of Patients at Risk

Nivolumab 10 mg/kg + Gem/Cis	12	11	4	2	2	1	0	0	0	0
Nivolumab 10 mg/kg + Pem/Cis	15	14	10	4	1	1	1	1	0	0
Nivolumab 10 mg/kg + Pac/Carb	15	12	5	2	1	1	1	1	1	0
Nivolumab 5 mg/kg + Pac/Carb	14	12	5	3	3	3	2	0	0	0

	12	12	11	10	6	4	4	4	1	0
	15	15	15	14	13	11	9	7	6	0
	15	15	14	11	9	9	7	6	3	0
	14	14	14	13	11	11	9	2	0	0

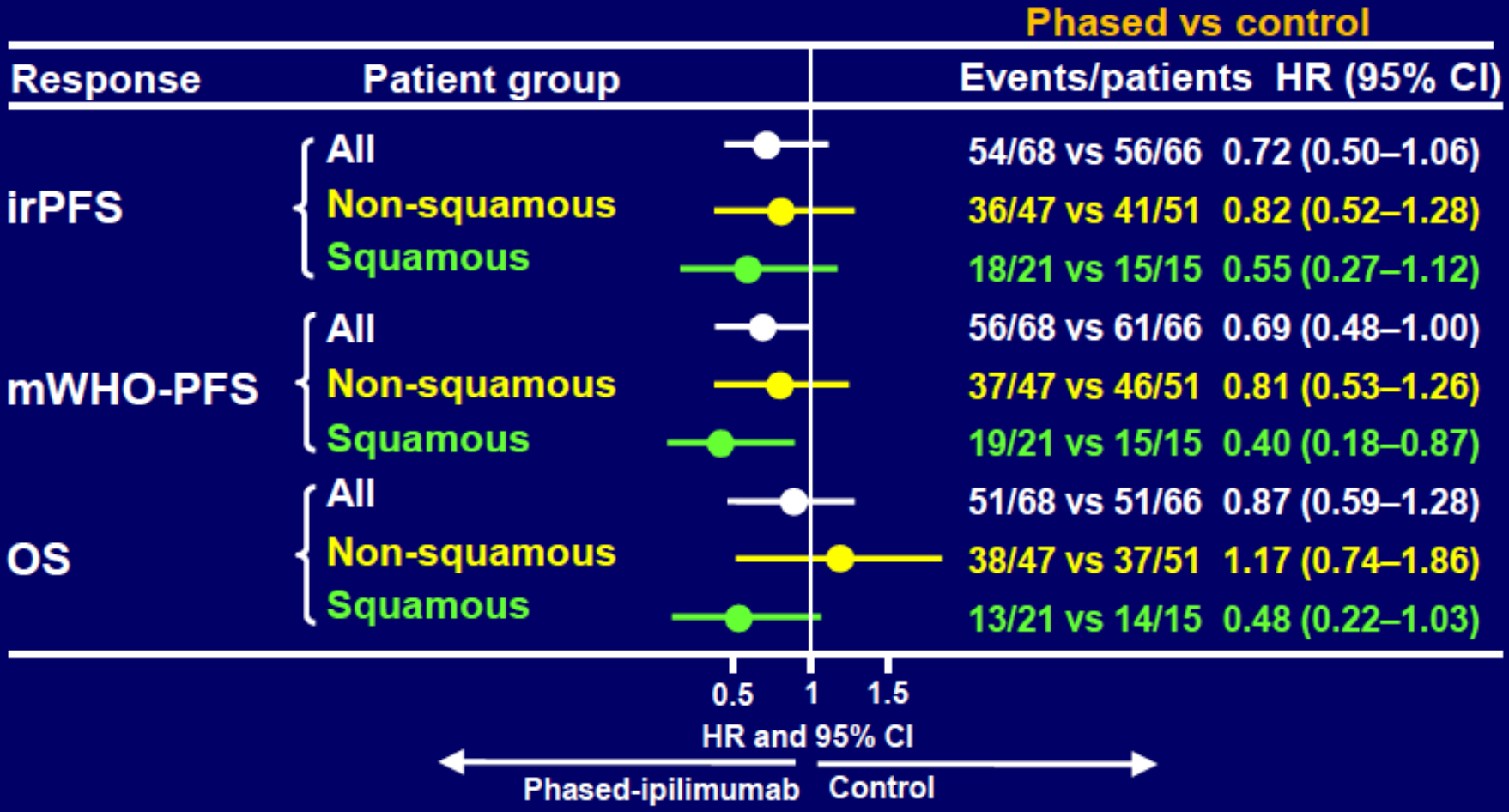
Ipilumumab Studies

Study design: NSCLC and ED-SCLC



1. Lynch T, et al. *J Clin Oncol*. 2012;30:2046–2054; 2. Reck M, et al. *Ann Oncol*. 2013;24:75–83.

Activity of phased-ipilimumab by baseline histology



Phase III Studies in Squamous and Small Cell Lung Cancer will report this summer

Caveats

Oncology history is paved with failed Phase III trials

- **Negative NSCLC Trials**
  - Erlotinib X2
  - GefitinibX2
  - MMPI x2 AG3340, BMS 275291
  - MMPI (Prinomostat AG3340)
  - FTI X3 (SCH66336, R115777,BMS)
  - PKC Antisense (ISIS 3521) X2
  - Bexarotene x2
  - Bevazizumab
  - Cetuximab
  - Sorafanib
  - PF Toll9 X2
  - Trail agonists
  - IGF-1R inhibitors
  - ASA404
  - Thalidomide
  - Multiple vaccines

