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Annual Meeting '12

LUNG CANCER

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Best of ASCO, İstanbul 2012

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Treatment of Metastatic NSCLC

- **EGFR targetted treatments**
  - **1st line: EGFR-mutated: Afatinib vs chemotherapy**
  - **2nd line:**
    - **TAILOR: Docetaxel vs erlotinib in EGFR-wild type**
    - **SELECT: Chemo± Cetuximab**

- **Chemotherapy**
  - **Treatment in ECOG PS 2 patients: Pem+carbo vs. Pem**
  - **Maintenance:**

- **Novel agents**
  - **ROS1: Crizotinib**
  - **k-ras mutant pts: Selumetinib**
  - **Immunotherapy: Anti-PD1**

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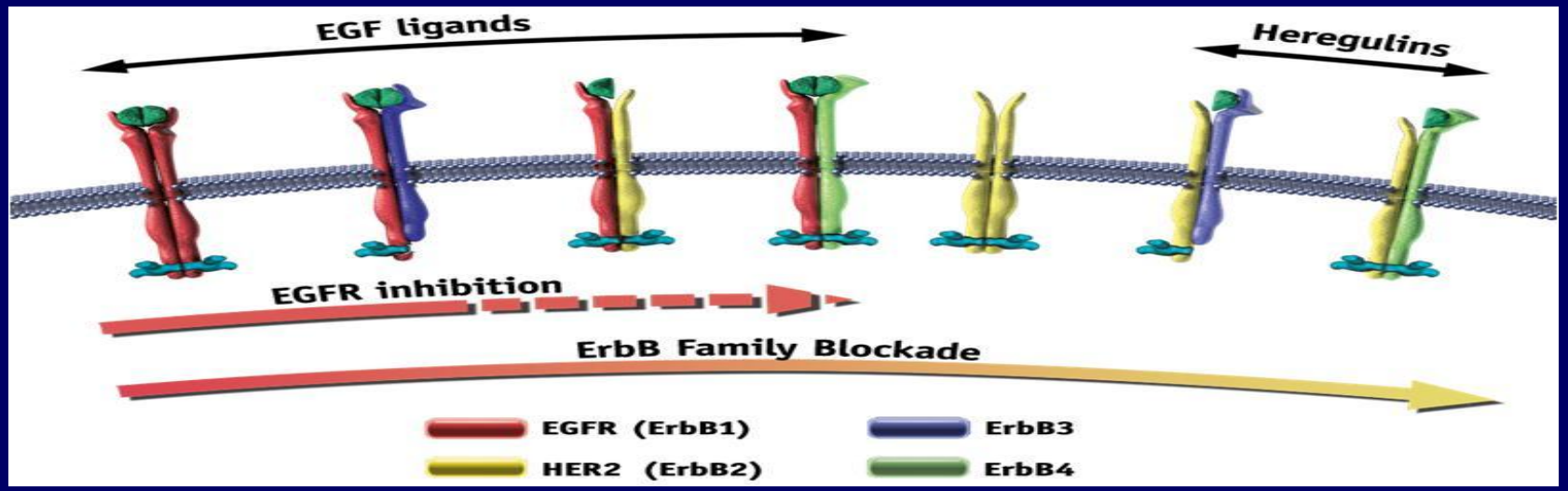
LUX-LUNG 3: Ph III, 1st line, EGFR mutated Afatinib vs. Pem/cis

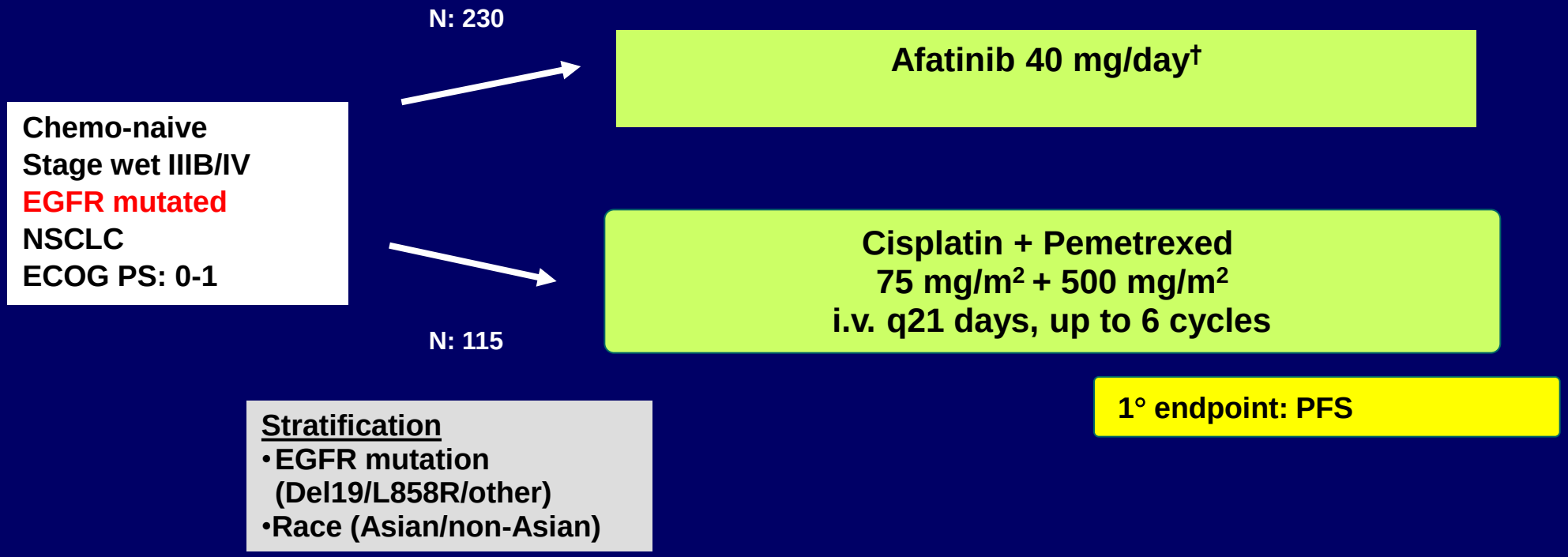
Yang et al (A#LBA7500)



- Afatinib is an orally available, irreversible ErbB Family Blocker, with high efficacy potential
  - Inhibition of ErbB Family receptor heterodimerization
  - *In vitro* activity against EGFR-resistant T790M mutation

Li D, et al. *Oncogene* 2008;27:4702–11.

EGFR mutated NSCLC: Afatinib vs. Pem/Cis



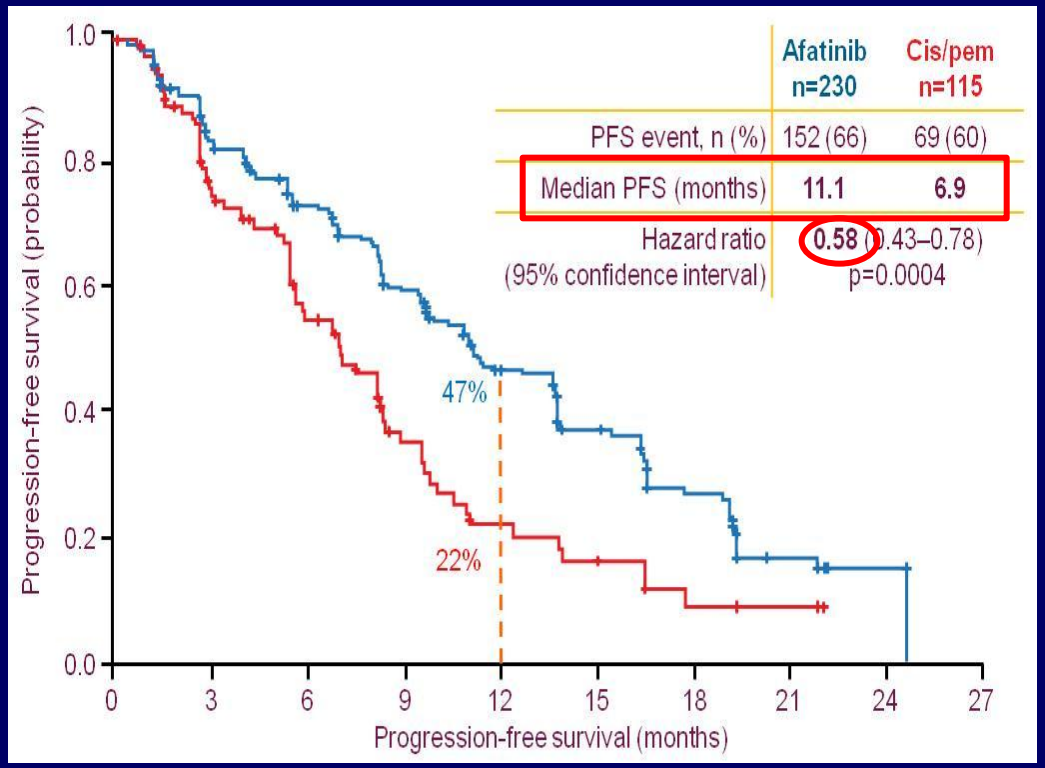
Med follow-up: 16.4 mo

† Dose escalated to 50 mg if limited AE observed in cycle 1. Dose reduced by 10 mg decrements in case of related G3 or prolonged G2 AE.

Primary endpoint: PFS

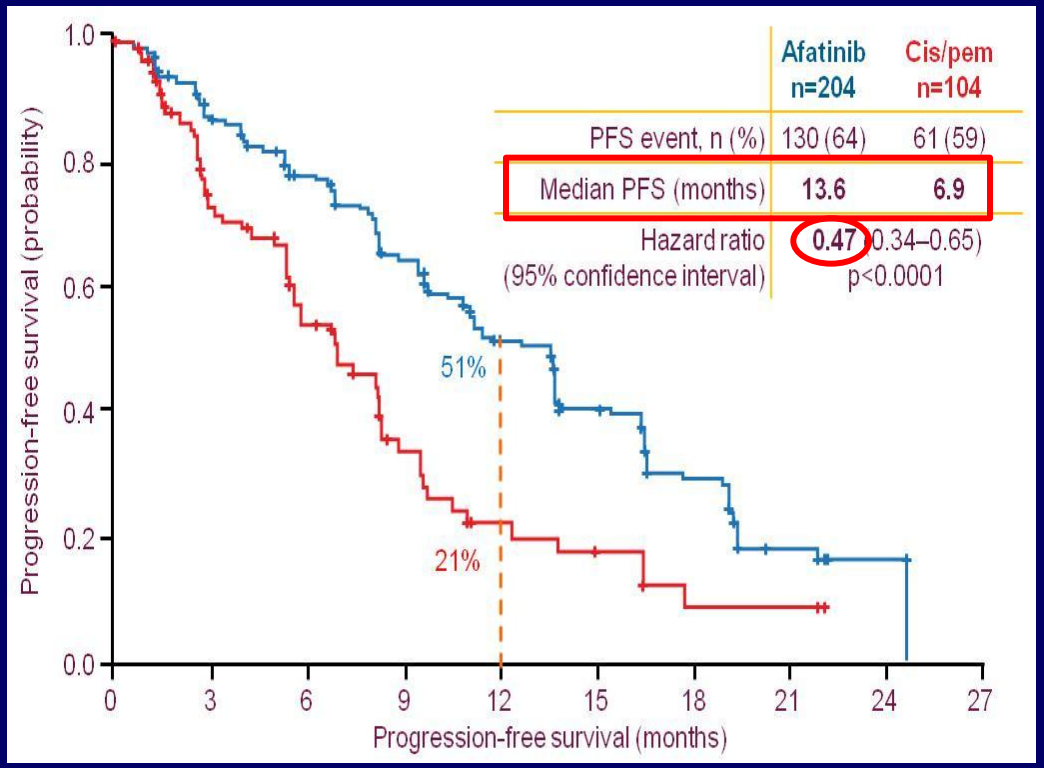
Independent review – all randomized patients

All Randomized patients



(n=345)

Common mutations (Del19/L858R)



(n=308)

Summary

- **Afatinib vs. Pem/Cis:**
  - **Increased PFS**
  - **More response (%56.1 vs. %22.6)**
  - **Better QOL**

- **Adverse events**
  - **Similar rates of Grade 3-4 AE**
  - **Afatinib: More Diarrhea , Rash/acne, Stomatitis/mucositis**

Selected trials of TKI 1st line EGFR mutation (+) NSCLC

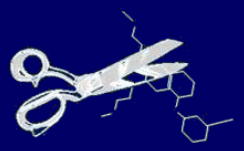
Study		RR	PFS	OS
IPASS	Carbo/Pac	41.3	5.5	.78 (0.5-1.2)
	Gefitinib	71.2	9.0	
EURTAC	Cis/Doc or Cis/Gem	15%	5.2	.80 (.47-1.37)
	Erlotinib	58%	9.7	
LUX LUNG 3	Cis/Pem	22.6	6.9	NR
	Afatinib	56.1	11.1 (13.6)	

Implications

- Afatinib > Pem/cis in 1st line, EGFR muta (+) NSCLC

- Afatinib:
  - Better than Erlotinib/gefitinib? (LUX-Lung 7)
  - Toxicity:
    - Similar?
    - Seems to have more toxicity
  - Does potential increased efficacy outweight any SAE?

