

ELCC 2014

**Can adaptive design help to
proceed in clinical trials in lung
cancer?**

5 reasons PRO!

Benjamin BESSE, MD, PhD



Disclosures (1)

- **No personal financial disclosures**
- **Institutional grants for clinical and translational research**
 - Abbott, Amgen, AstraZeneca, BMS, Boehringer-Ingelheim, Lilly, Pfizer, Roche-Genentech, Sanofi-Aventis, Clovis, GSK, Servier, EOS

Disclosures (2)

I am a clinician

Let's speak the stats language

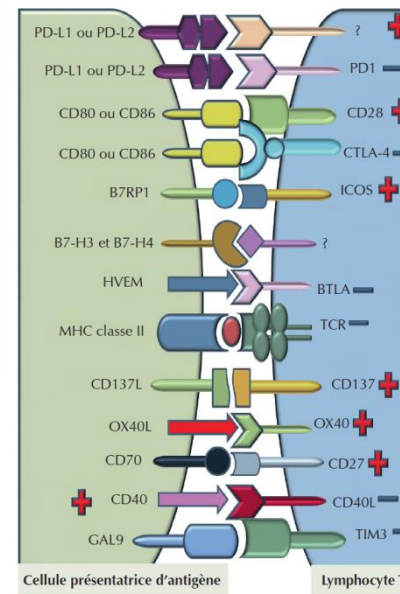
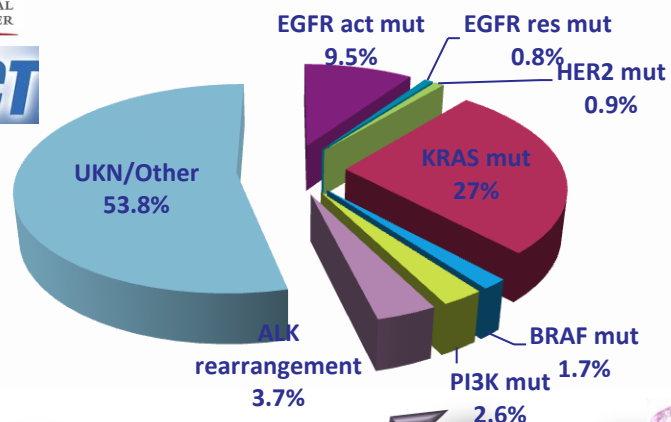
Disclosures (2)

I am a clinician

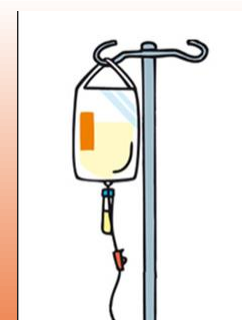
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**My primary endpoint is
to treat patients
the best I can**