Avg of 1,000 patients each

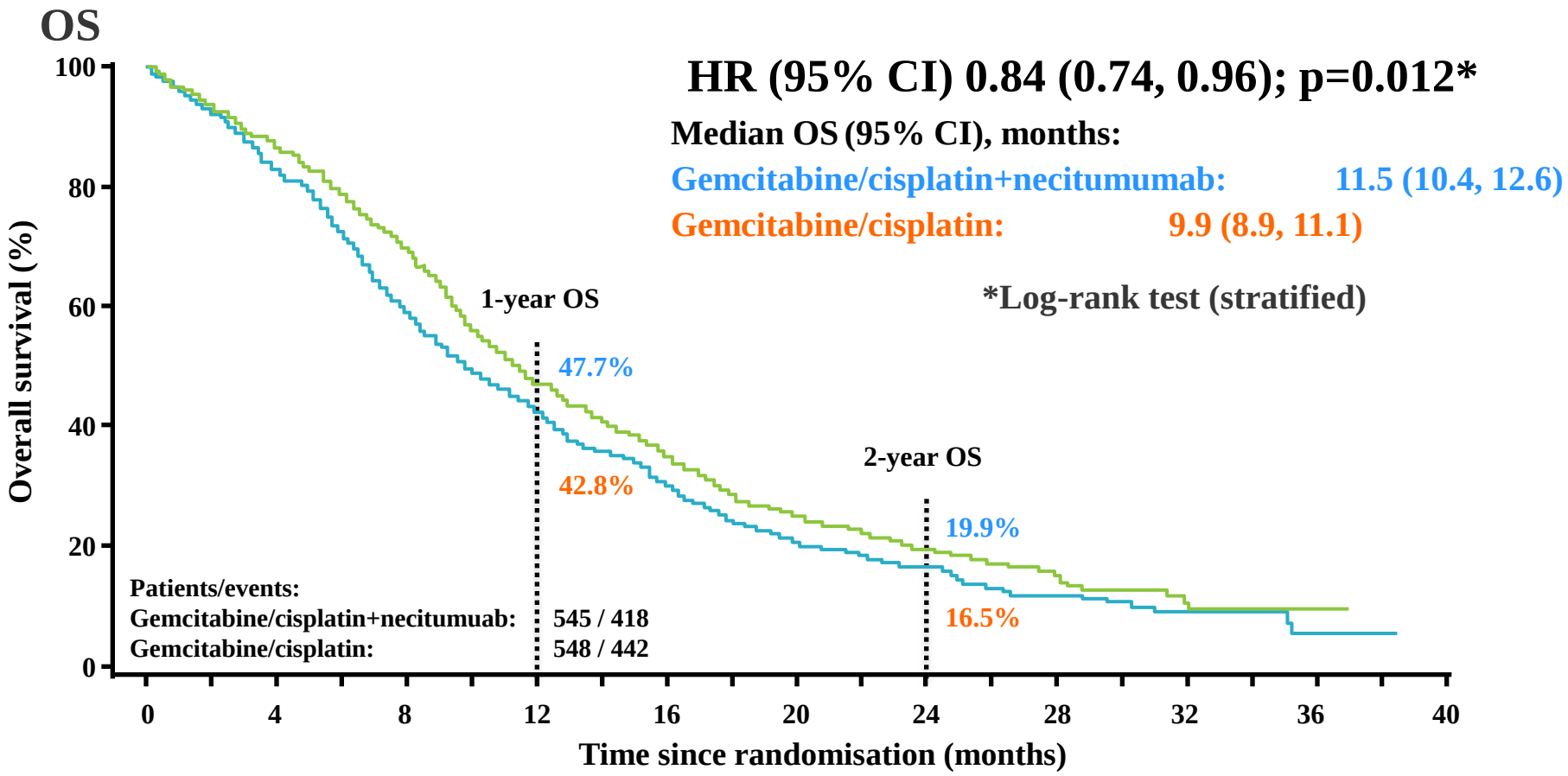
Negative SCLC Trials

- Pemetrexed
- Picoplatin
- Thalidomide
- GDC-0449
- IMC-A12

Courtesy David Carbone:
Modified from Paul Bunn and Solange Peters

Randomised Phase III trial of Necitumumab in Squamous Cell NSCLC

- **Key results**



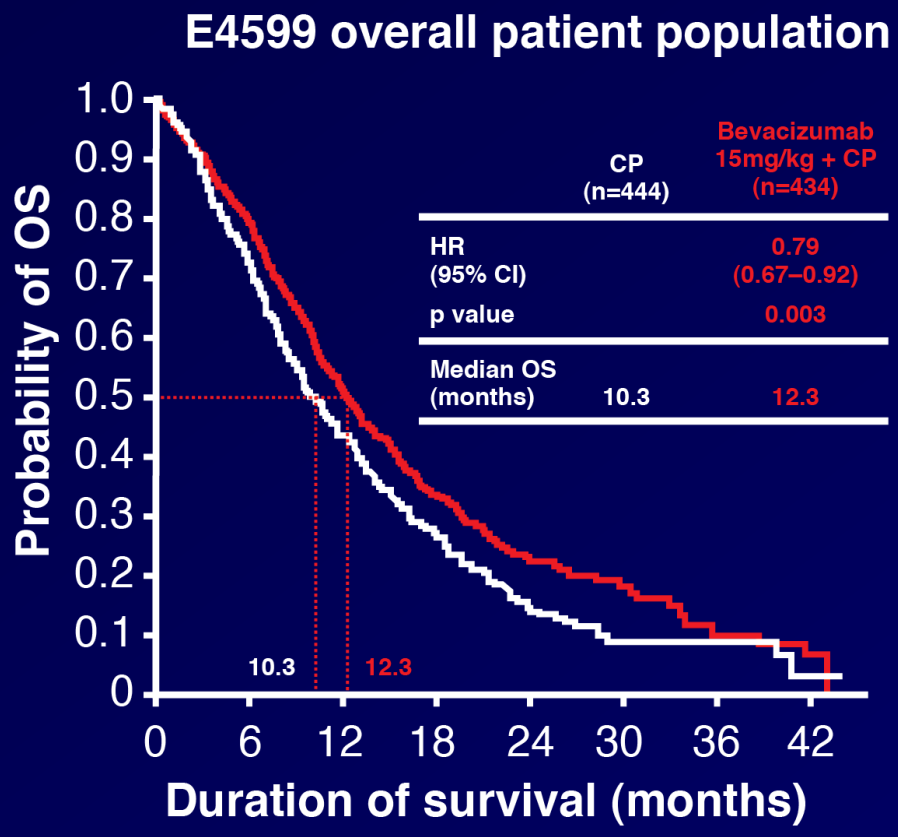
Follow-up time (median): Gemcitabine/cisplatin+necitumumab: 25.2 months; gemcitabine/cisplatin: 24.8 months

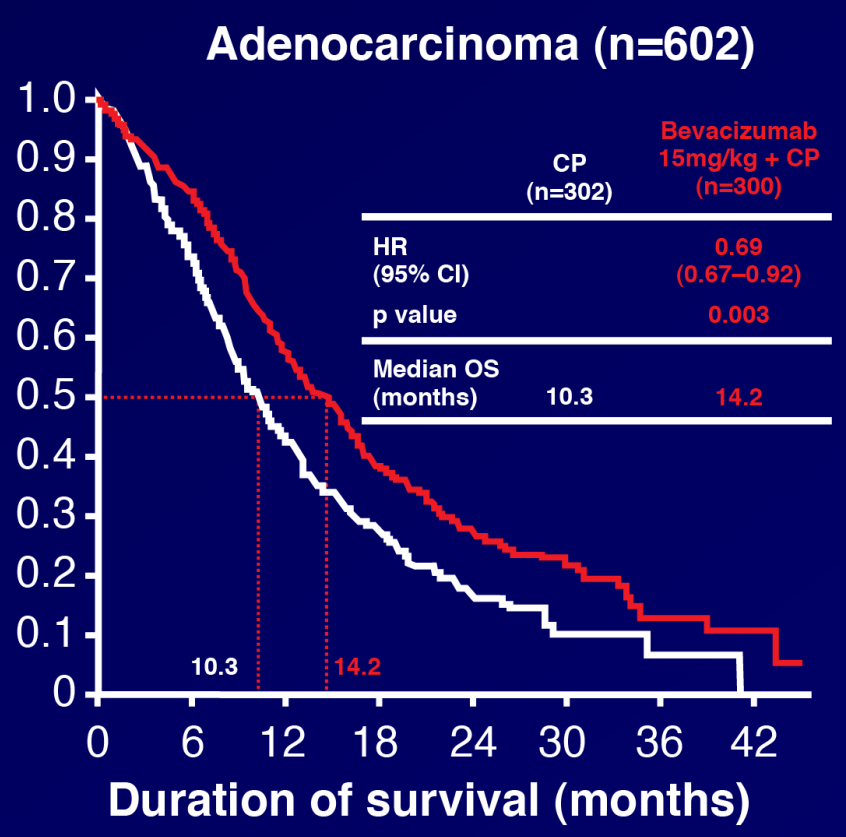
Thatcher et al. J Clin Oncol 2014; 32 (suppl 5; abstr 8008^)

Targeting VEGF can improve survival: Phase III trial of Bevacizumab in NSCLC (E4599)

E4599: 1st line paclitaxel/carboplatin +/- bevacizumab in nonsquamous

E4599: adenocarcinoma subset

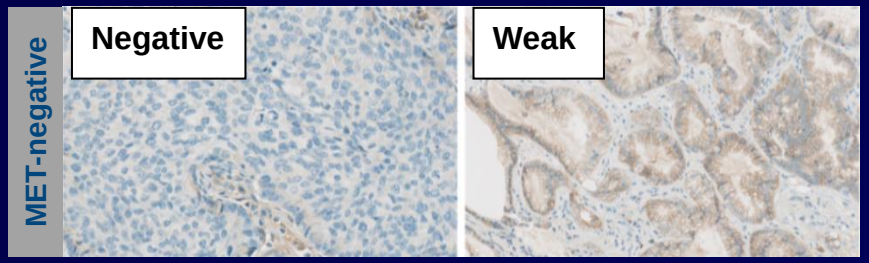


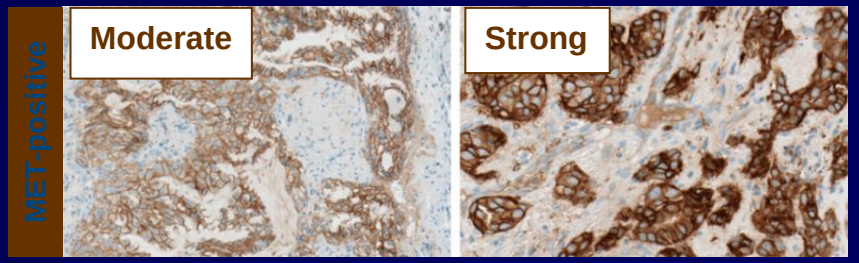


Sandler, et al. N Engl J Med 2006; Sandler, et al. J Thorac Oncol 2010.

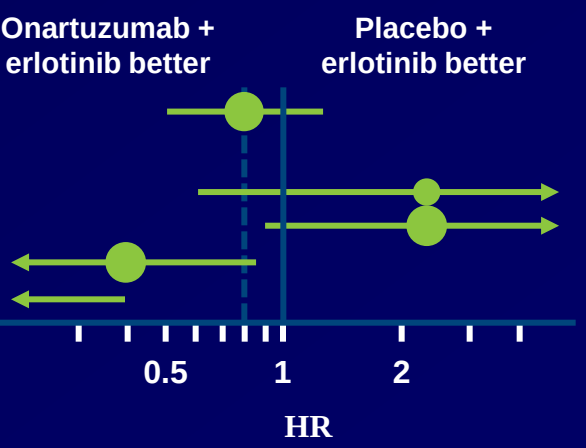
Phase II trial OAM4558g: OS benefit may be related to MET IHC score

- **'MET-positive' was defined as the majority (≥50%) of tumour cells with moderate or strong staining intensity**



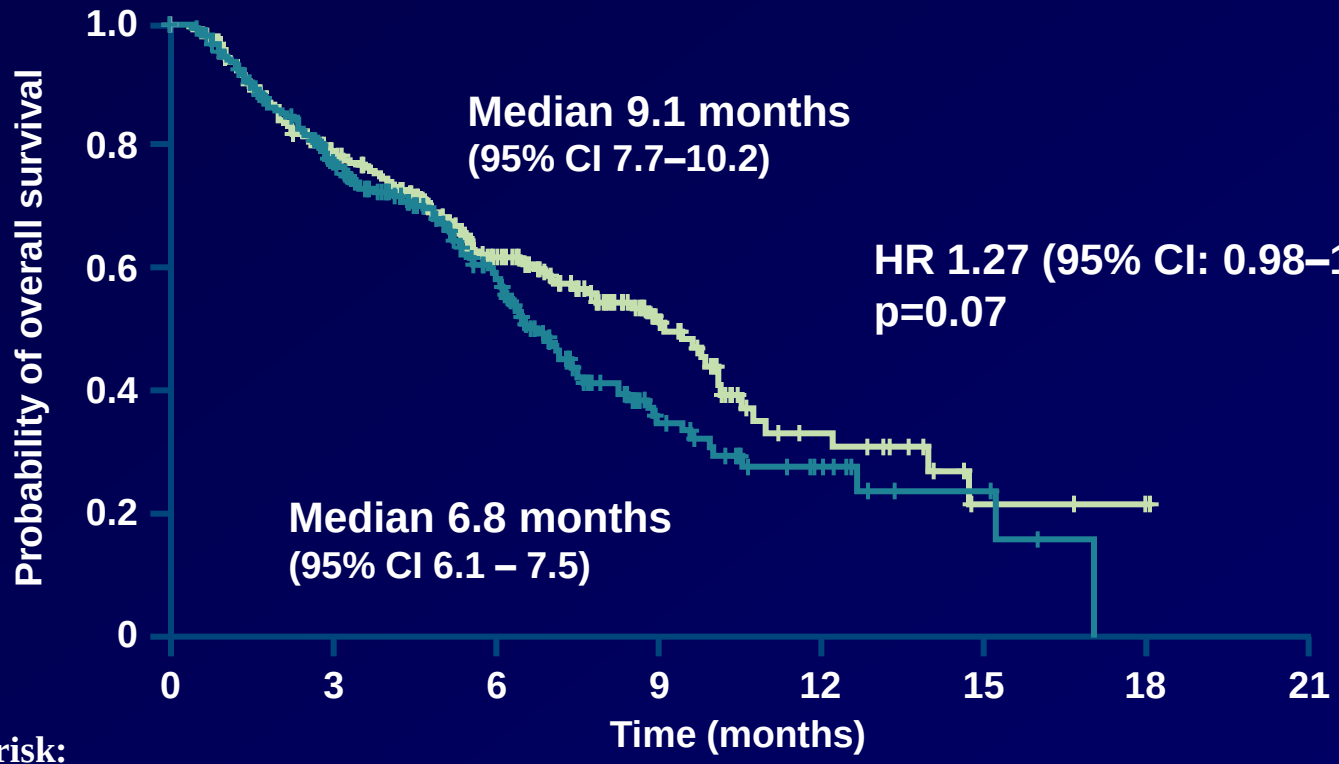


Baseline risk factor	Placebo + erlotinib n	Placebo + erlotinib Median (months)	Onartuzumab + erlotinib n	Onartuzumab + erlotinib Median (months)	HR
All patients	68	7.4	69	8.9	0.80
MET IHC status					
0	12		7	5.5	2.31
1+	19	15.3	24	8.6	2.30
2+	25	6.5	26		0.40
3+	6	2.9	9	11.1	0.04