- Largest trial in EGFR mutated pts
- Both Asian and European pts



TAILOR: 2nd line, Phase III Docetaxel vs. Erlotinib in EGFR-wild

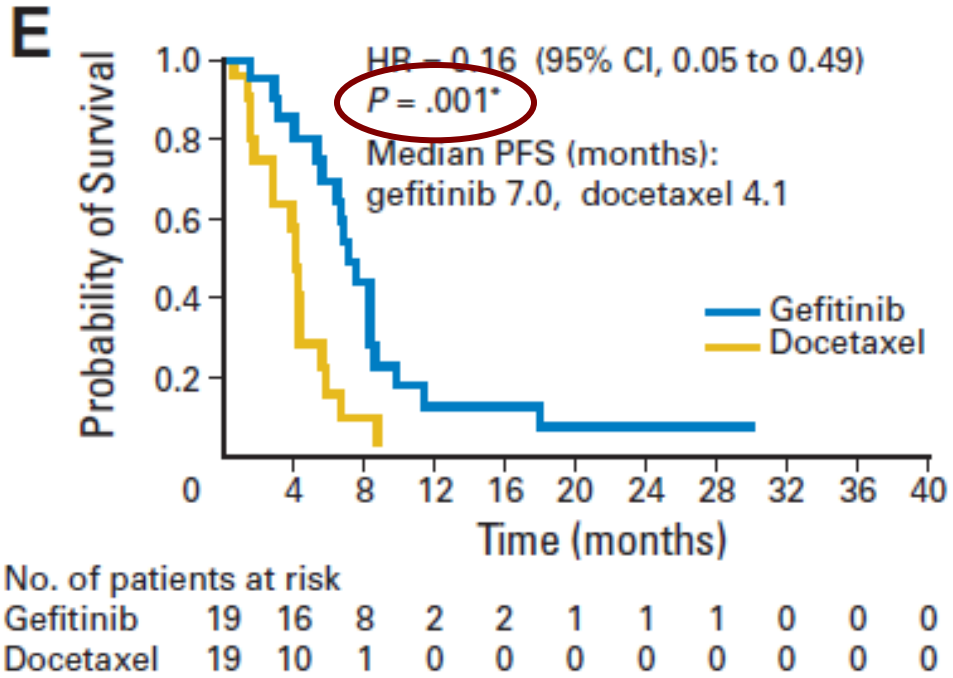
Garassino et al (A#LBA7501)

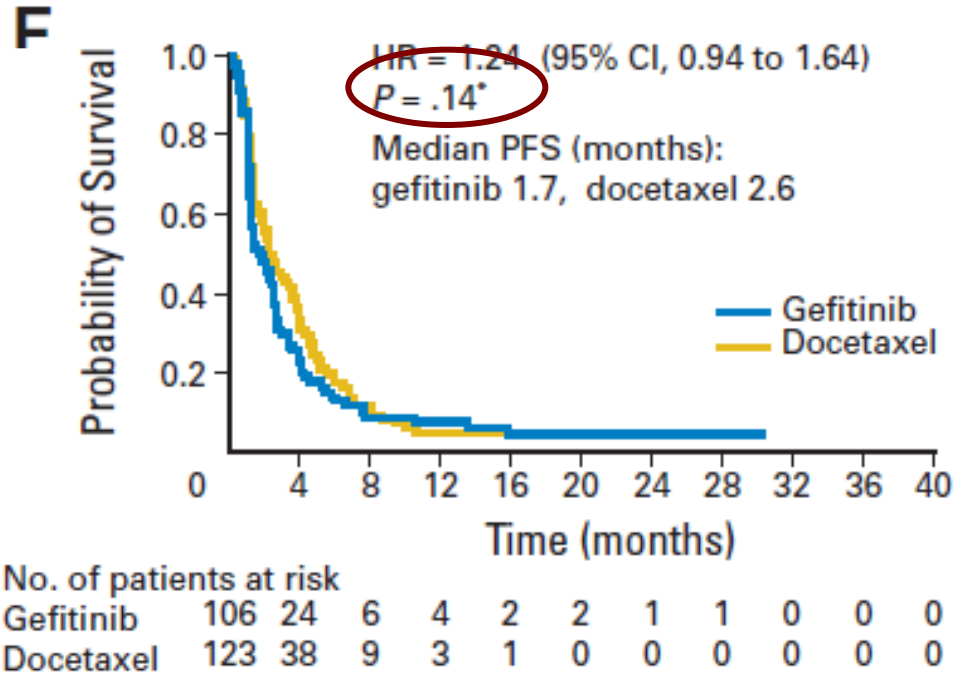
Unselected NSCLC, 2nd and 3rd line treatment

- EGFR TKI vs. chemotherapy (5 RCTs)
  - Similar OS*
  - INTEREST (Docetaxel vs. Gefitinib as 2nd or 3rd line): Similar outcome
  - Only 2 trials reported outcomes by EGFR mutational status (unplanned analyses) in about 18% of randomized patients

* Ciuleanu T, J Clin Oncol 2012; Kim ES, Lancet 2008; Maruyama R, J Clin Oncol 2008; Lee DH, Clin Cancer Res 2010; Vamvakas L, ASCO Proc 2010

INTEREST:
PFS according to EGFR mutation status
Unplanned analysis





EGFR mutation (+)

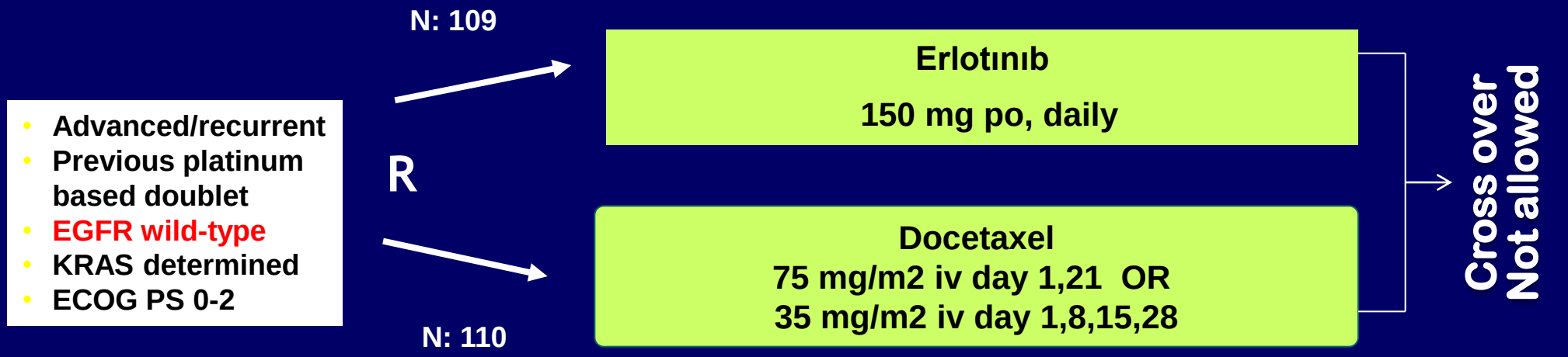
Gefitinib is better

EGFR wild type

Docetaxel and pemetrexed similar

JY Douillard et al. JCO 2009

2nd line Docetaxel vs. Erlotinib in EGFR-wild



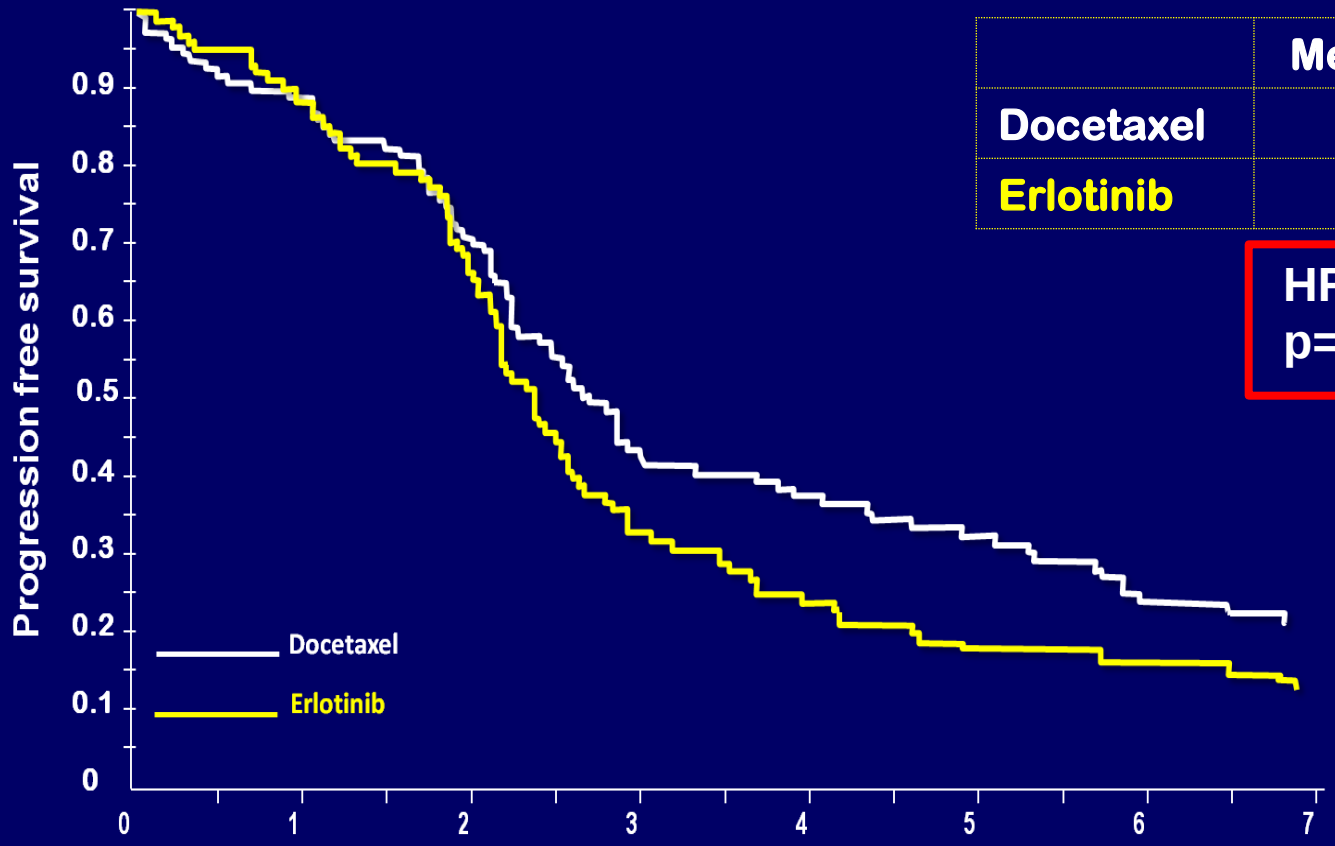
Stratification

- centre
- recurrent/progressed
- type of prior chemotherapy regimen (pem vs gem vs vnb)
- ECOG-PS (0-1 vs 2)
- adequacy of tissue sample (optimal vs suboptimal)

1° endpoint: OS
2° endpoint: PFS, ORR, QOL, safety

OS: Required number of deaths not yet reached

Better PFS with docetaxel



	Median mos.	6-mos PFS
Docetaxel	3.4	28.9%
Erlotinib	2.4	16.9%

HR 0.69 (95%CI 0.52-0.93)
p=0.014

Better Response Rate with Docetaxel

	Docetaxel n=94	Erlotınıb n=92	X^2 test
RR (CR+PR)	13.9 %	2.2 %	p=0.004
DCR (CR+PR+SD)	41.5 %	22.8 %	p=0.007

Conclusions and implications

- **TAILOR: Only prospective head-to-head trial comparing erlotinib vs docetaxel in wild-type EGFR patients**

- **2nd line treatment in EGFR wild-type pts:**
  - **Docetaxel > Erlotinib**

- **As in 1st line, do not use erlotinib without EGFR mutation analysis in 2nd line**

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    - **SELECT: Chemo± Cetuximab -> Negative trial**
- **Chemotherapy**
  - **Treatment in ECOG PS 2 patients: Pem+carbo vs. Pem**
  - **Maintenance:**
- **Novel agents**
  - **k-ras mutant pts: Selumetinib**
  - **ROS1: Crizotinib**
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- **Chemotherapy**
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  - **Continuation Maintenance**

- Novel agents
  - k-ras mutant pts: Selumetinib
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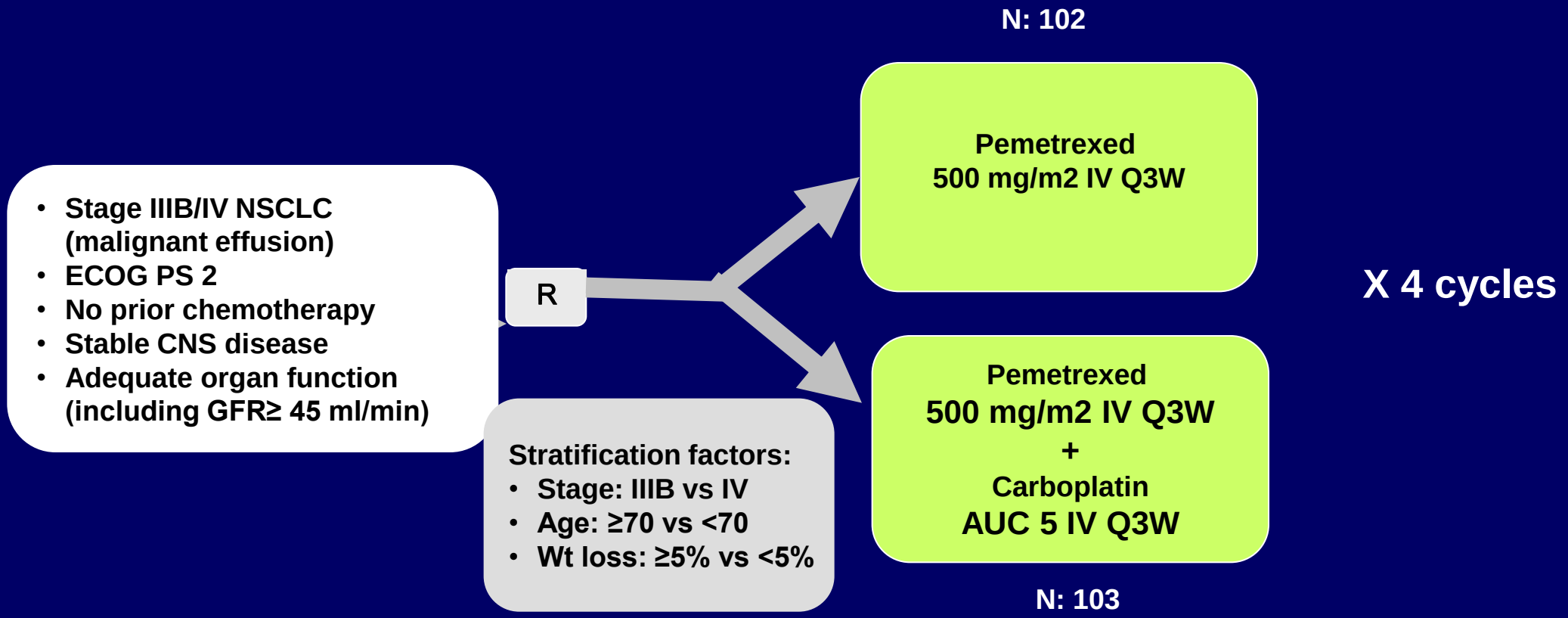
  - Immunotherapy: Anti-PD1