n=9911

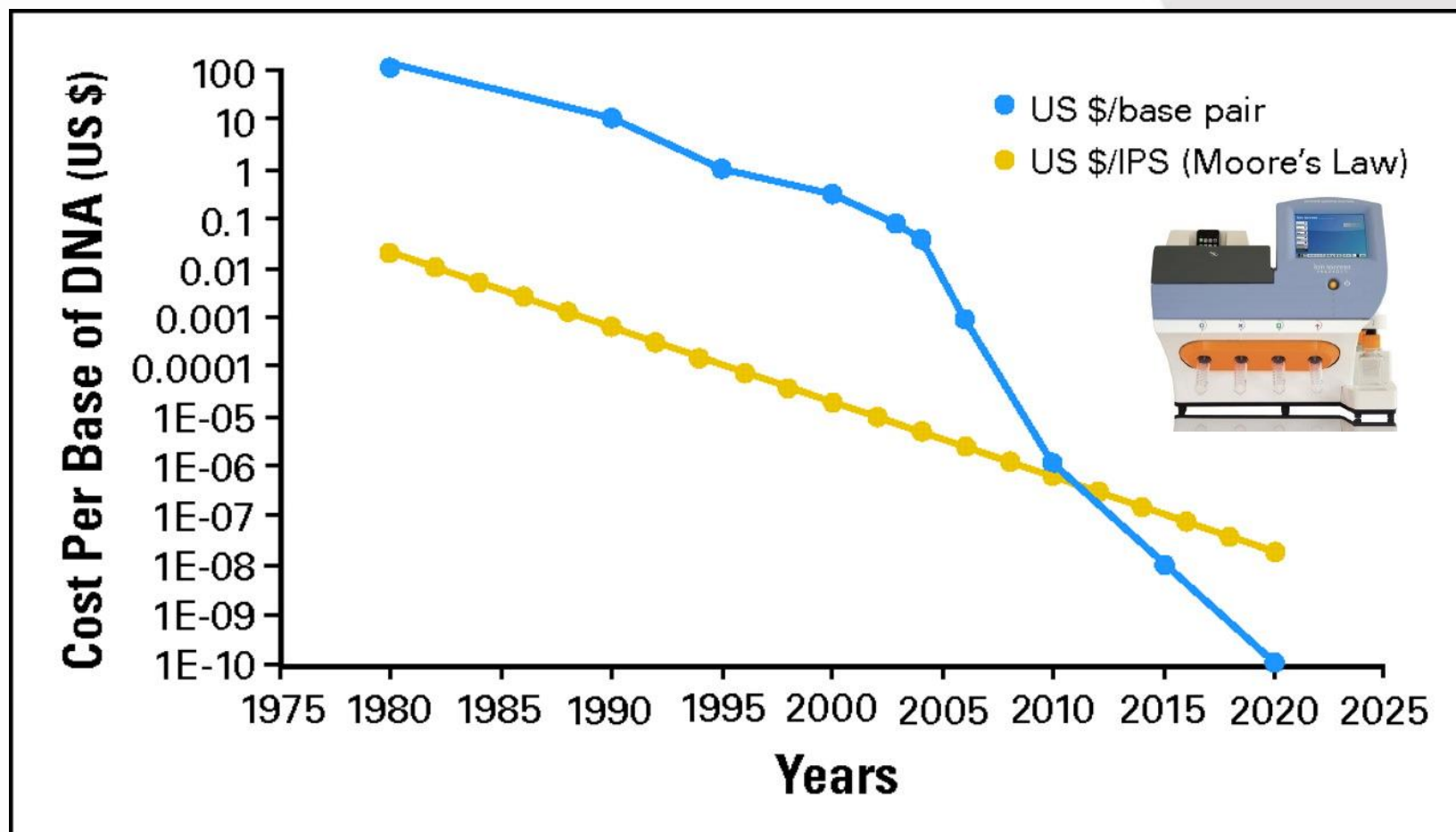


Molecular Profile



Immunological Profile

Molecular profile will be cheaper



MacConaill L E , Garraway L A JCO 2010;28:5219-5228

SPECTAlung

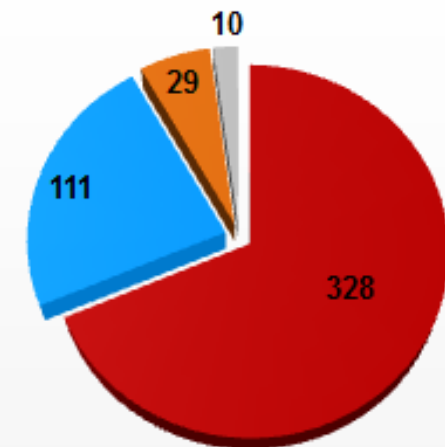


Screening Patients with Thoracic Malignancy for Efficient Clinical Trial Access

14MG Solid tumour panel v1

Panel footprint: 2.2 Mb

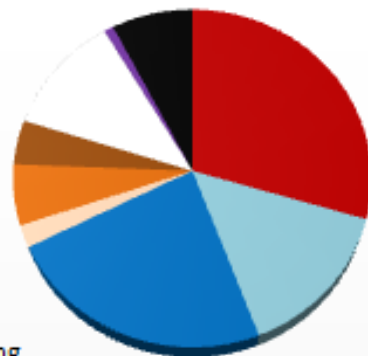
Panel features: 478



■ Genes (all exons)

■ Copy number variants

Confidential 9-March-2015

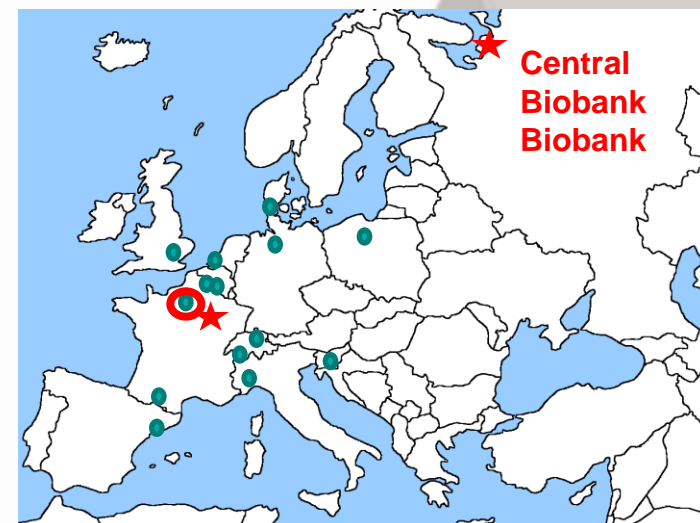


Function (genes)