Spigel DR et al, ASCO 2014

OAM4971g: Overall Survival Results



Number of patients at risk:							
Placebo + erlotinib	249	183	110	43	14	3	1
Onartuzumab + erlotinib	250	177	100	29	12	4	

Placebo + erlotinib (n=249)
Onartuzumab + erlotinib (n=250)
Censored

Spigel DR et al, ASCO 2014

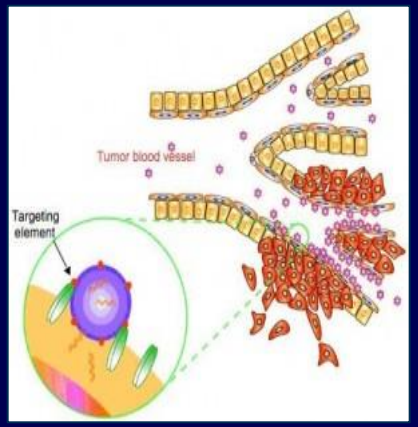
Summary Treatment Data

- Chemotherapy in unselected NSCLC patients 2 to 3 year survival rates of 10-20%, in adenocarcinomas and squamous cell lung cancer
- Maintenance strategies in non-squamous NSCLC patients have robust median survival rates of 15-17 months
- Immunotherapies, even in highly selected phase I and II studies, have modest response rates of ~20-40%
  - Survival currently based on small datasets!

Targeted Therapy

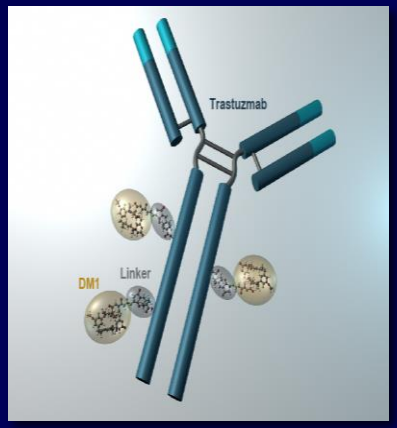
Real vs Notional

Right Target



Genetic validation; Rare phenotypes

Right Drug (or Combinations)