ECOG PS 2 patients: Pem+carbo vs. Pem

Lilenbaum et al (A#7506)



1° endpoint: OS
2° endpoint: PFS, ORR, safety

Protocol amendment in May 2009 to exclude patients with squamous cell histology – 14 patients had been enrolled at that time

Pre-medications:
- Vitamin B12: 1mg IM Injection
- Folic Acid: 350-1,000mcg po daily
- Dexamethasone 4mg po BID the day before,
- the day of, and the day after

Carbo +Pem vs Pem

Combination

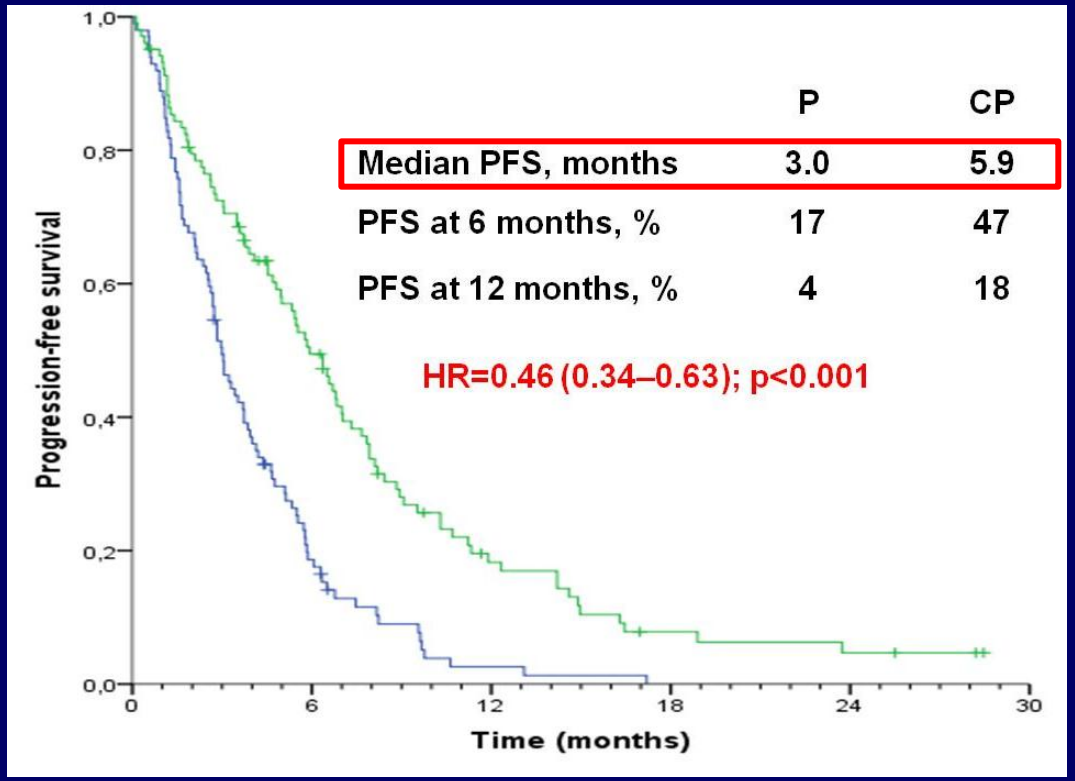
- **More pts completed therapy: 61% vs 39%**
- **Better ORR: 25% vs 10.5% (P < 0.029)**

Toxicity

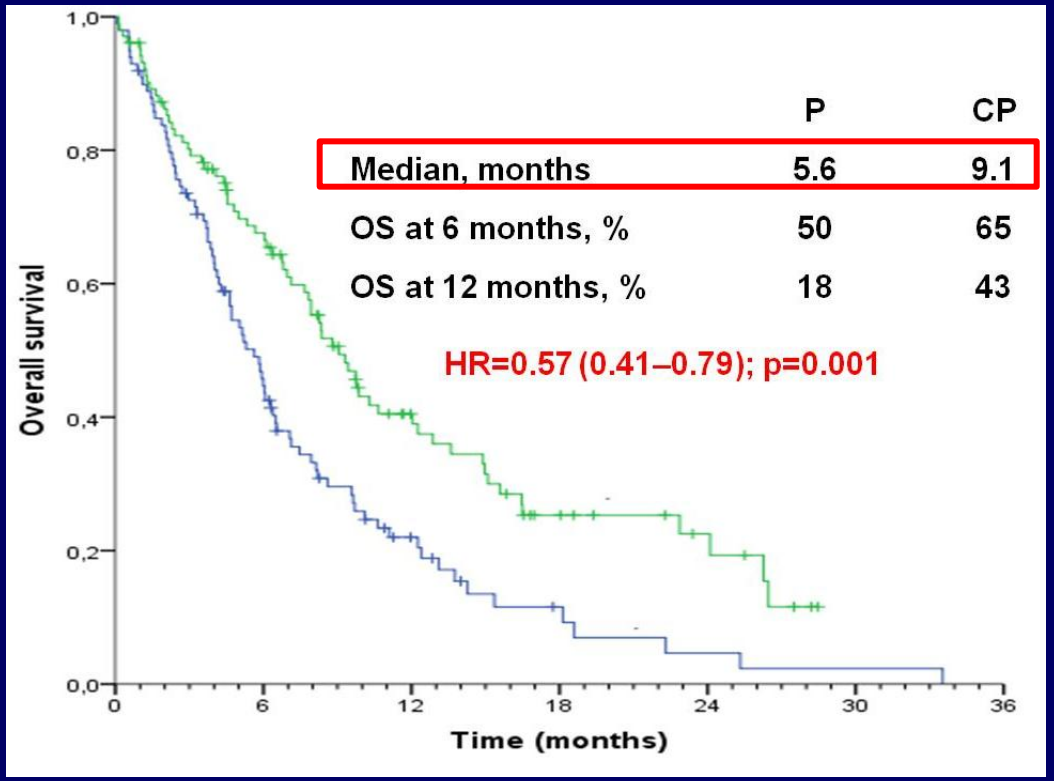
- **G3-4 toxicity: Similar between arms**
- **Toxic death:**
  - **CP: 3.9%, P: 0% (p: 0.121)**

Carbo+Pem: Better PFS and OS

PFS



OS



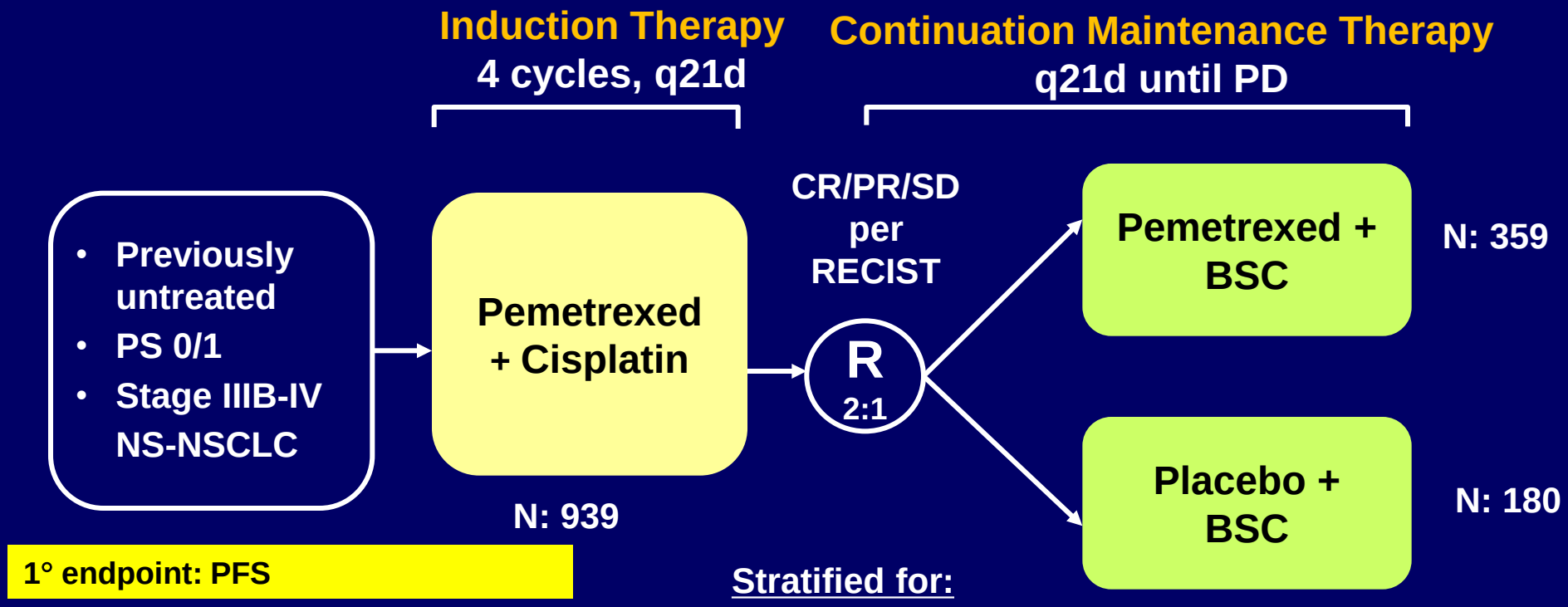
Implications for Practice

- In PS 2 patients:
  - Platin combinations better than single agent
  - Pem+carbo- > Tolerable

- PS 2 pts
  - Non-squamous: Pem+carbo >Pem
  - Gemcitabine+carbo
  - Weekly Paclitaxel + monthly carbo

PARAMOUNT: Maintenance with Pemetrexed after Pem+Cis induction

Paz-Arez et al (A#LBA7507)



1° endpoint: PFS

Med follow-up: 12.5 mo

Stratified for:

- PS (0 vs 1)
- Disease stage (IIIB vs IV) prior to induction
- Response to induction (CR/PR vs SD)

Continuation maintenance with pemetrexed: Improves survival

	Pemetrexed	Placebo	HR	P value
OS from randomization	13.9 mo	11 mo	0.78 (0.64–0.96)	0.0195
OS from induction	16.9 mo	14 mo	0.78 (0.64–0.96)	0.0191
PFS	3.9 mo	2.6 mo	0.60 (0.50-0.73)	<0.0001

Benefit in all subgroups

PARAMOUNT: Conclusions

- Survival is significantly improved with pemetrexed continuation maintenance therapy (HR=0.78)
- First study to show continuation maintenance has an impact on the disease course of advanced NSCLC (including PFS and OS)
- A change in the treatment paradigm

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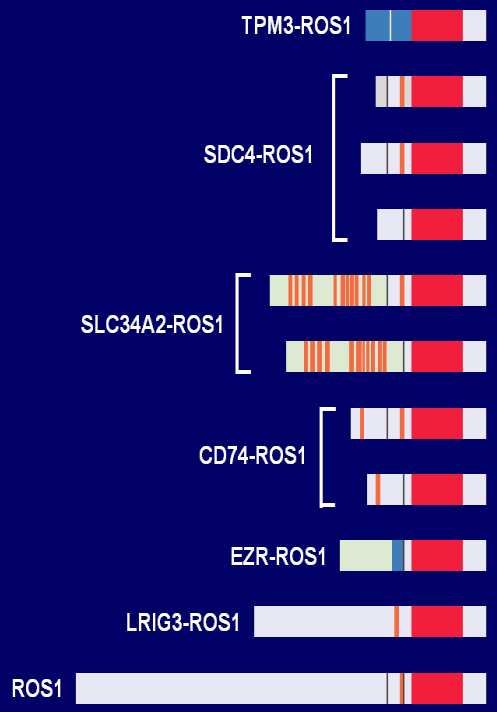
  - ROS1: Crizotinib
  - k-ras mutant pts: Selumetinib
  - Immunotherapy: Anti-PD1

Crizotinib in advanced NSCLC with ROS1 rearrangement

Shaw et al (A#7508)