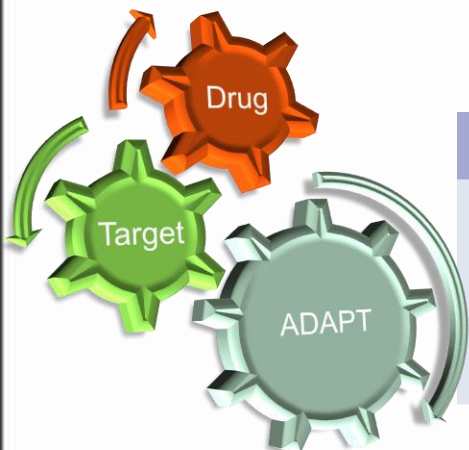
- Signalling
- Transcription factor
- Transcriptional control
- Apoptosis
- DNA damage response
- Cell cycle control
- Miscellaneous/Unknown
- Immune-related
- Structural components

14m
genomics

Online molecular portrait
Prospective clinical data
500-1000 tumors / yr

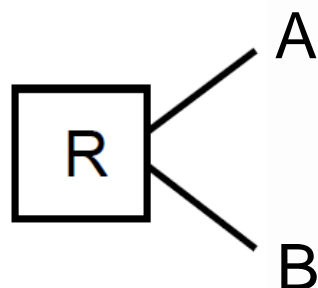


Welcome to 21th century, Mr Buyse!

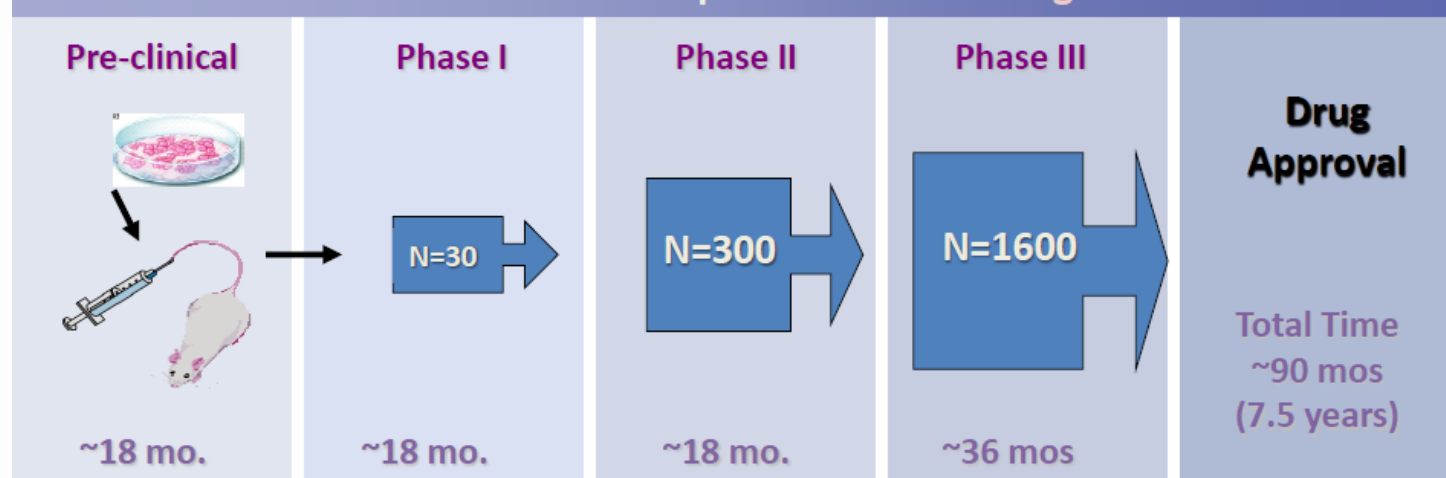


Phases of Development of New Biomarker linked to New Drug

Confirm Target	Integrate Biomarker	Biomarker Informative?	Clinical Validation	Clinical Application of Biomarker
Assay Development	Assay Performance	Assay Validation	Co-Primary Endpoint	



Phases of Development of a New Drug



Stat's Sweet Home



Family picture



My Stat cares



He uses Adaptive Design

DEFINITION OF ADAPTIVE DESIGN

“An adaptive design is one that **allows adaptations in trial procedures and/or statistical procedures after initiation of the trial** without undermining the validity and integrity of the trial.”