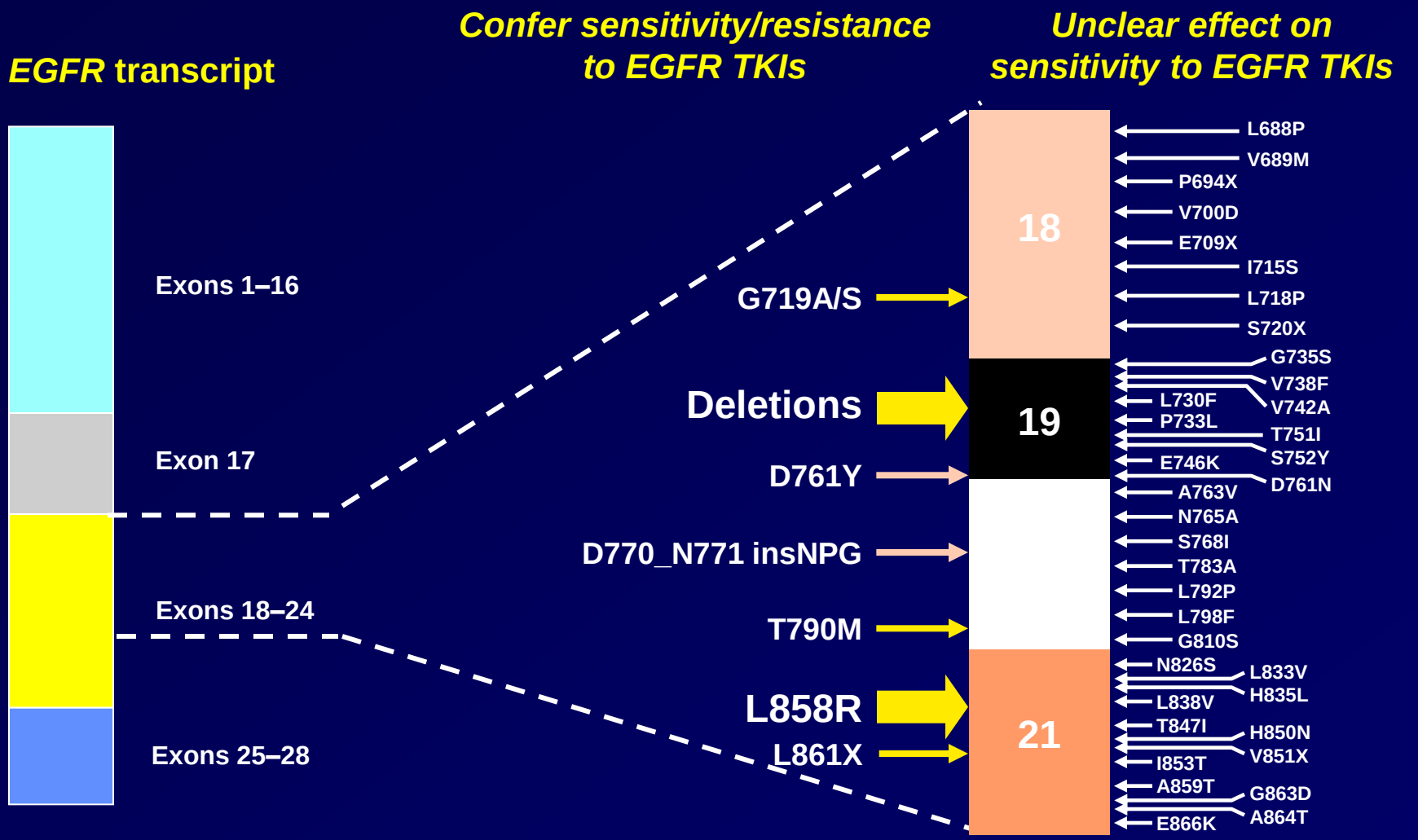


Selective design and delivery; Combinations for complex diseases

Right Patient

Phenotyping and genotyping

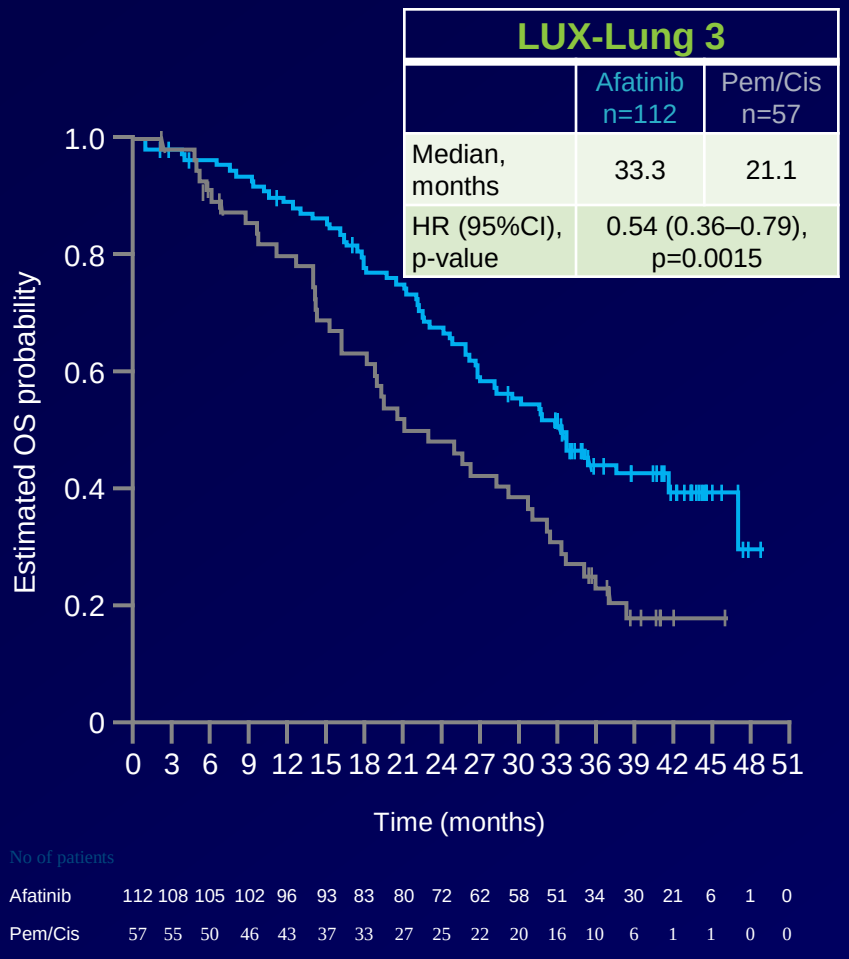
Mutations identified in *EGFR* gene

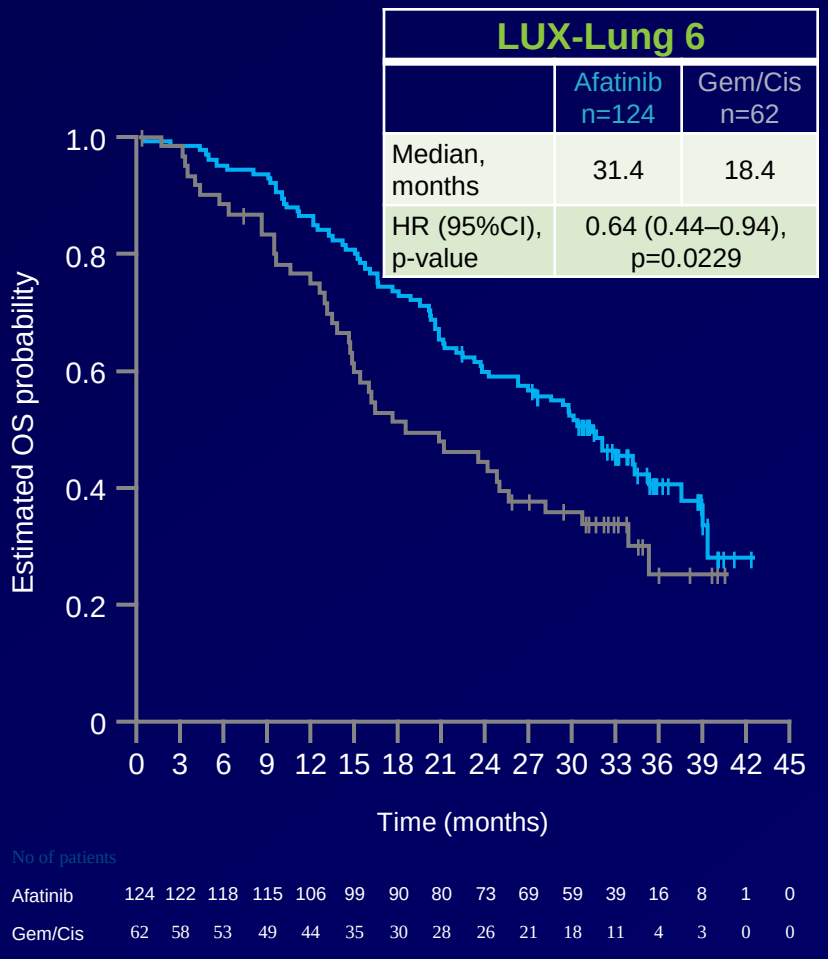


Riely, et al. Clin Cancer Res 2006

Afatinib OS in Del19 subgroup

Mutation categories



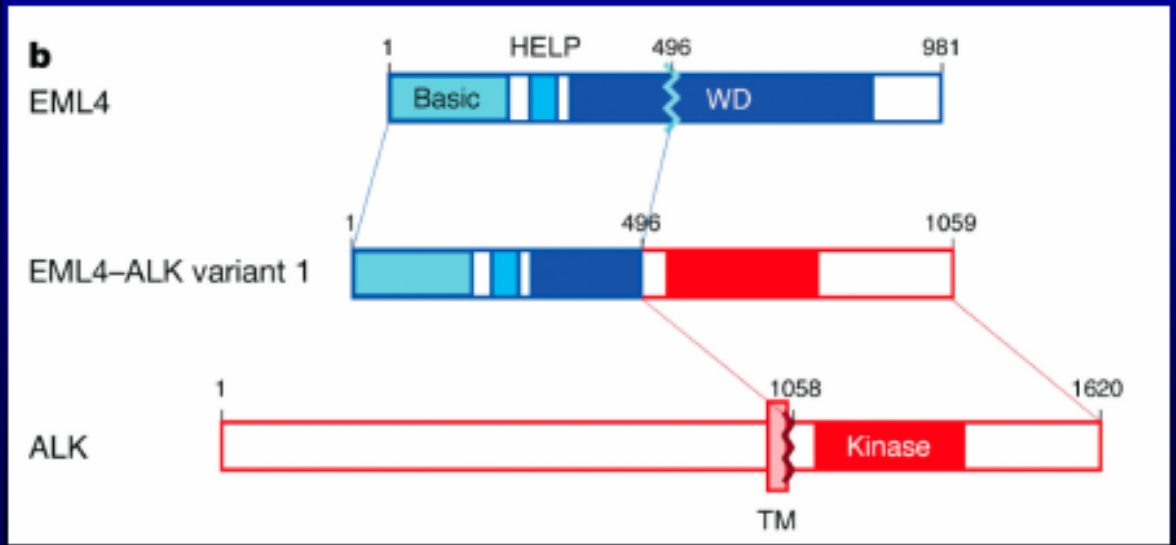


Yang JCH, et al. ASCO 2014: abstract 8004 and oral presentation.

Vol 448|2 August 2007|doi:10.1038/nature05945 nature

Identification of the transforming *EML4–ALK* fusion gene in non-small-cell lung cancer

Manabu Soda[1,2], Young Lim Choi[1], Munehiro Enomoto[1,2], Shuji Takada[1], Yoshihiro Yamashita[1], Shunpei Ishikawa[5], Shin-ichiro Fujiwara[1], Hideki Watanabe[1], Kentaro Kurashina[1], Hisashi Hatanaka[1], Masashi Bando[2], Shoji Ohno[2], Yuichi Ishikawa[6], Hiroyuki Aburatani[5,7], Toshiro Niki[3], Yasunori Sohara[4], Yukihiko Sugiyama[2] & Hiroyuki Mano[1,7]



***EML4-ALK* frequency:**

~4% (64/1709)

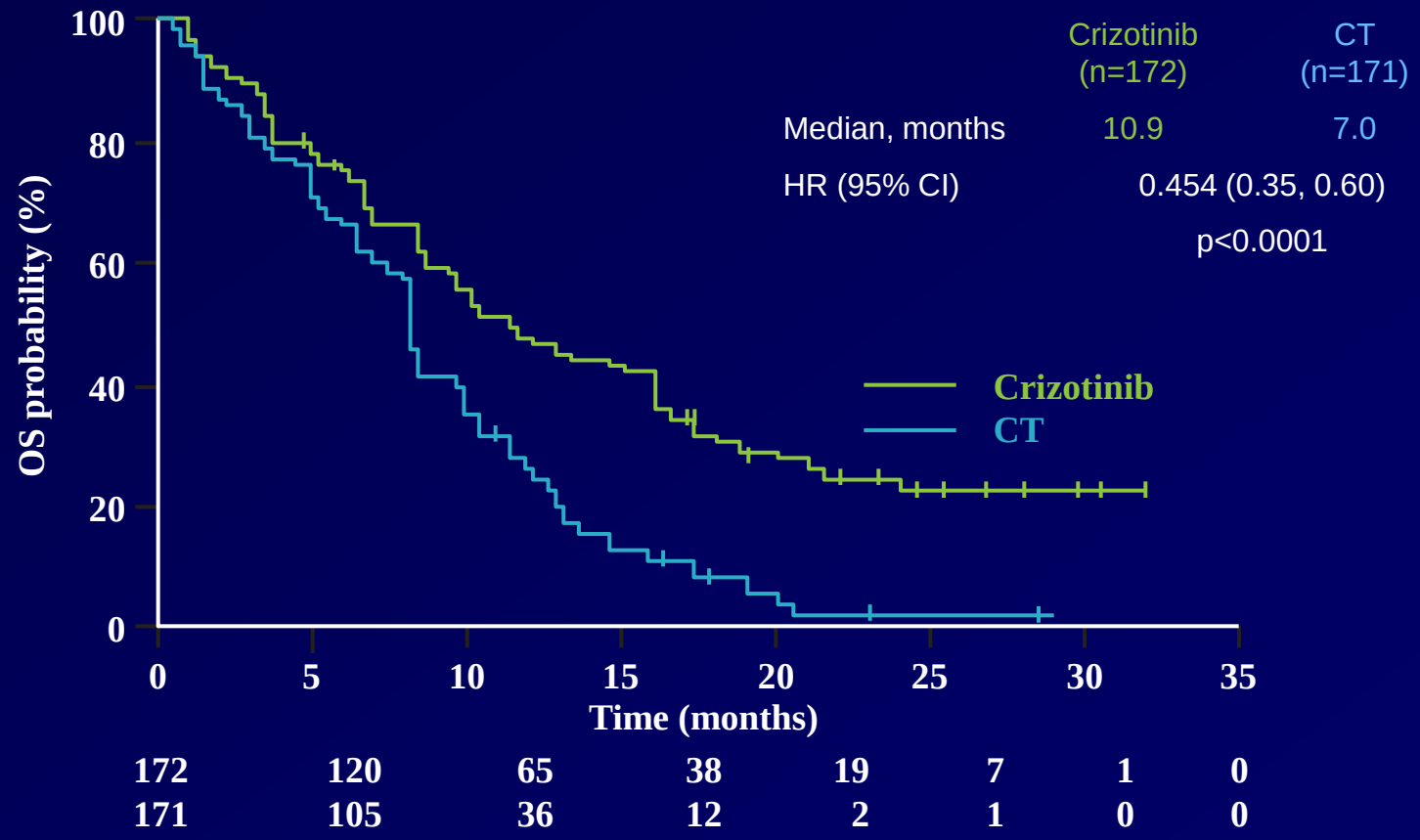
Primarily lung adenocarcinoma

Soda M *et al*. *Nature 2007*; 448:561-666

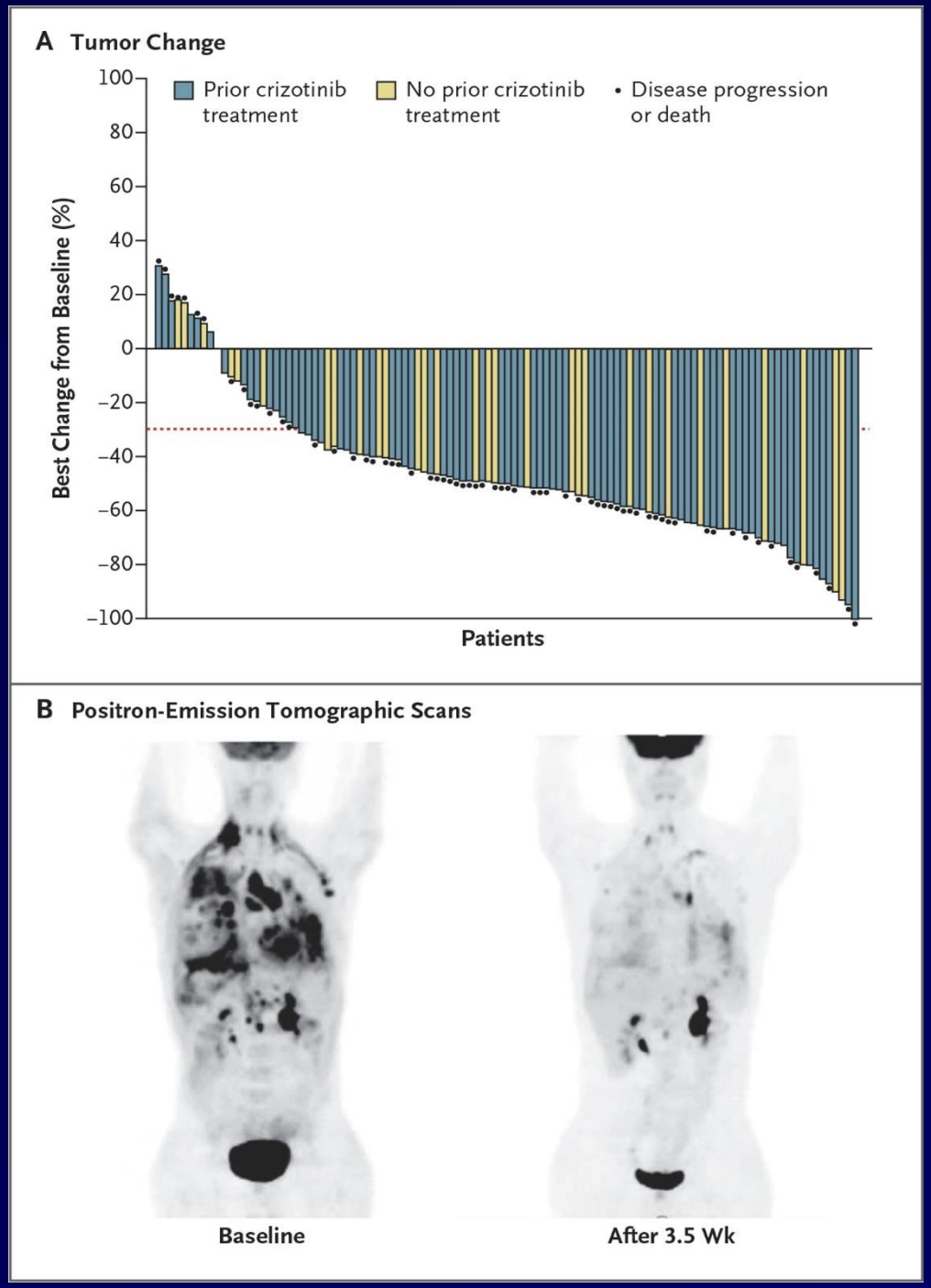
Crizotinib versus pemetrexed-platinum in advanced *ALK*-positive non-squamous NSCLC: results of a phase III study (PROFILE 1014)