ROS1 Rearrangements in NSCLC

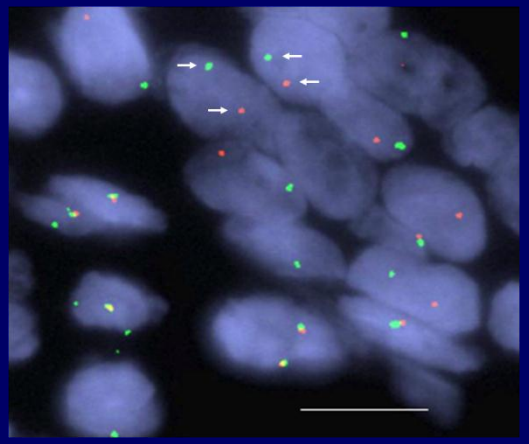


- Present in ~1% of NSCLC cases (also found in some GBMs and cholangiocarcinomas)
- ROS1: Encodes receptor tyrosine kinase
- Enriched in:
  - Younger
  - Never or light smokers
  - Adenocarcinoma
- No overlap with other oncogenic drivers

Bergethon et al., JCO 30(8): 863-70, 2012; Takeuchi et al., Nat Med 18(3): 378-81, 2012

Phase 1 Study of Crizotinib (PROFILE 1001)

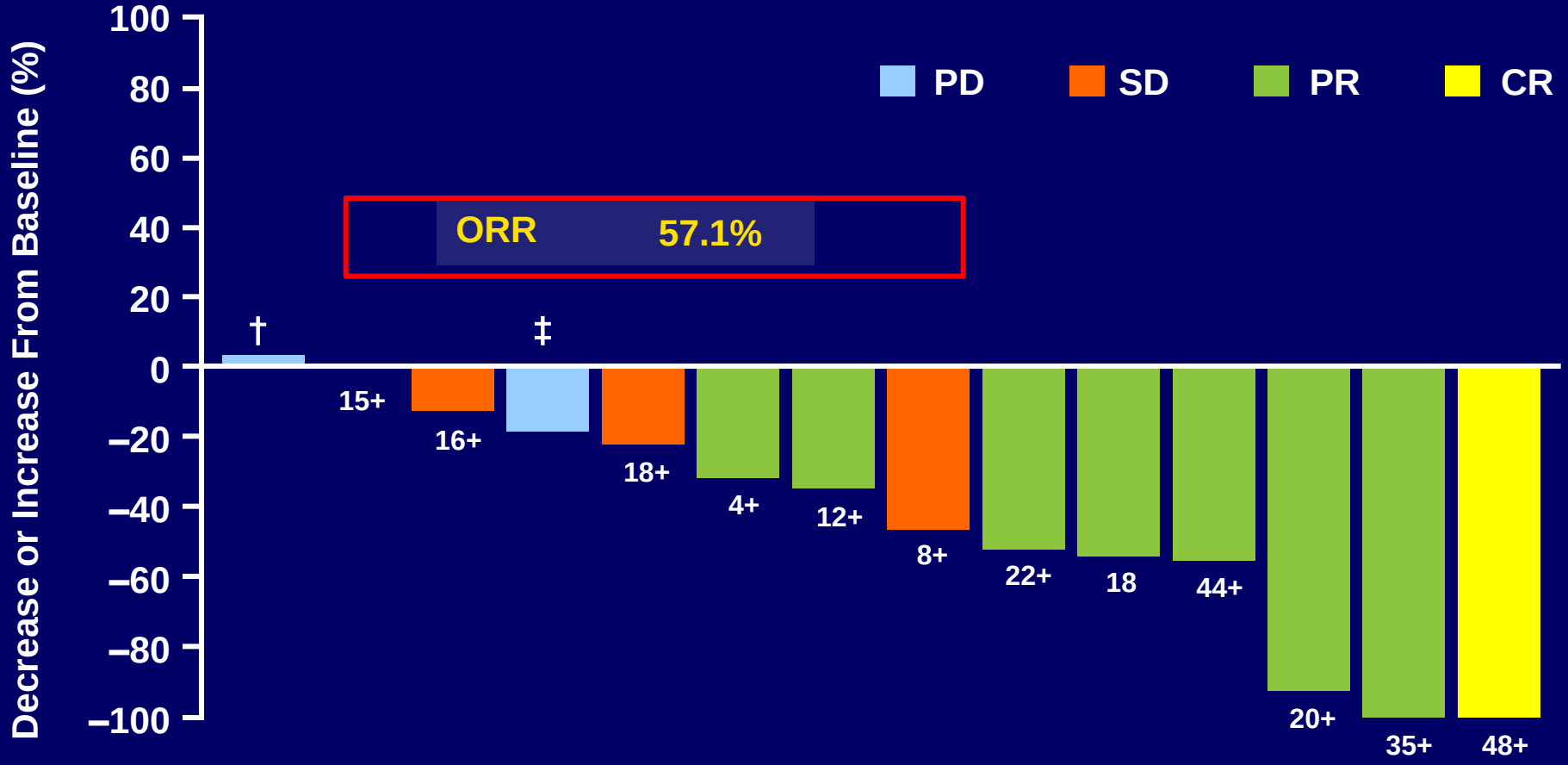
- N: 15
- ROS1 rearrangement(+)



“Break-Apart” FISH Assay for ROS1 Rearrangement

- Crizotinib: TKI of c-MET, ALK and ROS1

Tumor Responses to Crizotinib in Patients with Advanced ROS1+ NSCLC (N=14*)



*Response-evaluable population. †Tumor ROS1 FISH-positive, but negative for ROS1 fusion gene expression. ‡Crizotinib held for >6 wks prior to first scans which showed PD. **+, Treatment ongoing.**

Summary

- **ROS1 rearrangement**
  - **A distinct subset of NSCLC**
  - **A new therapeutic target in lung cancer**
- **Crizotinib: Marked antitumor activity in patients with advanced ROS1-positive NSCLC**

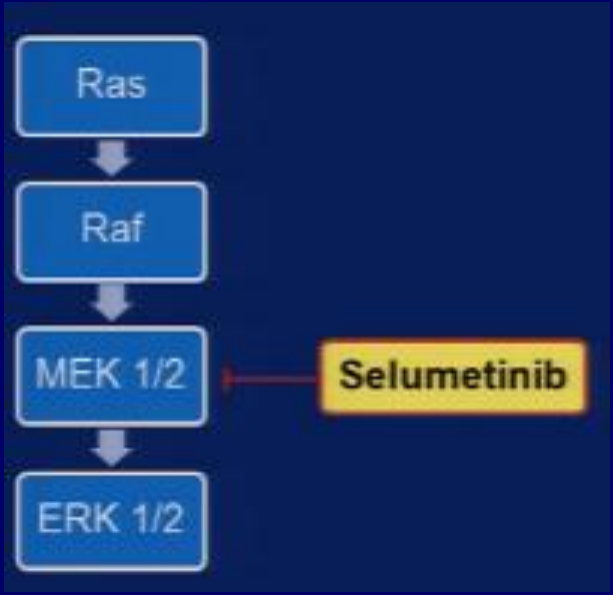
Doce ± Selumetinib in k-ras mutant advanced NSCLC as 2nd line

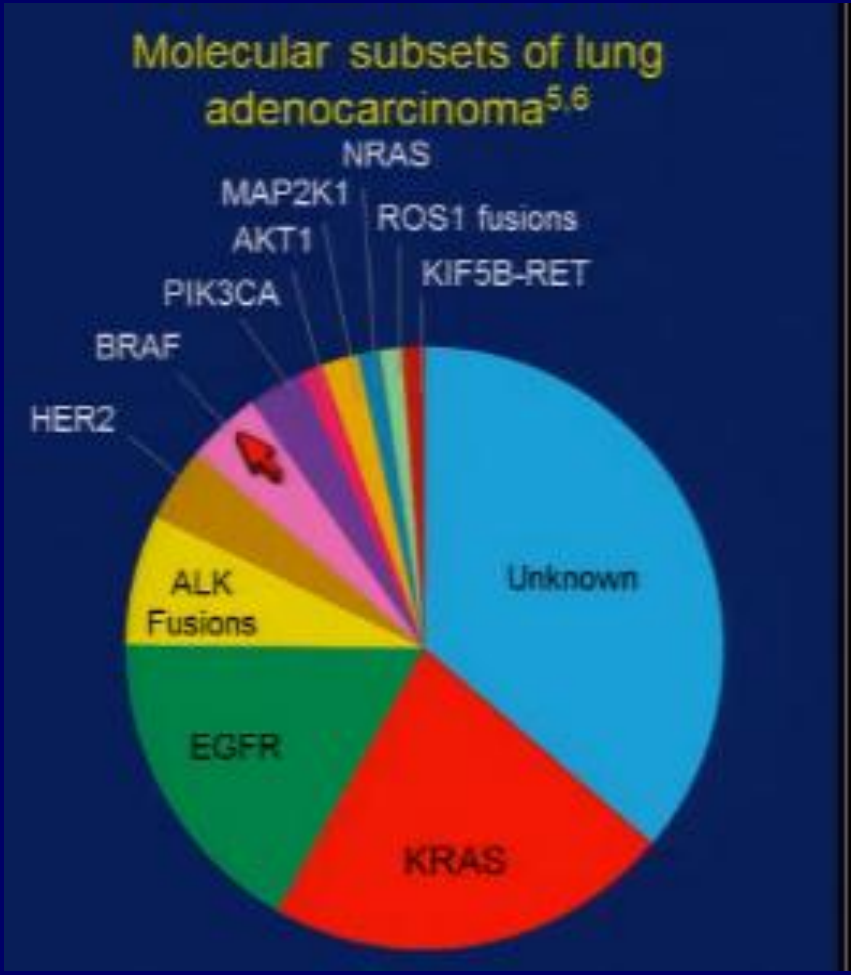
Janne et al (A#7503)

K-ras mutant NSCLC

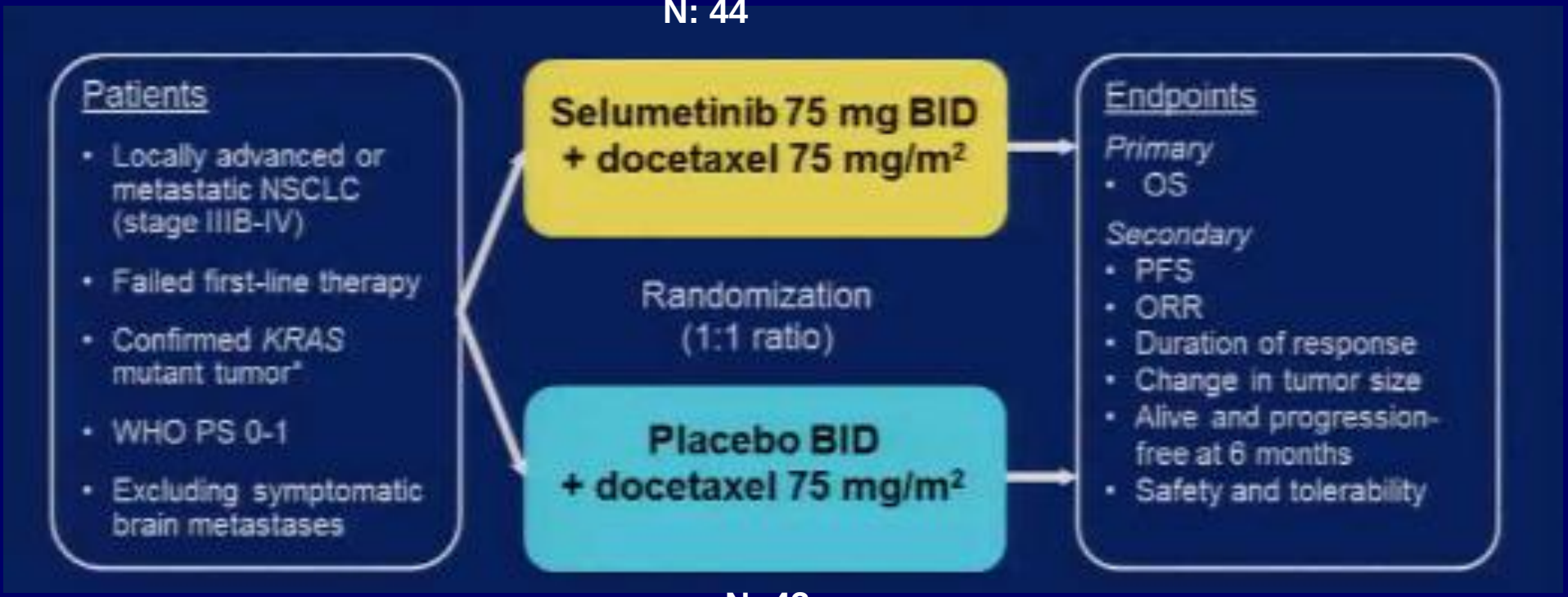
- %20
- Resistant to EGFR TKI
- Effectiveness of chemotherapy may be reduced

Selumetinib





Doce ± Selumetinib in k-ras mutant NSCLC: Phase II double blind



1° endpoint: OS
2° endpoint: PFS, ORR, safety

Janne et al (A#7503)

Addition of selumetinib to docetaxel

- **Non-significant increase in OS**
  - **9.4 mo vs. 5.2 mo (HR: 0.80, P=0.20)**
- **Toxicity increased**
- **Improved RR (37% vs 0%, P<0.0001)**
- **Improved PFS**
  - **5.3 mo vs. 2.1 mo (HR: 0.58, P=0.0138)**

Janne et al (A#7503)