- Key results
  - Addition of crizotinib significantly improved PFS but not OS compared with CT alone

PFS



Mok et al. J Clin Oncol 2014; 32 (suppl 5; abstr 8002)

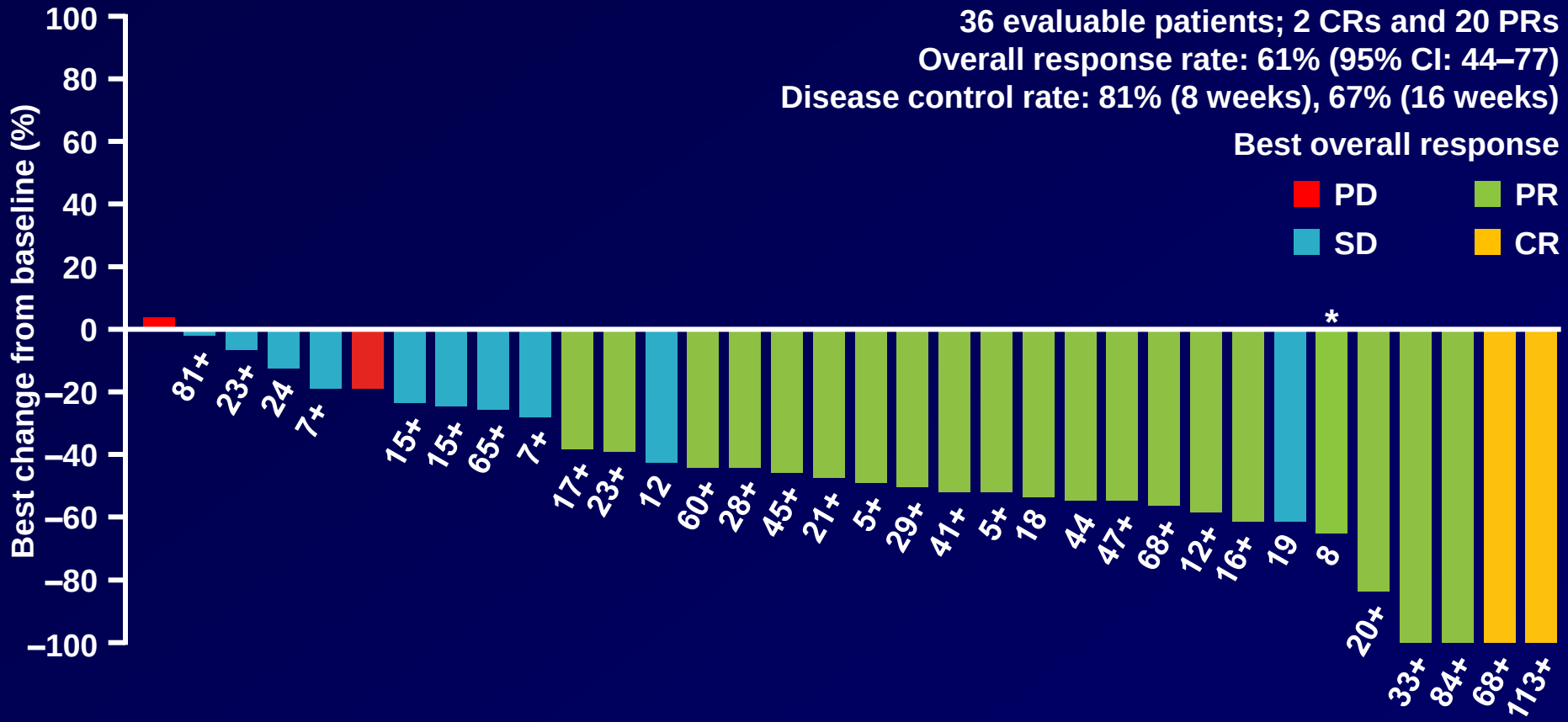


Response to Ceritinib in *ALK*-Rearranged Non–Small-Cell Lung Cancer (NSCLC)

Shaw AT et al. N Engl J Med 2014;370:1189-1197

Advanced *ROS1*-positive NSCLC[a]

Best Tumor Responses in Evaluable Patients to Crizotinib



+Treatment ongoing; duration of response/SD is from first documentation of tumor response/first dose to the time of PD or death. For ongoing patients, duration of response/SD is from first documentation of tumor response/first dose to last available on-treatment scan. Duration is in weeks.

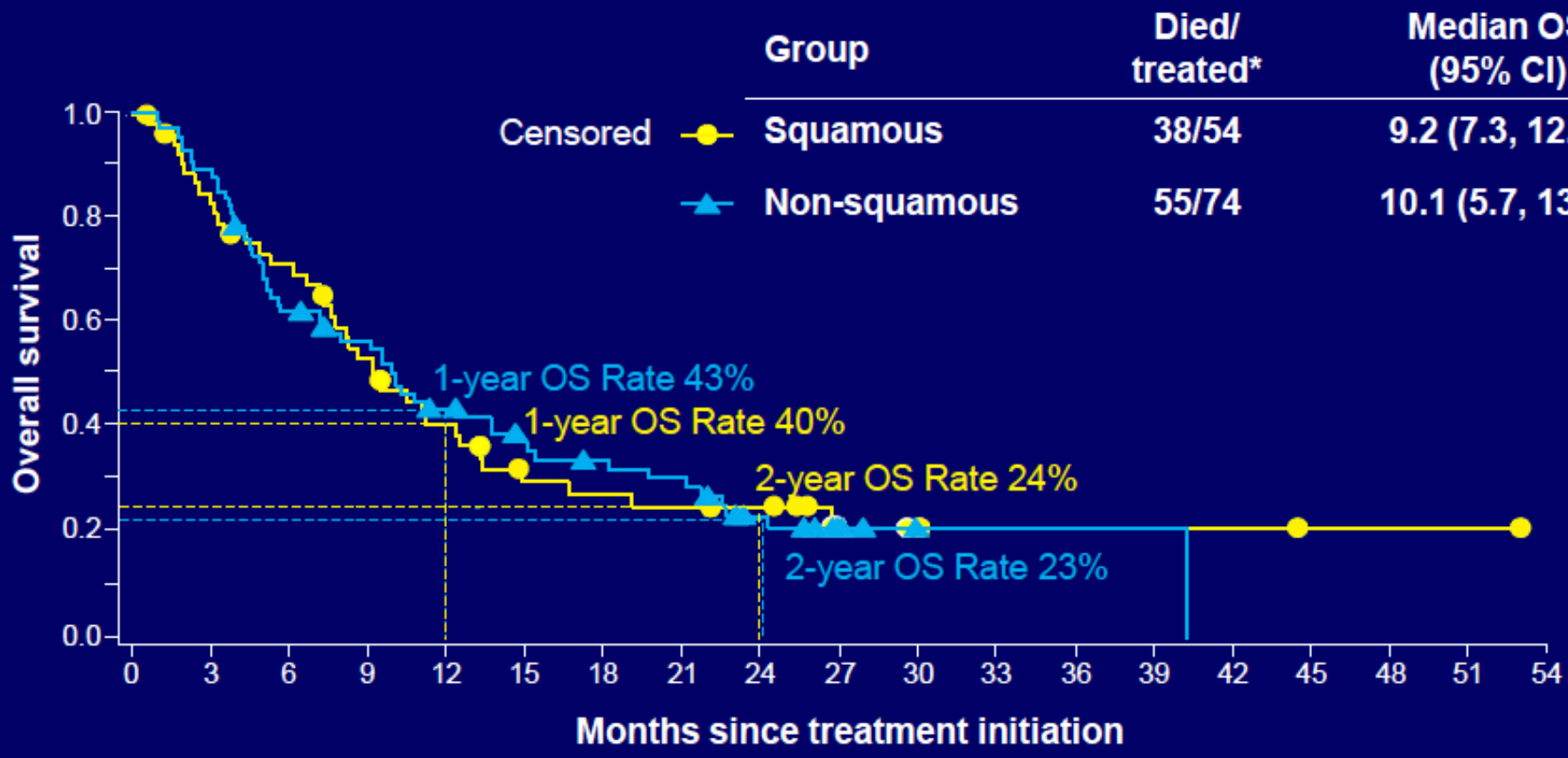
[a]Excludes patients with early death (n=2)

*This patient *ALK*+

Data as of April 24, 2013.

What Predicts Benefit for PDL1 derived therapies?

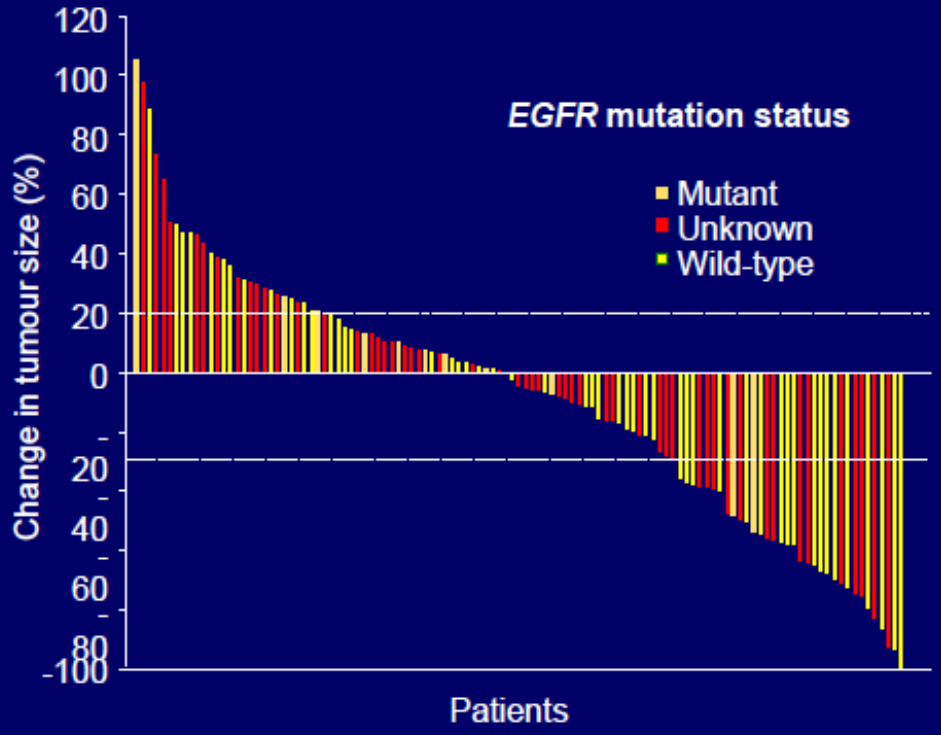
OS by Histology

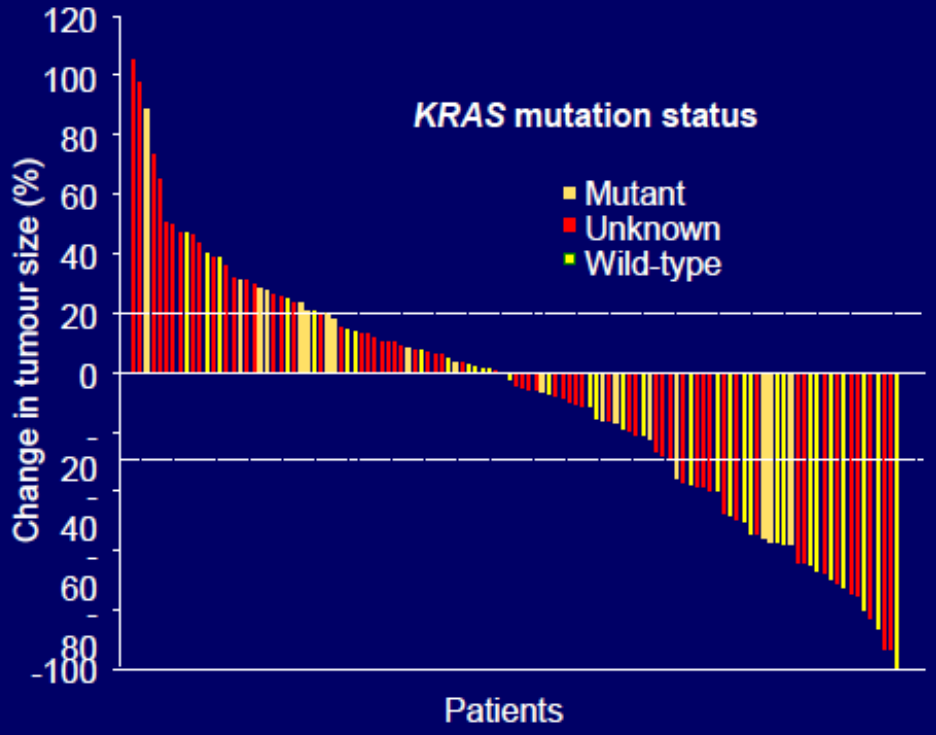


- 1- and 2-year OS rates were similar between histologies

Histology not Predictive!

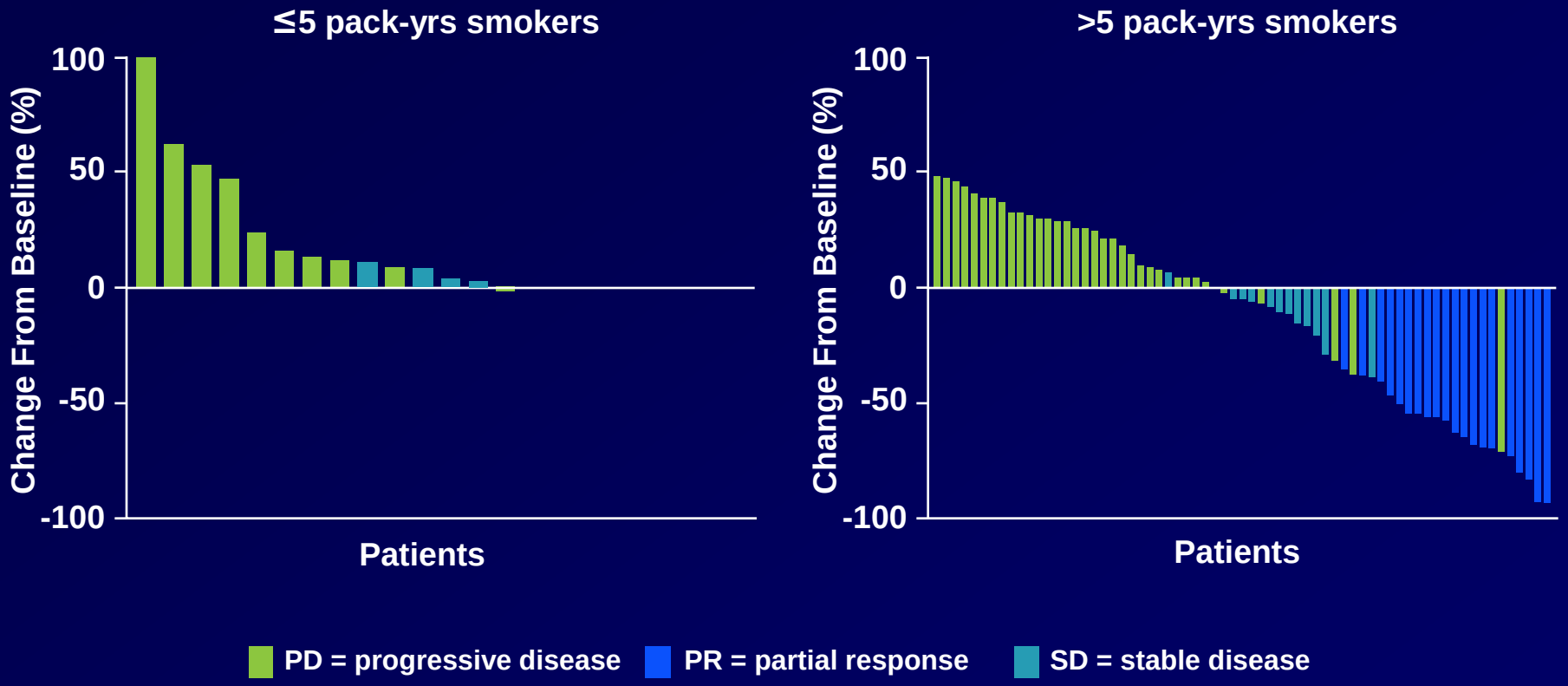
No association between best change in target lesion tumour burden and *EGFR* or *KRAS* mutation status





Mutation Status Not Predictive!

Response by smoking exposure and according to RECIST in NSCLC



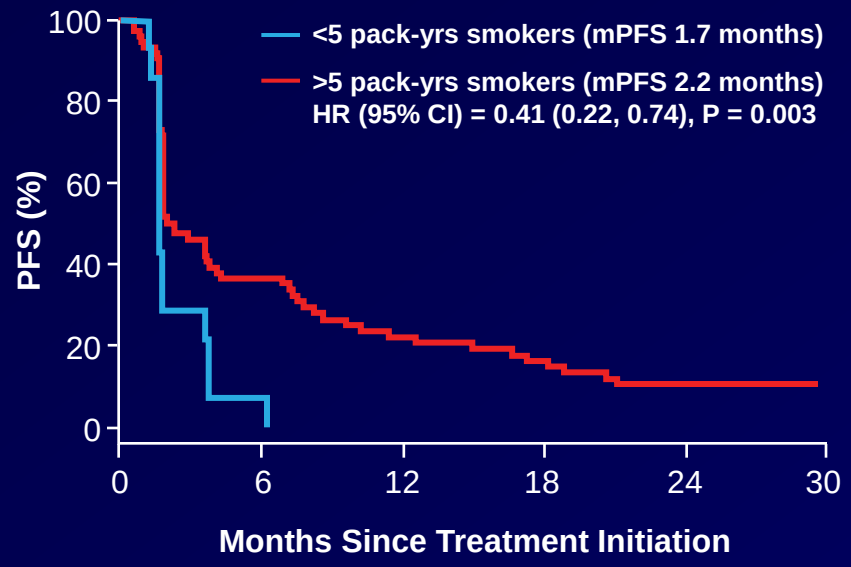
- Response rates were higher in patients with a longer history of smoking exposure

PD = progressive disease; PR = partial response; RECIST = response evaluation criteria in solid tumours; SD = stable disease.

Hellmann MD, et al. Poster 1229PD presented at ESMO 2014 (Abstract 6111).