Conclusion

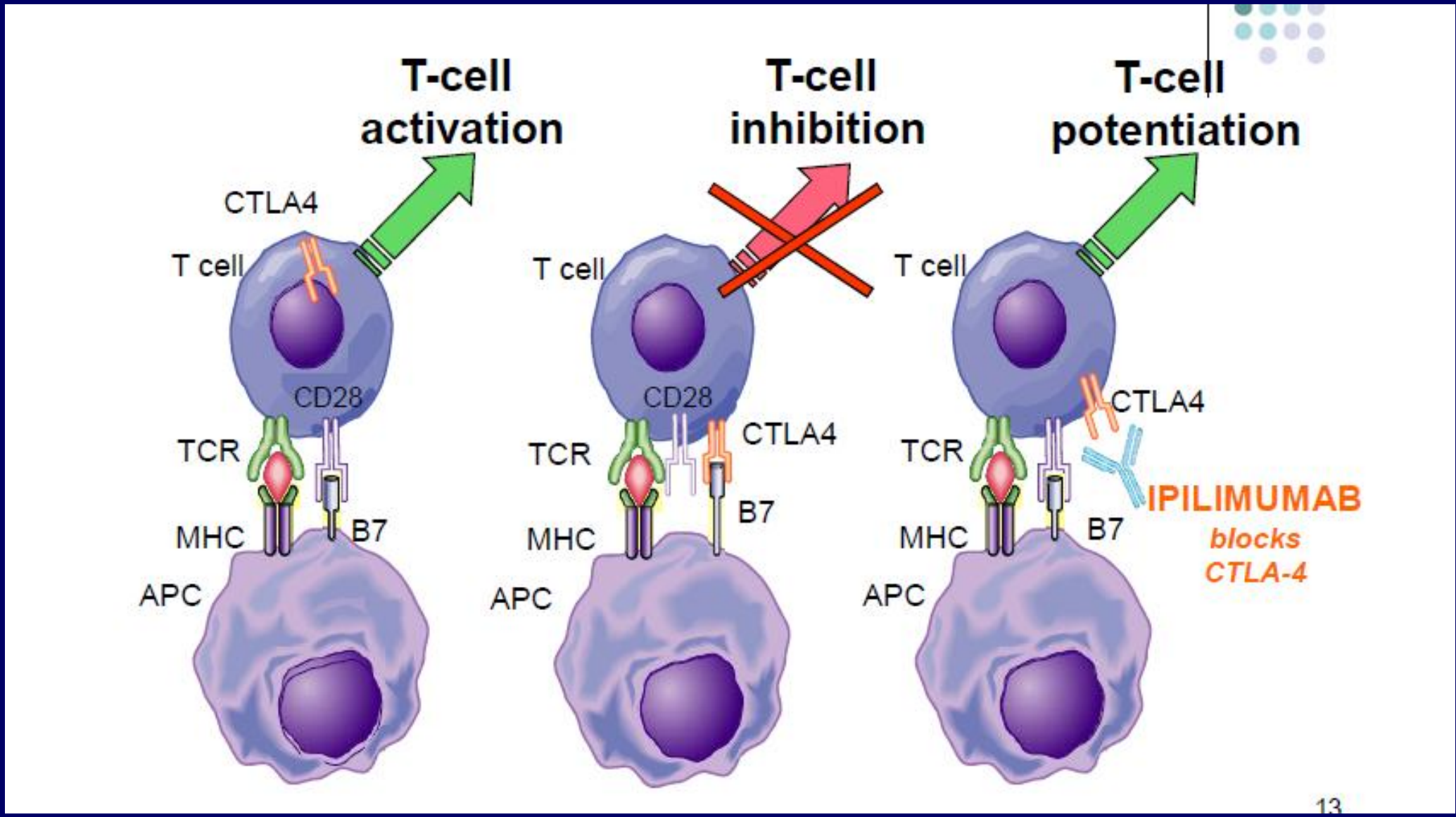
- 1st prospective study demonstrating clinical benefit in k-ras mutant NSCLC
- OS (primary endpoint): not improved significantly -> Negative trial
- Promising, further investigation needed

Anti-PD-1 (BMS-936558, MDX-1106) in advanced NSCLC

Brahmer et al (A#7509)

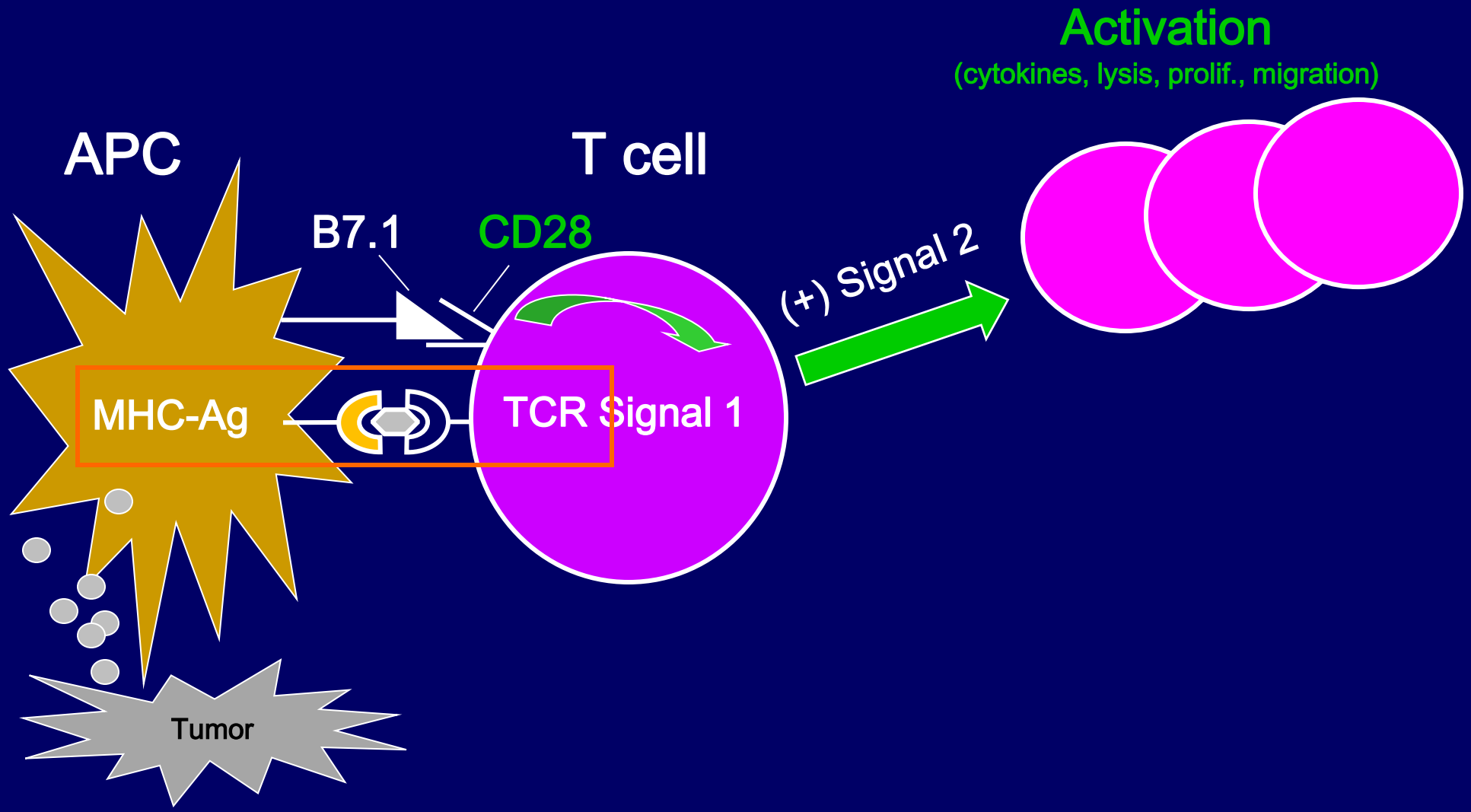
- **Immunotherapy in NSCLC: Not successful**
- **Tm resist immune attack by inducing tolerance among tumor-specific T cells**
- **Check-point inhibitors in NSCLC:**
  - **Preliminary evidence of activity with CTLA-4 and chemotherapy [1,2]**
    - **İpilumumab +Pacli/carbo: Improve PFS**
    - **Esp. in squamous cell ca**

[1]Lynch TJ, et al. J Clin Oncol. 2012. [2]Genova C, et al. Expert Opin Biol Ther 2012.



CTLA-4 and CD28 interaction: Happens primarily in the priming phase of T-cell response within lymph node

Role of PD-1 in Suppressing Antitumor Immunity



Keir ME et al, Annu Rev Immunol 2008; Pardoll DM, Nat Rev Cancer 2012

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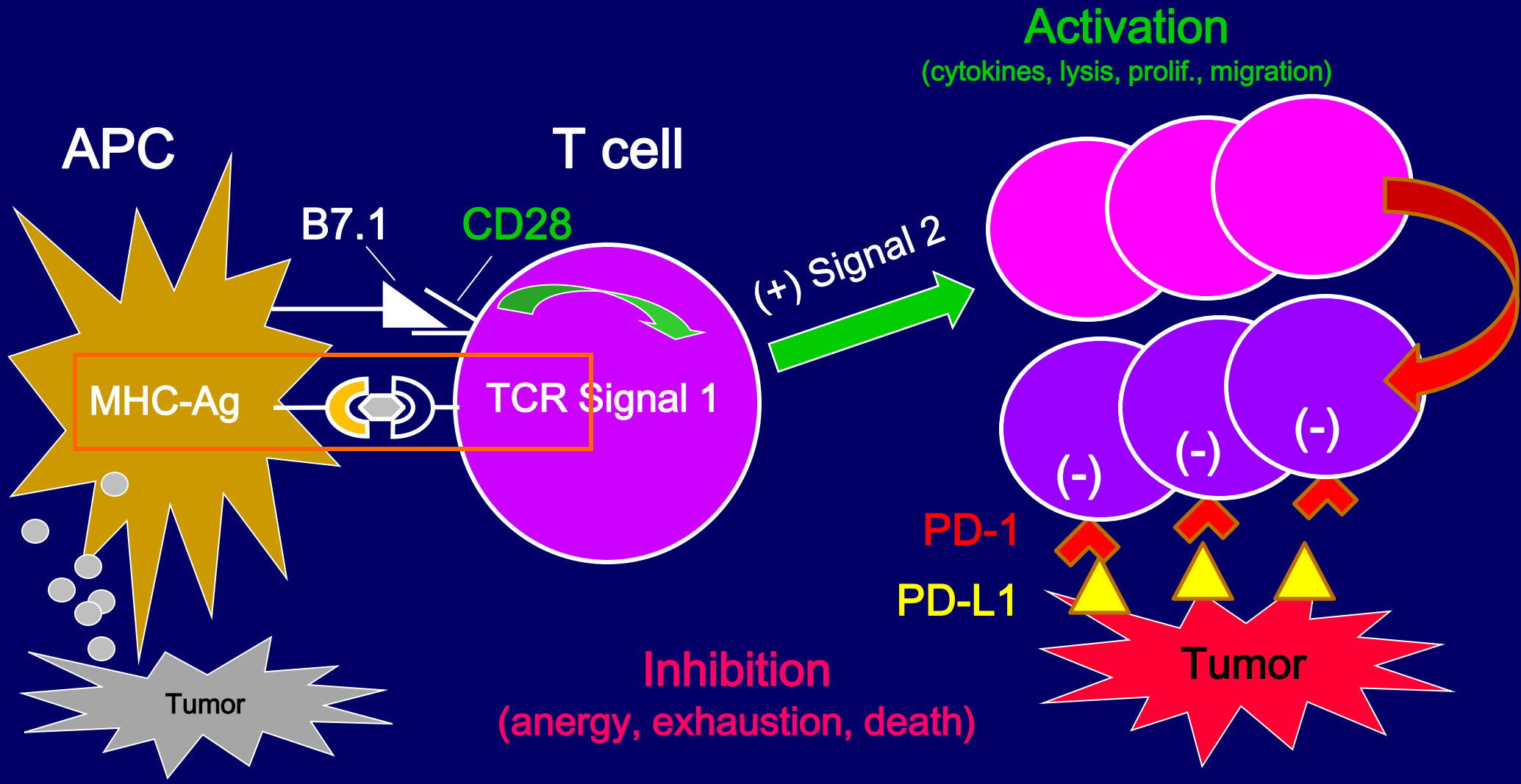

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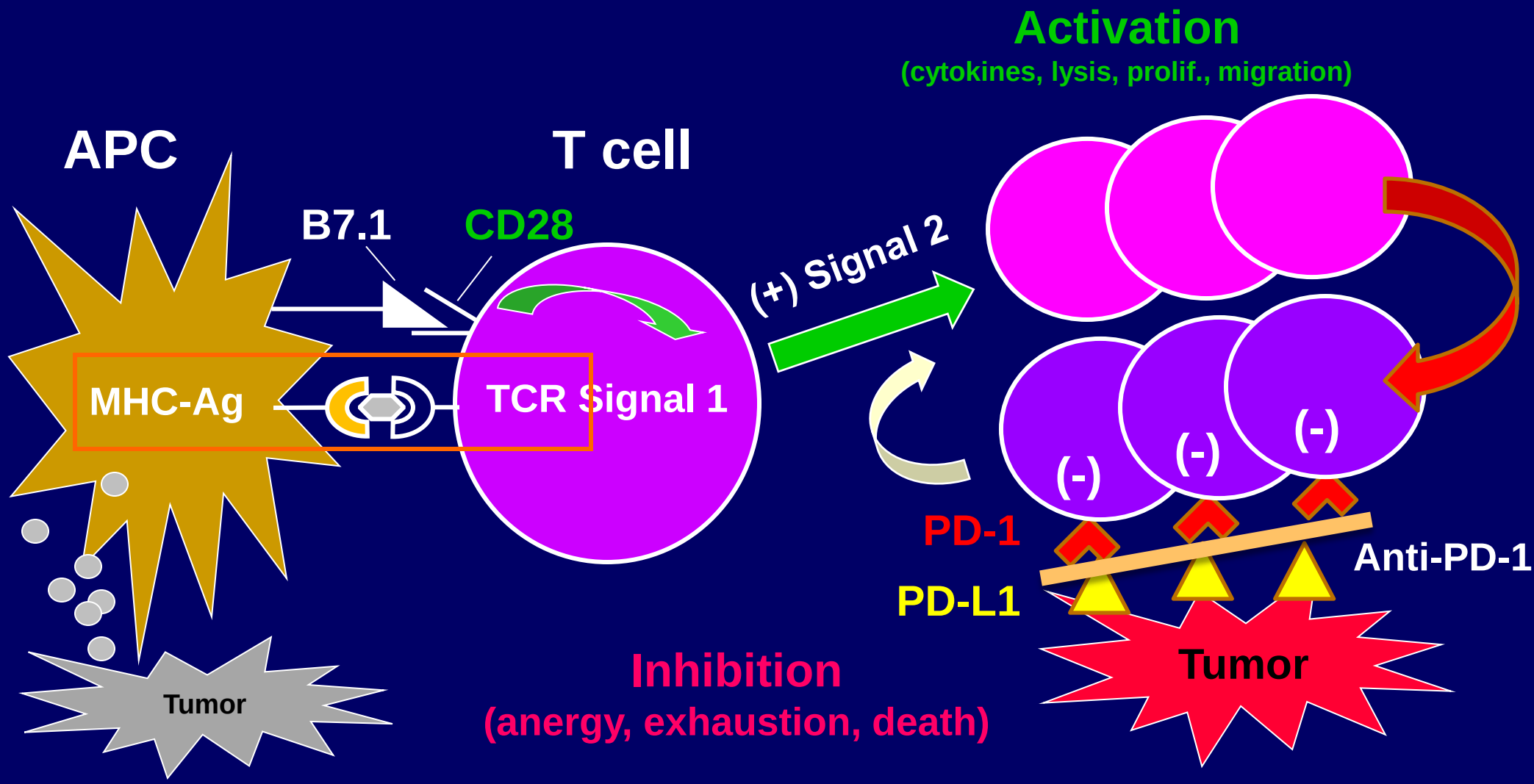
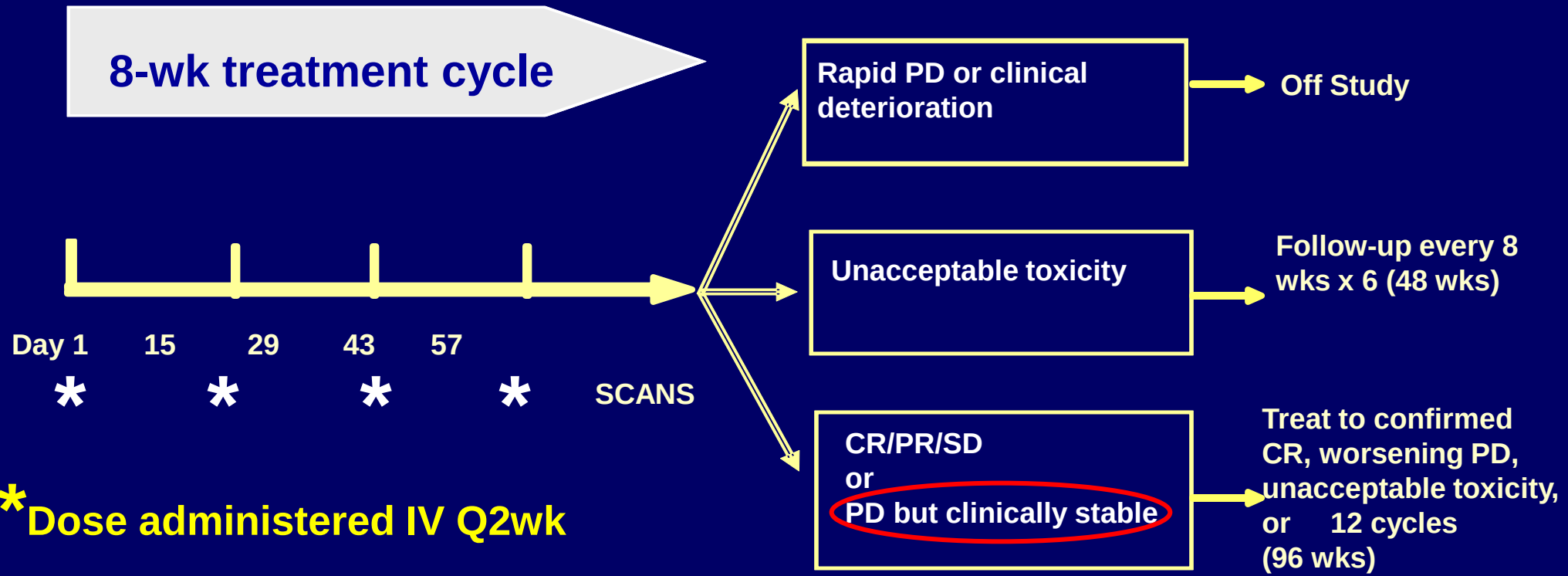


Keir ME et al, Annu Rev Immunol 2008; Pardoll DM, Nat Rev Cancer 2012

Phase I Multi-dose Regimen

BMS-936558: Anti-human PD-1 blocking Ab



*Dose administered IV Q2wk

Doses tested for NSCLC: 1, 3, 10 mg/kg

Eligibility: Advanced MEL, RCC, NSCLC, CRC, or CRPC with PD after 1-5 systemic therapies

Baseline Characteristics

Baseline Characteristic	n=122
Median age (range), yr	65 (38-85)
Male, no. (%)	74 (61)
Tumor histology, no. (%)*	
Squamous	47 (39)
Non-squamous	73 (60)
ECOG PS, no. (%)†	
0-1	117 (96)
2	2 (2)
Number of prior therapies, no. (%)‡	
1-2	49 (40)
≥3	67 (55)
Nature of prior therapy, no. (%)	
Platinum-based chemotherapy	115 (94)
Tyrosine-kinase inhibitor	41 (34)
Radiotherapy	40 (33)

*Unknown: 2 (2%). †Not reported: 3 (2%). ‡Not reported: 6 (5%).

Evaluation of safety:
122 NSCLC pts

Evaluation for clinical activity:
76 NSCLC pts

Key Safety Results

Adverse Events (AEs)	Ipilimumab[1] N= 131 (%)	BMS-936558 N=122 (%)
Any AE	96.9	64
Grade 3 - 4	45.8	8
Diarrhea	32.8	6
Grade 3 - 4	5.3	1
Fatigue	42	18
Grade 3 - 4	6.9	2
Dyspnea / Pneumonitis	14.5	5
Grade 3 - 4	3.9	3*
Any immune-related AE	61.1	?
Grade 3 / 4	14.5	?

1 Hodi et al. NEJM 2010

* 2 deaths

Clinical Activity of BMS-936558 in NSCLC Patients

Pop	Dose (mg/kg)	Pts n	ORR n (%)	Duration of Response (mo)	SD ≥24 wk n (%)	PFSR at 24 wk (%)
ALL NSCLC	1-10	76	14 (18%)	1.9+ to 30.8+	5 (7)	26

Parameter	BMS-936558 Dose, mg/kg		
	1	3	10
ORR, No. patients* (%)			
Squamous	6/18= 33%		3 (43) n=7
Non-squamous	7/56= 12.5%		4 (13) n=31

- 3 NSCLC patients had a persistent reduction in baseline target lesions in the presence of new lesions but were not classified as responders for the ORR calculation

Conclusions

- **Anti-PD1 Ab**
  - **safe in heavily pretreated NSCLC patients**
  - **Durable clinical benefit was seen in both squamous and non-squamous NSCLC**

- **Preliminary data:**
  - **Response correlates with PD-L1 expression in pretreatment tumor biopsies**

SCLC /Stage III NSCLC/ Others

SCLC /Stage III NSCLC/ Others

- **SCLC:**
  RT starting with 1st or 3rd cycle of cis-etoposide in limited stage

- **Stage III NSCLC:**
  Consolidation vs none after concomitant chemoRT

- **Squamous cell ca:** Genomic alterations

- **Diagnosis:** Accuracy of FDG-PET

SCLC /Stage III NSCLC/ Others

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- **Squamous cell ca: Genomic alterations**

- **Diagnosis: Accuracy of FDG-PET**

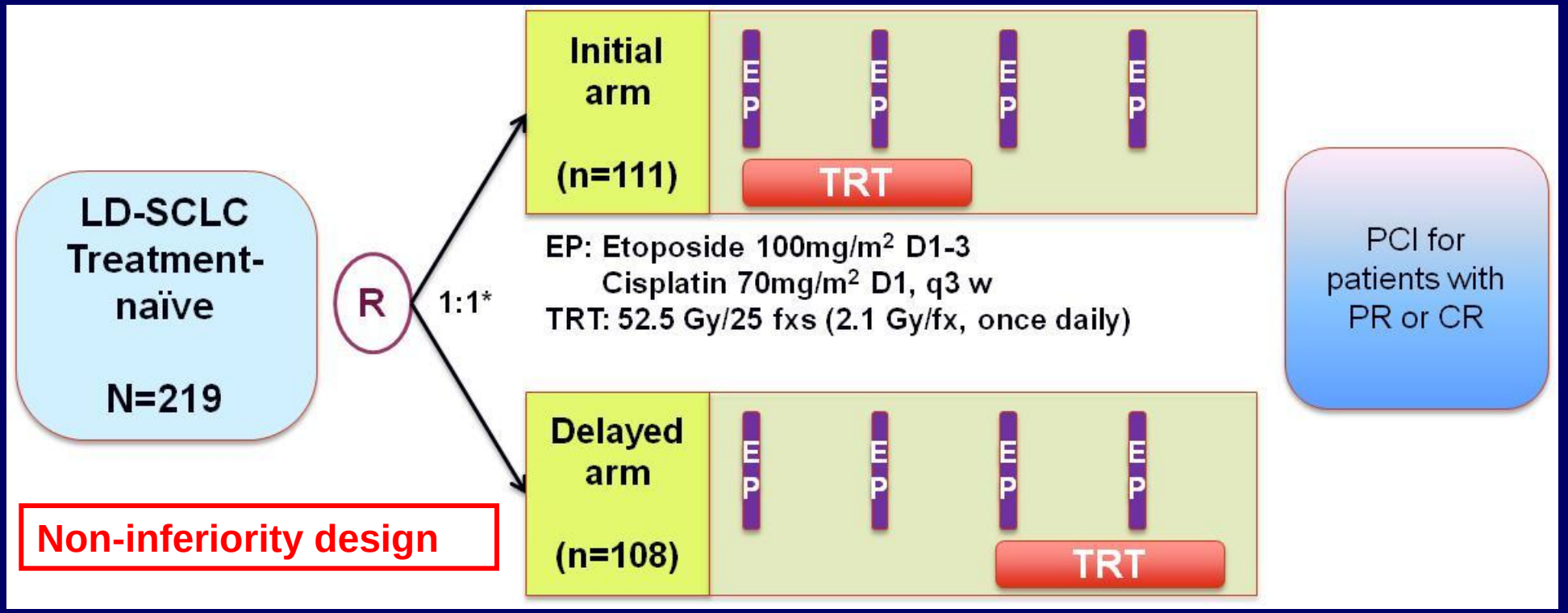
Limited Stage SCLC: Concurrent Thoracic Radiotherapy (TRT) with Either the 1st Cycle or the 3rd Cycle of Cisplatin and Etoposide Chemotherapy

K. Park et al. (A#7004)

Background

- Standard in limited stage: concurrent thoracic radiotherapy (TRT) with chemotherapy
- Optimal timing: Not defined
- Limitations in early initiation of TRT given with the 1st cycle
  - Potentially enlarged radiation fields due to initial planning for bulky tumors
  - Complexity of administering TRT results in delayed overall treatment for LD-SCLC

Study design



- **Primary end point: Complete response rate (WHO criteria)**
- **Secondary end point: ORR, OS, PFS, and toxicity (NCI-CTC ver. 2.0)**

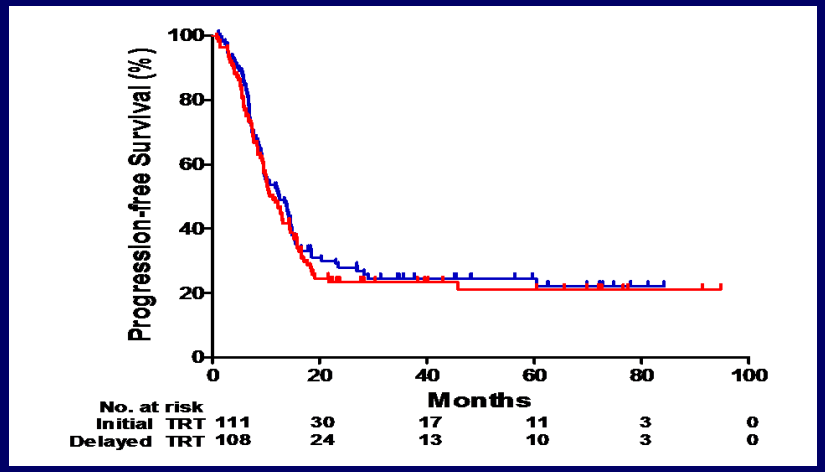
- *Stratified by the institute
- Response evaluation: every 2 cycles during treatment, every 3 mo. for 1 Y, and then every 6 mo.