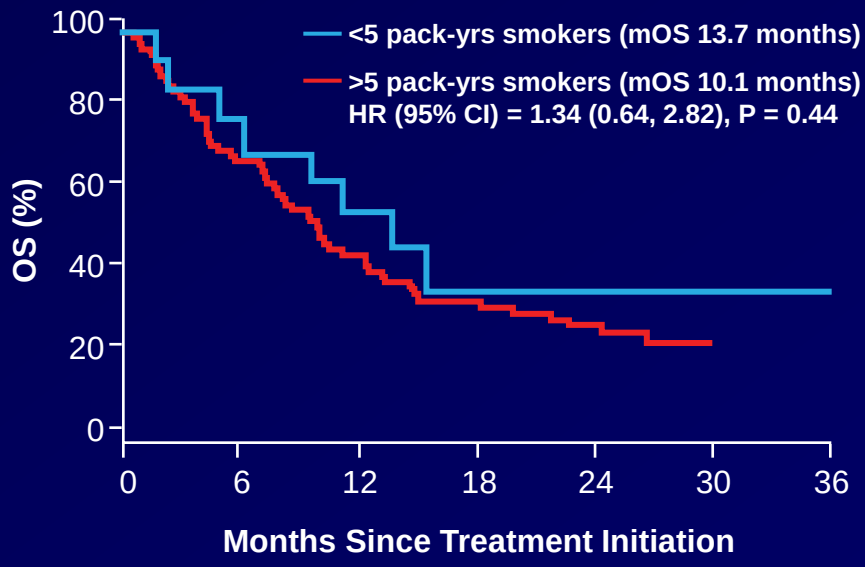
PFS and OS by smoking exposure

PFS by smoking exposure



≤5 pack-yrs smokers	14	3	1	1	1	1
>5 pack-yrs smokers	75	28	16	12	7	1

OS by smoking exposure



≤5 pack-yrs smokers	14	11	7	3	2	2	2
>5 pack-yrs smokers	75	51	32	22	15	1	1

- In >5 than <5 pack-yrs smokers
  - PFS was significantly longer (2.2 vs 1.7 months, respectively)
  - OS was similar (10.1 vs 13.7 months, respectively)

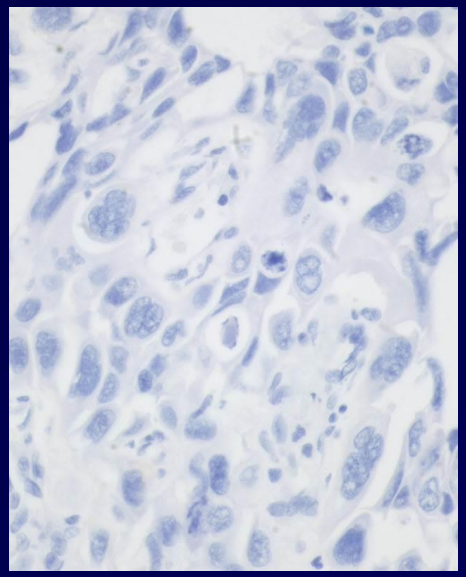
Smoking status predictive for response, not survival

CI = confidence interval; HR = hazard ratio; mOS = median OS; mPFS = median PFS; OS = overall survival; PFS = progression-free survival.

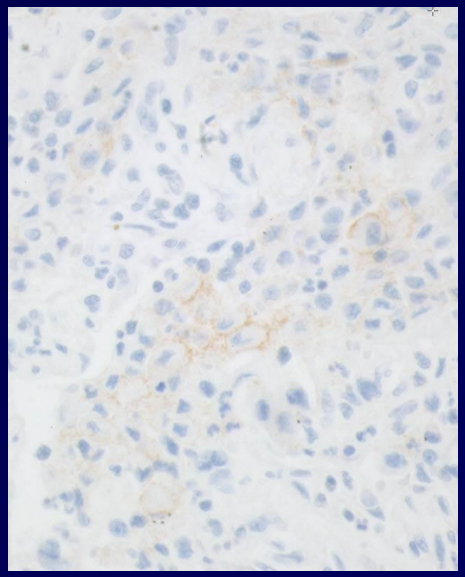
Hellmann MD, et al. Poster 1229PD presented at ESMO 2014 (Abstract 6111).

PDL1 Expression

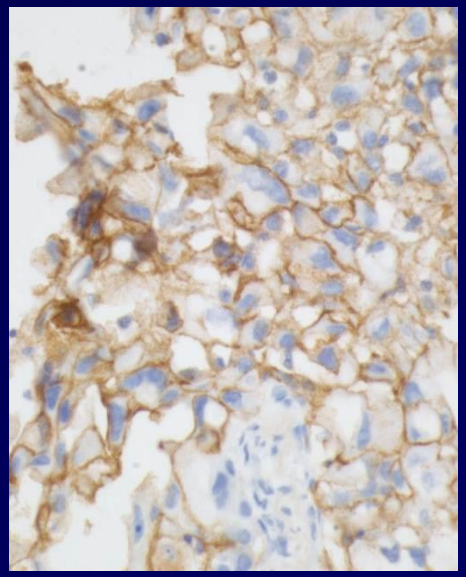
Pembrolizumab in NSCLC:
PD-L1 NSCLC Sample Immunohistochemical Staining using the 22C3 antibody



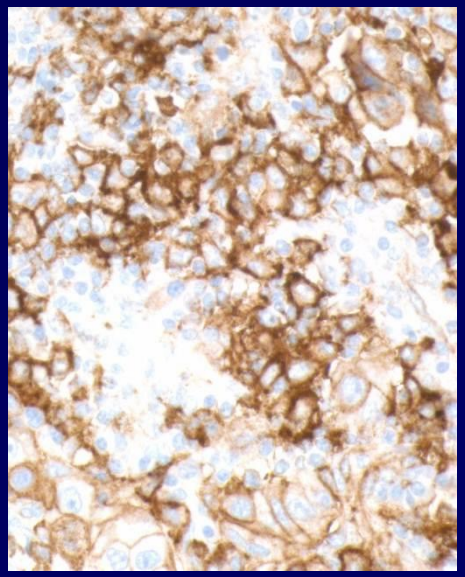
Staining intensity: 0+
PD-L1 = 0% positive



Staining intensity: 1+
PD-L1 = 2% positive



Staining intensity: 2+
PD-L1 = 100% positive



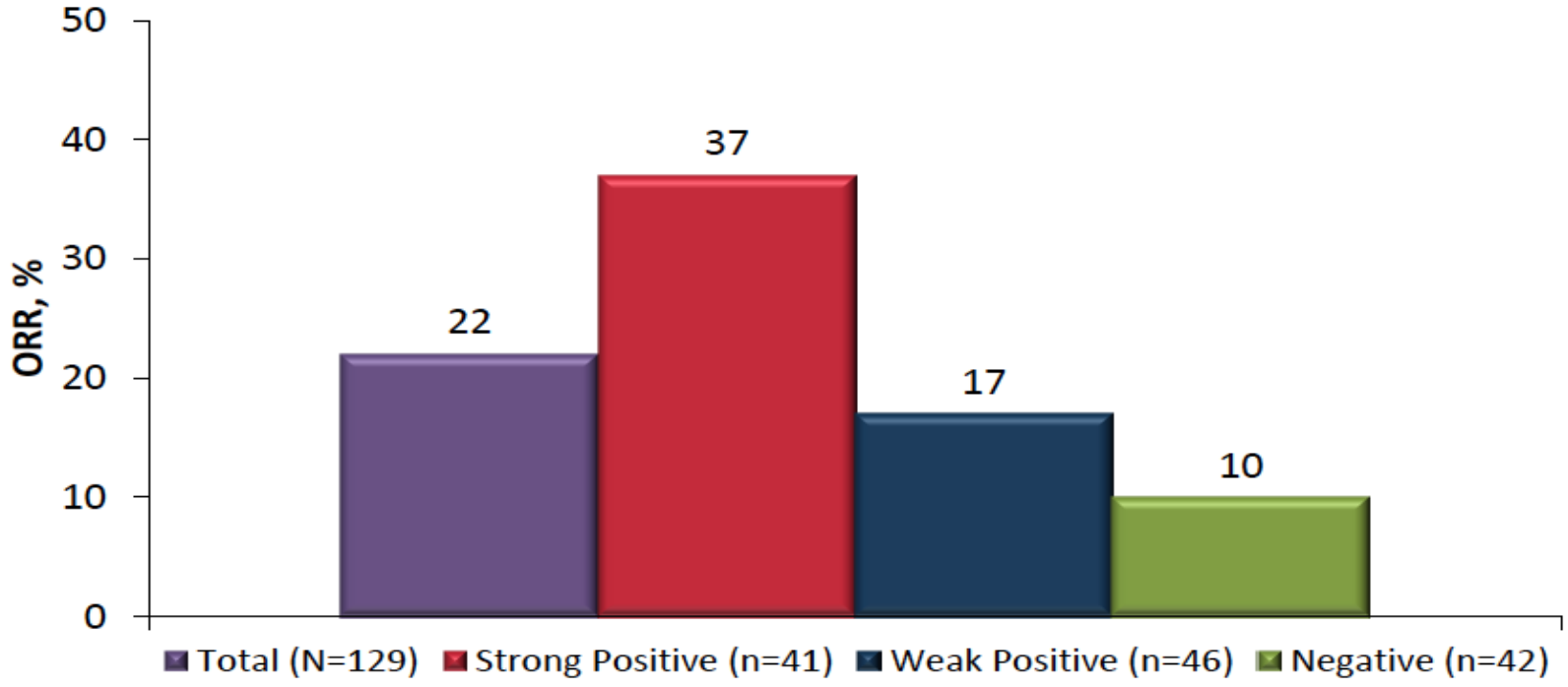
Staining intensity: 3+
PD-L1 = 100% positive

PD-L1-Negative — **PD-L1-Positive**

Gandhi L et al, AACR 2014

Response Rate by Level of PD-L1 Expression

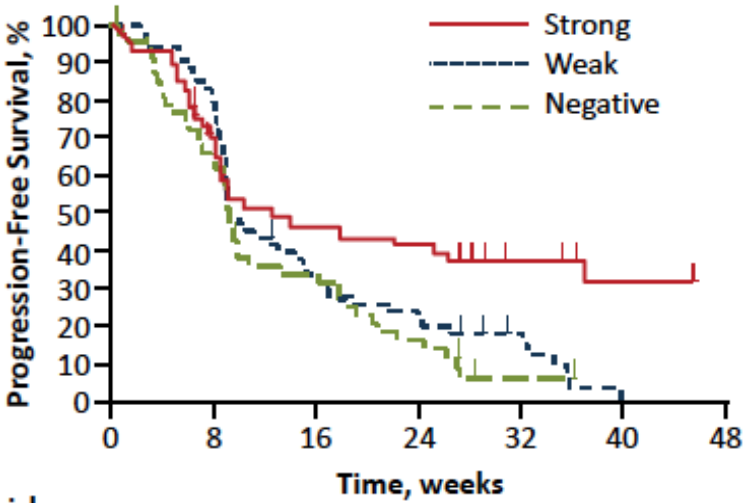
(RECIST 1.1, Central Review)



RR = Response rate (confirmed and unconfirmed complete and partial response)
PS=Proportion score. Strong PD-L1 positive staining was considered ≥50% of tumor cells, and weak was defined as staining between 1-49% of positively staining tumor cells. Negative had no tumor staining for PD-L1.