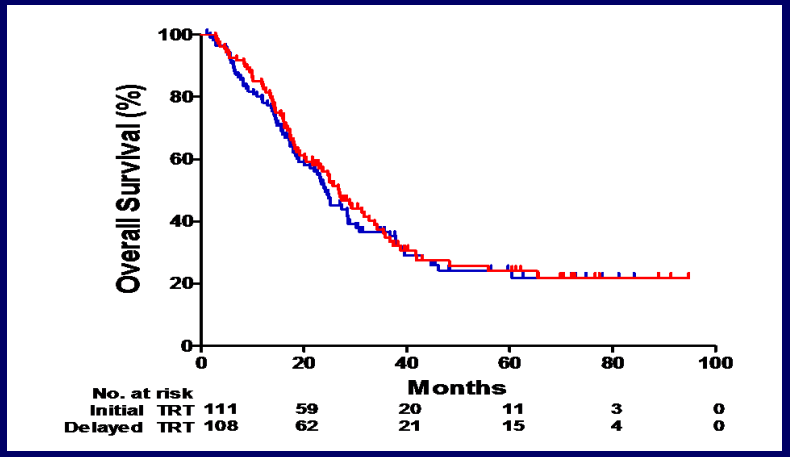
Results

- CR rates are similar

	Initial Arm (n = 111)	Delayed Arm (n = 108)	95% CI of the difference
CR	40 (36.0%)	41 (38.0%)	(-14.7%, 10.9%)

- PFS and OS are similar





- TRT with the 3rd cycle of EP: Lower incidence of neutropenic fever (21.6% vs. 10.2%)

Conclusion

Concurrent TRT with the 3rd cycle of EP chemotherapy was non inferior to the 1st cycle of EP chemotherapy

SCLC /Stage III NSCLC/ Others

- **SCLC:**
  RT starting with 1st or 3rd cycle of cis-etoposide in limited stage

- **Stage III NSCLC:**
  Consolidation vs none after concomitant chemoRT

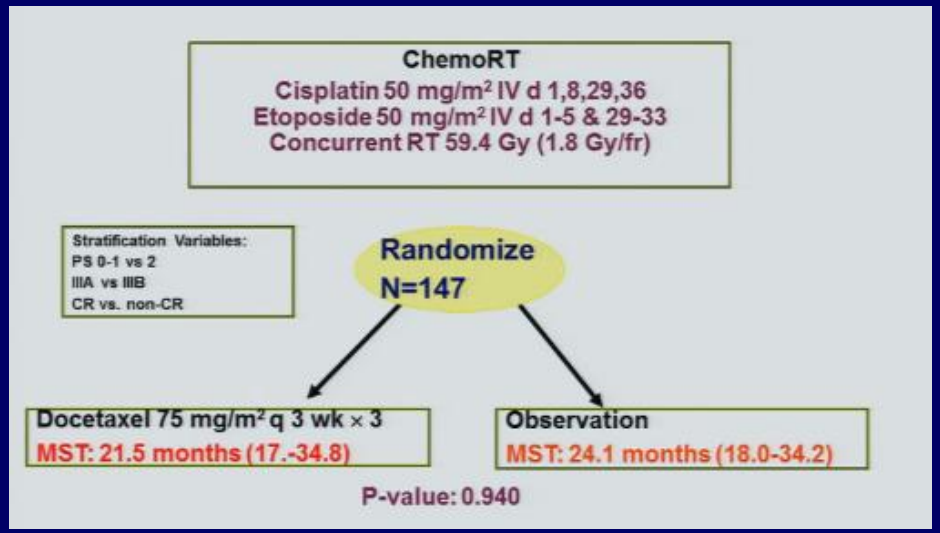
- **Squamous cell ca: Genomic alterations**

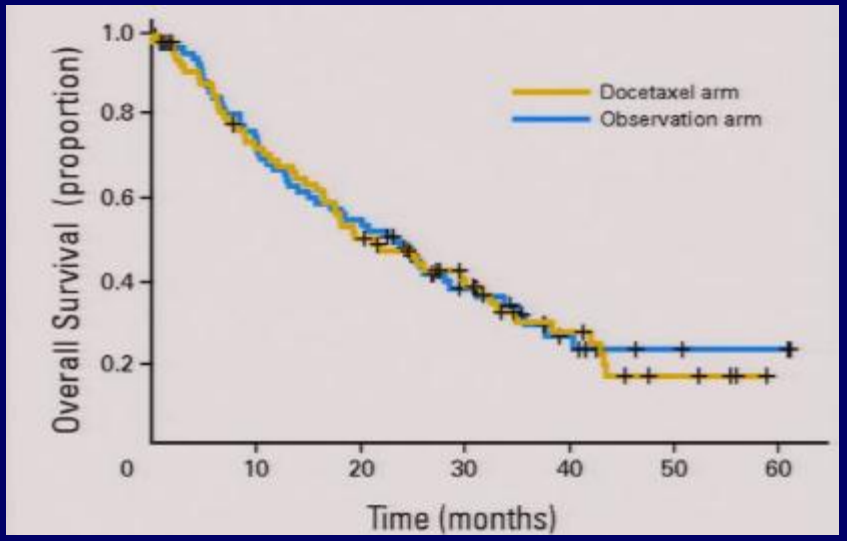
- **Diagnosis: Accuracy of FDG-PET**

Stage III NSCLC: Consolidation or not

Background

- **Standard LA-NSCLC: Concurrent chemoradiotherapy**
- **Consolidation chemotherapy:**
  - **Limited data: Few randomized studies**
  - **HOG LUN 01-24 trial: n: 243 → Consolidation did not improve survival**





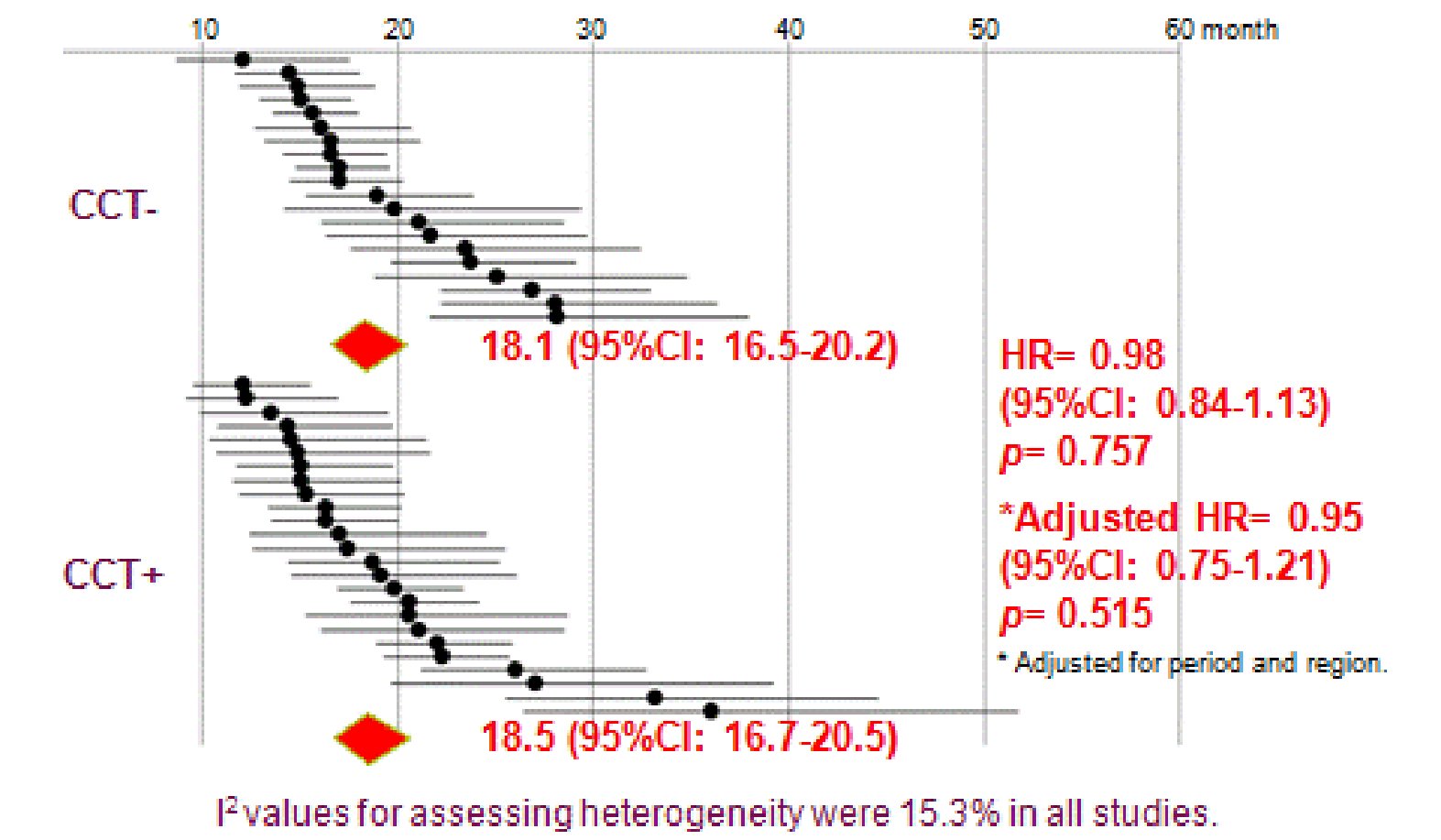
1) Hanna N et al; J Clin Oncol 26: 5755-5760, 2008.

A pooled analysis of the literature:
Yamamoto et al (A#7000)

- Systematically searched PubMed for phase II or phase III trials published between January 1, 1995 and October 31, 2011.

- 45 studies, n: 3447
  - CCT(-): 1740 pts
  - CCT(+): 1707 pts

Individual and pooled median OS



Toxicities throughout the whole treatment courses were comparable.

Stage III NSCLC: Consolidation or not
IMPLICATIONS

- Many oncologists are uncomfortable with only 2 cycles of chemo in stage III dis
  - Stage II-IIIA: Adjuvant 4 cycles
  - Neoadjuvant: 3 cycles
- Systemic relapses remain an important issue
- Will we change our practice based on these trials?
  - Metanalysis: Heterogenous trials, Phase II and III together
  - Rando trials: small sized (<300 pts)
- Many ongoing trials are built on consolidation platform

Consolidation or not

- **Consolidation: Not improve survival**
- **Consolidation chemotherapy after concomitant chemoRT: can not be recommended**

SCLC /Stage III NSCLC/ Others

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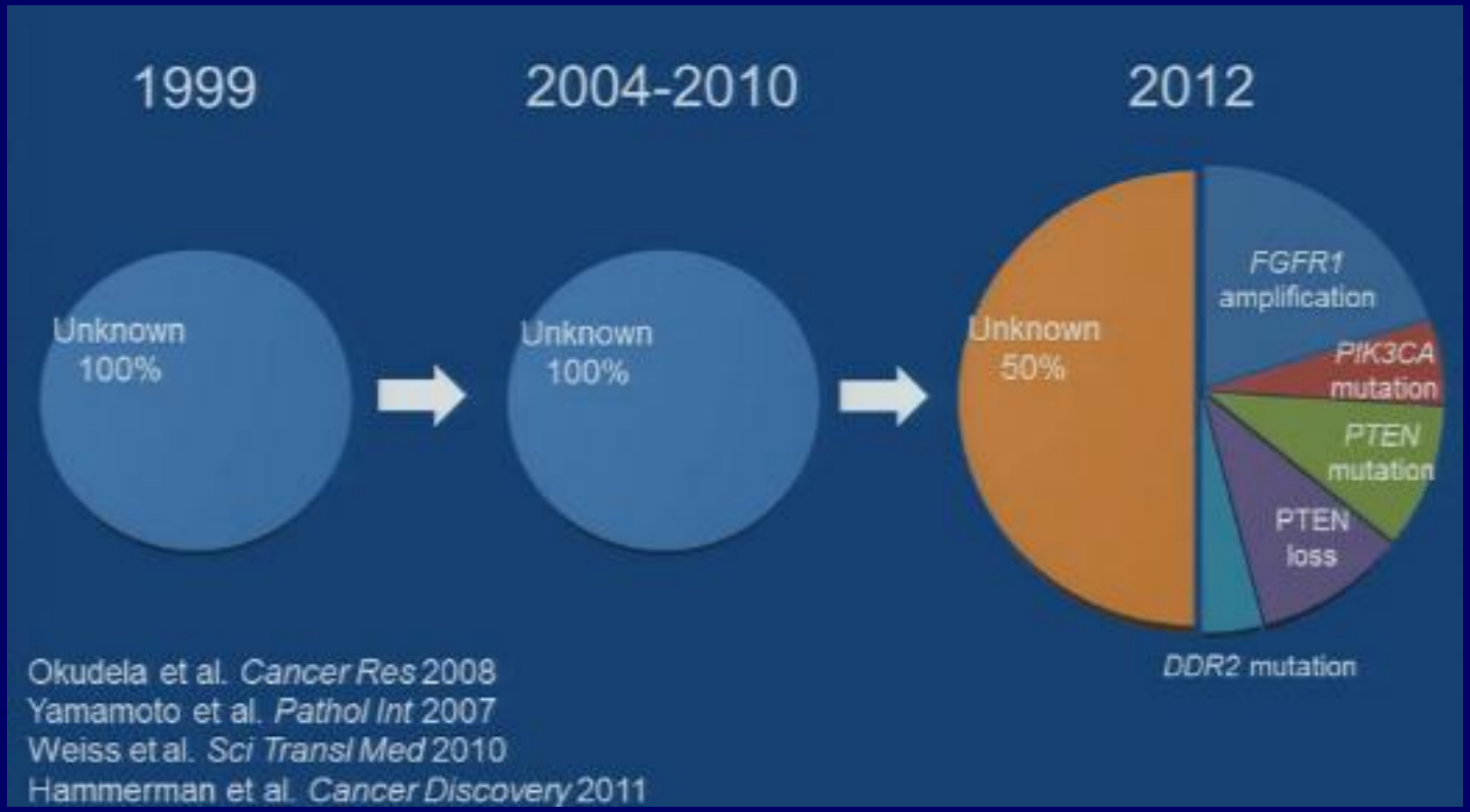
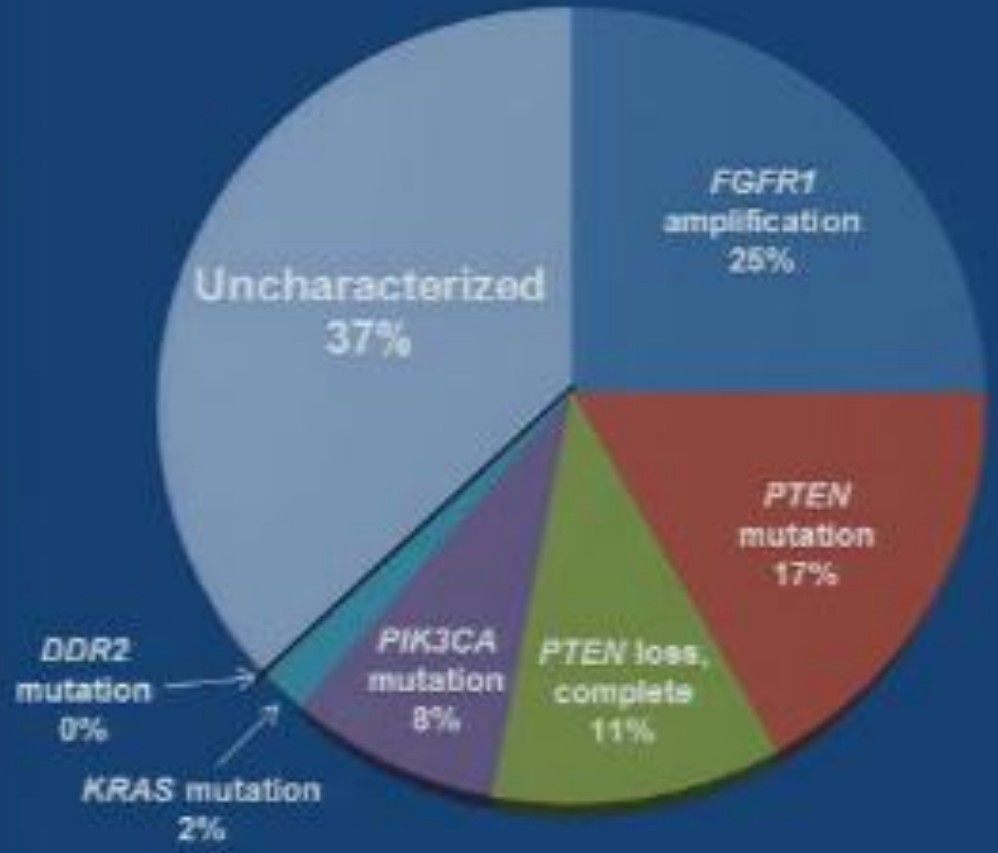
Squamous cell carcinoma: Genetic alterations and actionable targets