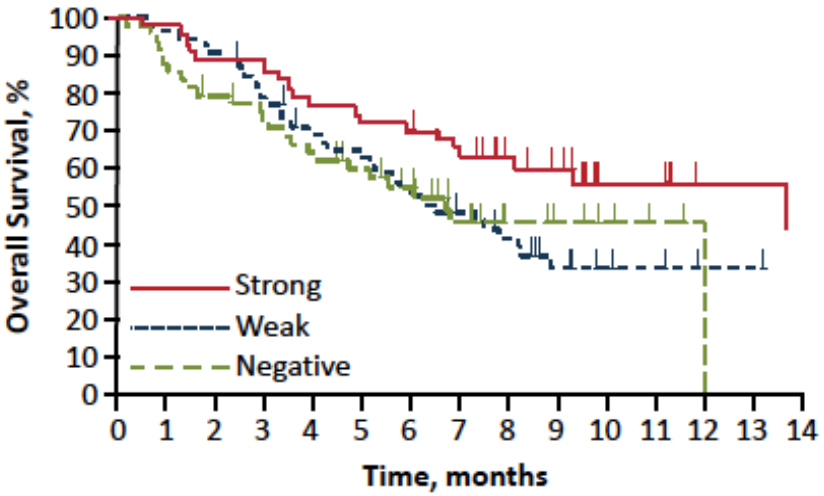
Kaplan-Meier Estimates of Survival

PFS (RECIST v1.1, Central Review)



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

OS



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

- PFS was longer in patients with PD-L1 strong-positive versus PD-L1 weak-positive/ negative tumors (HR, 0.52; 95% CI, 0.33-0.80)
- OS was longer in patients with PD-L1 strong-positive versus PD-L1 weak-positive/ negative tumors (HR, 0.59; 95% CI, 0.35-0.99)

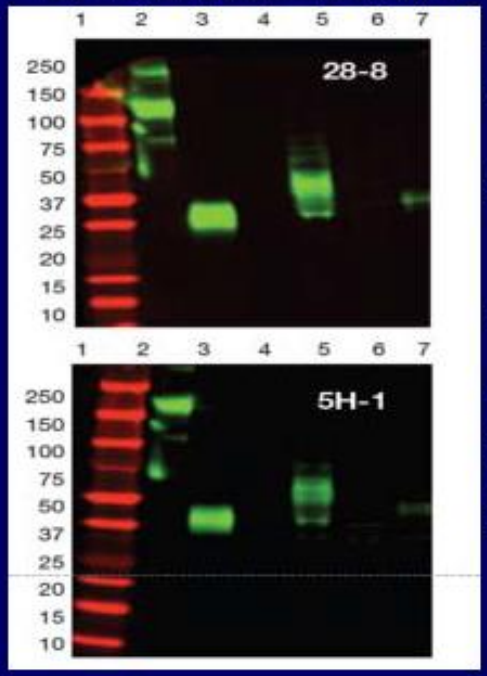
Garon EB et al, ESMO, 2014

Characterisation of 28-8 anti-PD-L1 antibody

Affinity of 28-8 for PD-L1 protein by surface plasmon resonance analysis

	K_a (1/Ms)	K_d (1/s)	K_D (pM)
5H-1	1.54×10^5	3.77×10^{-5}	294
28-8	3.6×10^5	4.2×10^{-5}	100

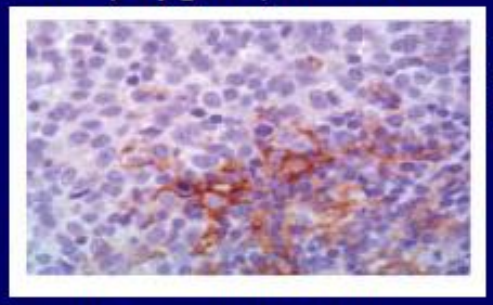
Western blot analysis of 28-8 for PD-L1 protein binding



Lanes

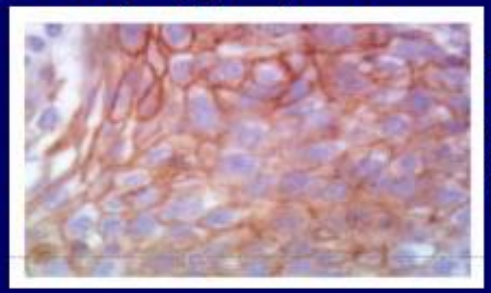
1. Molecular weight standard
2. 0.1 µg rHuB7-H1 #156-B7 (PD-L1-fc fusion)
3. 0.1 µg rHuPD-L1-biotin (extracellular domain)
4. Blank
5. CHO-PD-L1
6. CHO control
7. ES2

28-1, 2 µg/mL, melanoma



Positive staining of macrophages and scant mononuclear cells (60x)

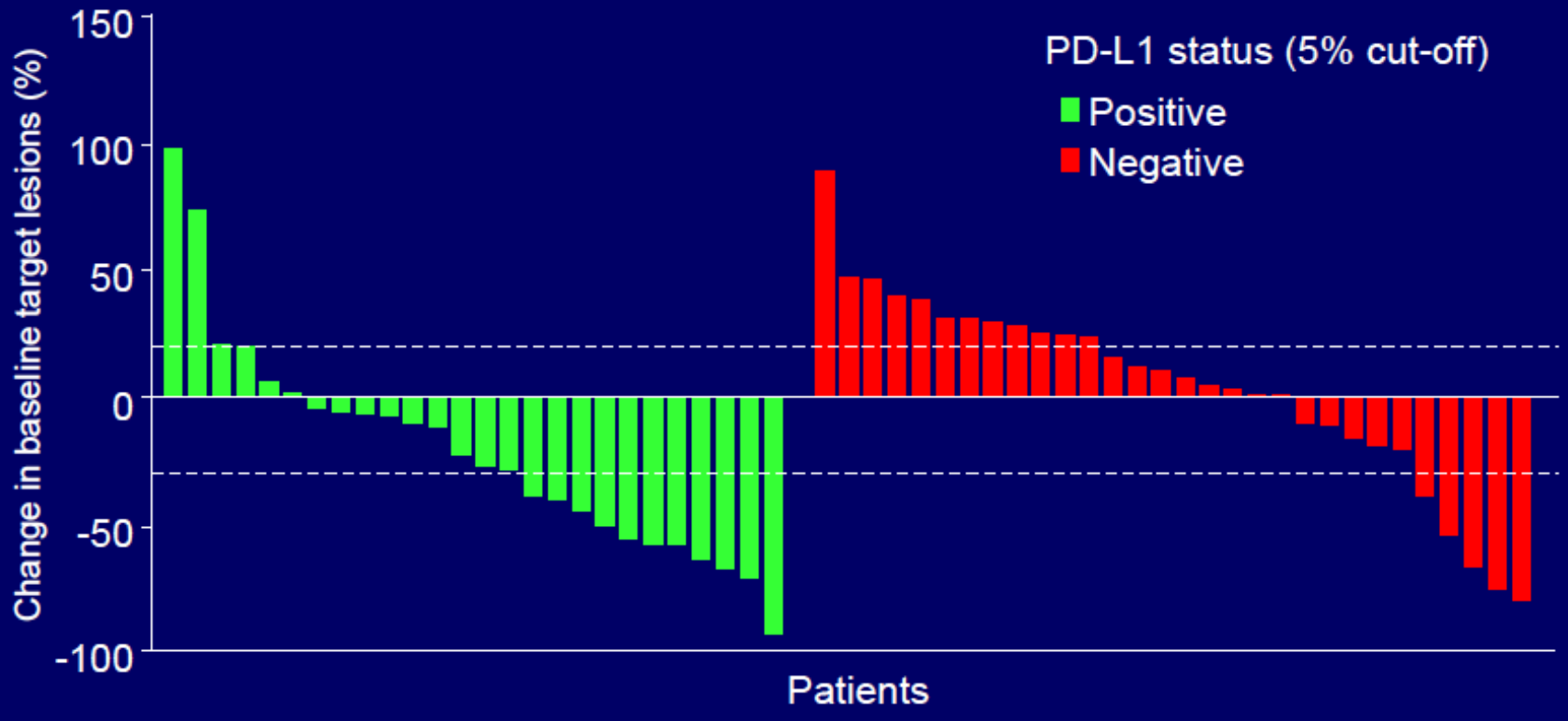
28-1, 2 µg/mL, NSCLC



Moderate and weak plasma membrane staining of frequent tumour cells (60x)

Adapted from Grosso J, et al. Poster presented at ASCO 2013 (Abstract 3016).

Best change in target lesion tumour burden by PD-L1 expression



- **Nivolumab activity was observed in patients with PD-L1+ tumours as well as in some patients with PD-L1⁻ tumours**
- **More patients with PD-L1⁺ than PD-L1⁻ tumours had a decrease in tumour burden**

Brahmer JR, et al. Poster 293 presented at ASCO 2014 (Abstract 8112)

OS and PFS by PD-L1 expression

PD-L1 tumour status	mOS months (95% CI)	mPFS months (95% CI)
Positive	7.8 (5.6, 21.7)	3.6 (1.8, 7.5)
Negative	10.5 (5.2, 21.2)	1.8 (1.7, 2.3)

- PD-L1 expression appeared to have no clear association with PFS or OS

PDL1 expression Predictive?

Brahmer JR, et al. Poster 293 presented at ASCO 2014 (Abstract 8112)

No obvious logic in pre-selecting patients based on current data

Current biomarker selection is, at best, an enrichment strategy

Protein Based Biomarkers in NSCLC

- Always difficult
- EGFR IHC remains of limited value with EGFR TKIs or monoclonal antibodies
- VEGF, VEGF receptor expression and other markers of angiogenesis not of value in selecting patients for anti-angiogenic therapy
  - Much work to be done!

Personal Experience

- Seven patients with PD1/PDL1 targeted agents 1st line setting
- All pre-selected based on IHC scores
  - 1 PR
  - 1 SD
  - 5 PDs – progress quickly
- Agents well tolerated but results appear modest

THE TIMES

No. 67524 THURSDAY AUGUST 8 2002 2W WW

Summary

- Today chemotherapy and mutation defined targeted therapies remain the 1st line treatments of choice in NSCLC
- Immune therapy holds promise with proven efficacy in second line treatment of squamous cell NSCLC vs docetaxel chemotherapy
  - Data for 1st line therapy immature
  - The good news is we don't have too long to wait to find out the answer
- Biomarker of questionable value
  - Activity seen in positive and negative cases with all assays in development

Prof Soria's and Our Dilemma…..

so much to choose from but which one and for which patient?!