Govindan et al (A#7006), Paik et al (A#7505)



Multiplex Testing Of Squamous Cell Lung Cancers To Direct Treatment

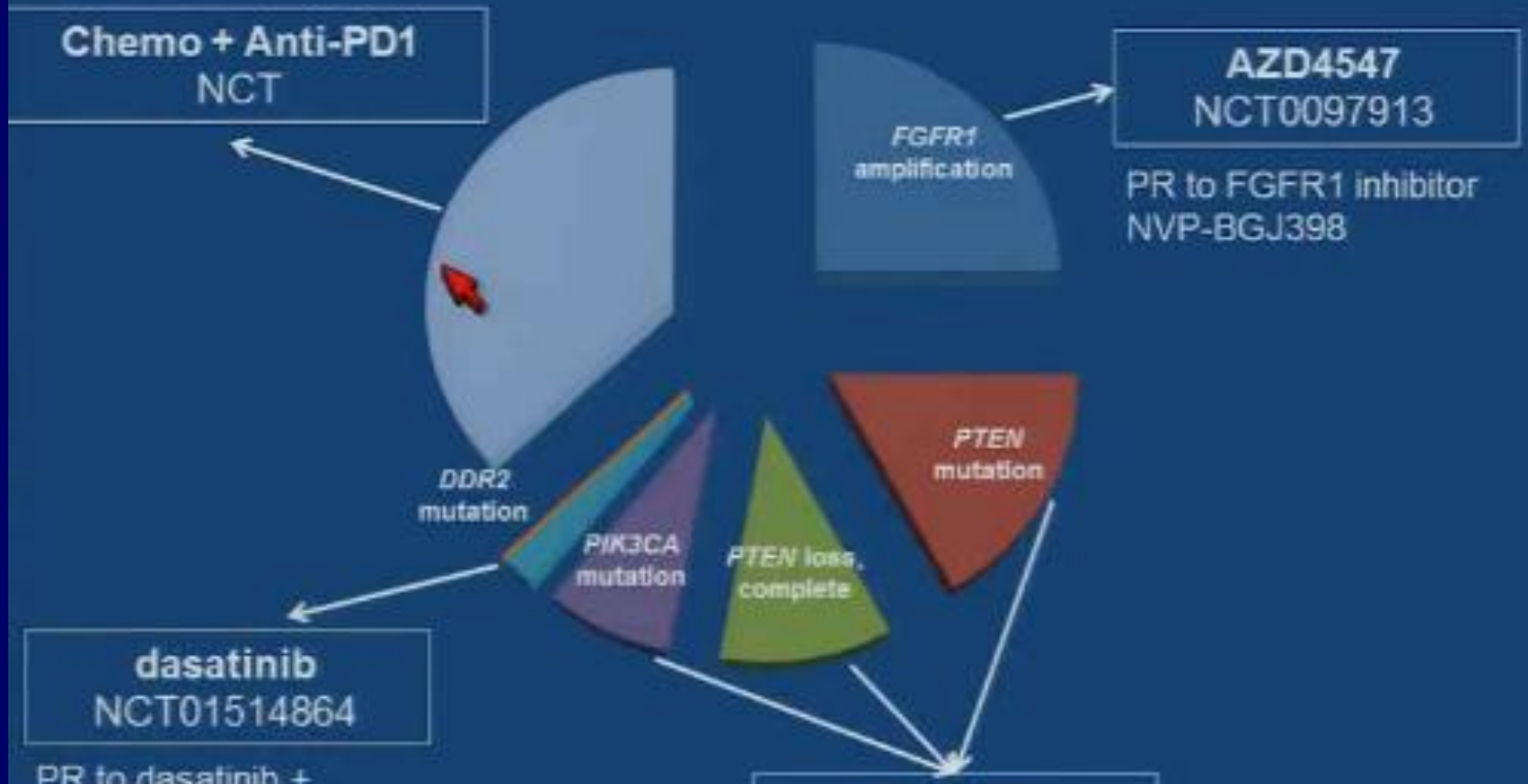
SQ-MAP integrated results



Target	N	Frequency	95% CI
FGFR1 Amplification	13/52	25%	15-38%
PTEN mutation	3/18	17%	5-37%
PTEN loss	3/27	11%	3-26%
PIK3CA mutation	4/52	8%	2-17%
KRAS mutation	1/52	2%	1-9%
DDR2 mutation	0/18	0%	0-15%

Multiplex Testing Of Squamous Cell Lung Cancers To Direct Treatment

SQCLC matched therapies Memorial Sloan-Kettering



Hammerman et al. *Cancer Discov* 2011
Wolf et al. *AACR* 2012

SCLC /Stage III NSCLC/ Others

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- **Diagnosis: Accuracy of FDG-PET**

Accuracy of FDG-PET to diagnose lung cancer in the ACOSOG Z4031 trial

Grogan et al (A#7008)

Background

- NCCN guidelines: FDG-PET for diagnosis of suspected NSCLC

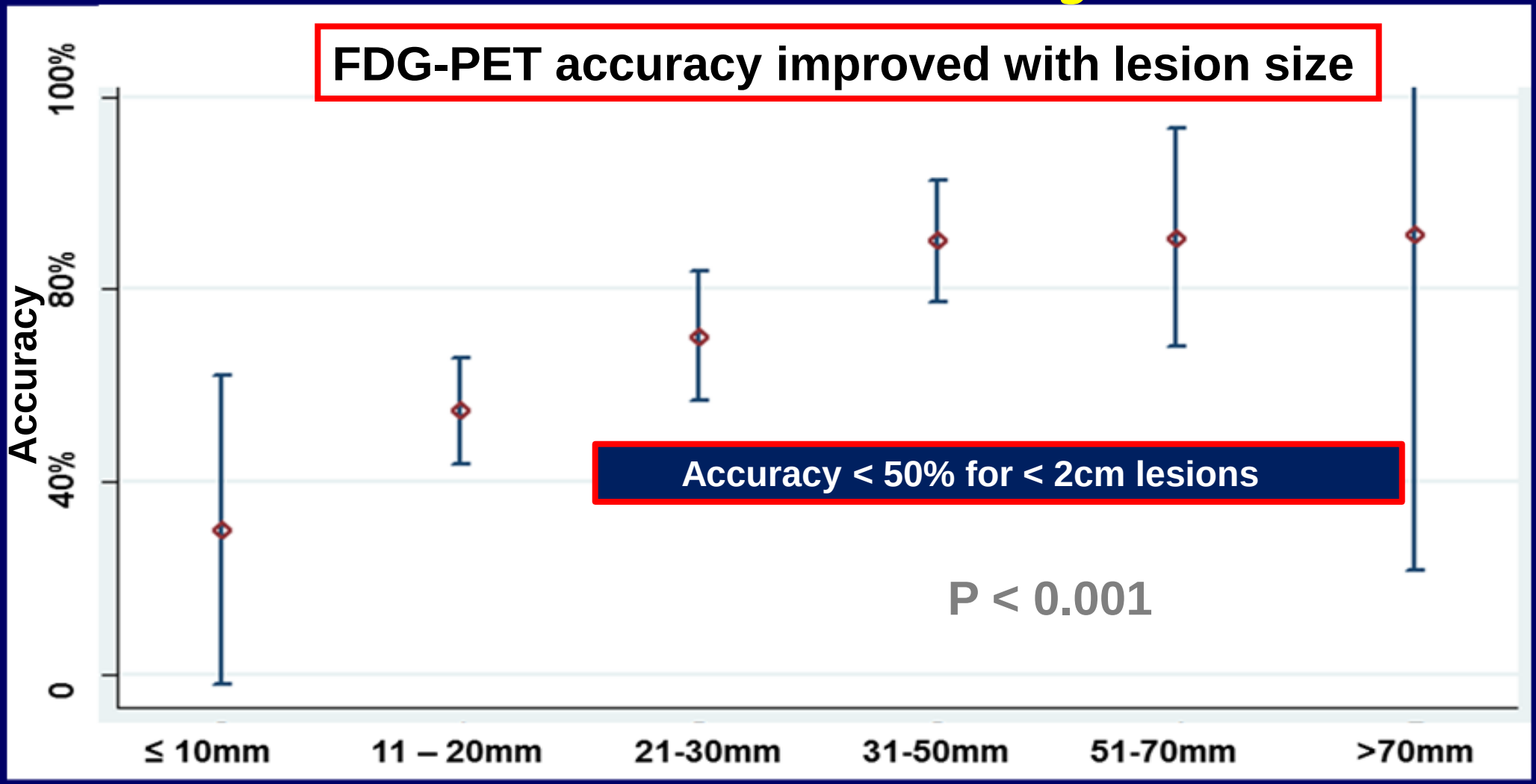
- Trial:
  - Accuracy of FDG-PET to diagnose NSCLC in patients undergoing resection for c-Stage I disease in a national population
  - n:682

[1]Gould et.al. JAMA 2001
[2]Deppen et.al. Ann Thor Surg 2011
[3]Croft et.al. Lung Cancer 2002

Results – FDG-PET

	ACOSOG Z4031	Metaanalysis
Malignancy	566 (83%)	
Accuracy (TP+TN)/N	73%	
Sensitivity	82%	94%
Specificity	31%	83%
Positive Predictive Value	85%	
Negative Predictive Value	26%	

FDG-PET Results by Size



Take Home Messages
CURRENT PRACTICE

- **FDG-PET in diagnosis: We need to question our relience on PET.**
- **Stage III NSCLC: No data to support use of consolidation chemotherapy after concurrent chemoRT.**
- **Limited stage-SCLC: We can delay RT up until 3rd cycle**
- **EGFR mutation status is important not only in 1st line but also 2nd line treatment selection**
  - **EGFR wild NSCLC: Docetaxel > Erlotinib**

Take Home Messages
CURRENT PRACTICE

- **ECOG PS 2 patients: Platin combination is better than single agent**
  - **Pemetrexed +carbo >Pemetrexed**

- **Maintenance:**
  - **What we knew -> Switch maintenance improves OS**
  - **After ASCO 2012 –> Continuation maintenance with pemetrexed also improves OS**

Take Home Messages
FUTURE

- **Making great progress in molecular understanding of NSCLC**
  - **Squamous cell: Genomic alterations ->Actionable targets**
- **Afatinib: A new 1st line treatment option against EGFR-muta (+) NSCLC**
  - **Better than 1st generation EGFR TKI?**
- **Novel agents:**
  - **ROS1: Crizotinib**
  - **K-ras: Selumetinib is promising**
- **Immunotherapy: Anti-PD1 antibody (BMS-936558) ->MOST PROMISING AGENT OF ASCO**