ADAPTIVE DESIGN TRIALS



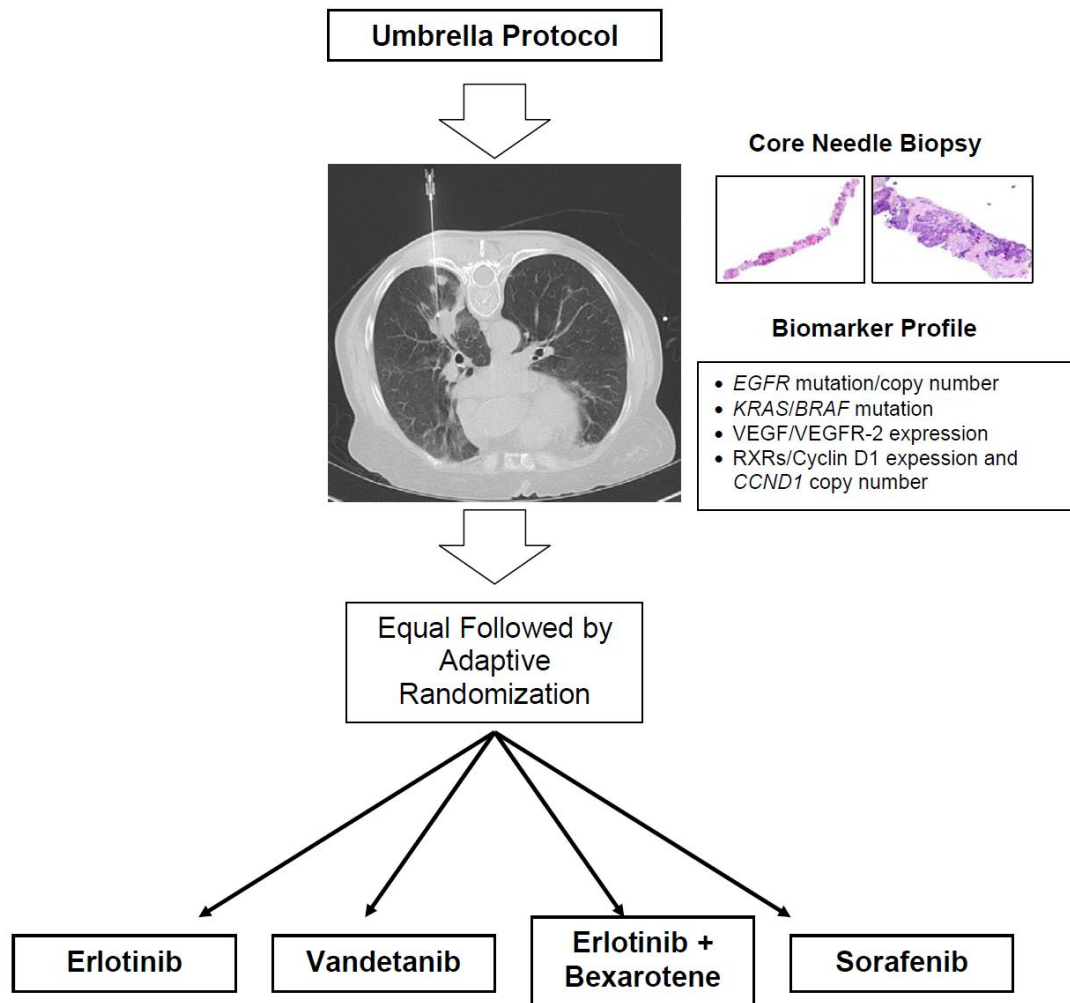
- 10 types :
 - an adaptive randomization design,
 - an adaptive group sequential design,
 - a flexible sample size re-estimation design,
 - a drop-the-losers design,
 - an adaptive dose-finding design,
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Battle Trial



Battle

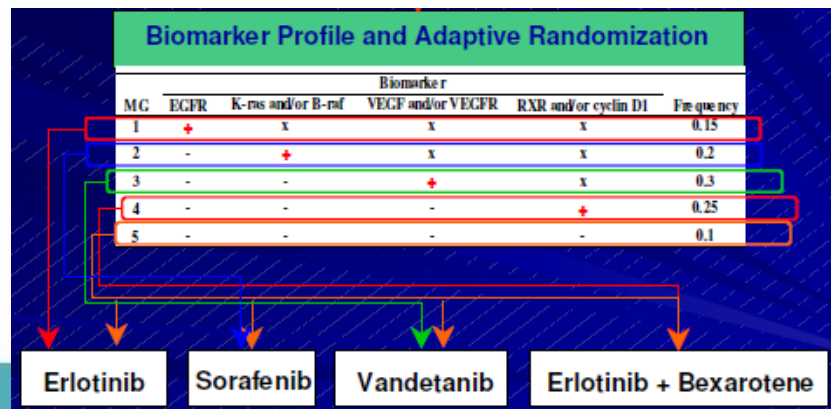
Total Randomized
N = 255

Equal Randomization
N = 97

Erlotinib	Vandetanib	Erlotinib + Bexarotene	Sorafenib
N = 25 N eval = 25	N = 23 N eval = 23	N = 21 N eval = 21	N = 28 N eval = 26

By Marker Group

EGFR:	8	16	11	10
KRAS/BRAF:	2	1	2	2
VEGF:	10	2	3	5
RXR/CycD1:	1	0	1	3
None:	4	4	4	6



Battle

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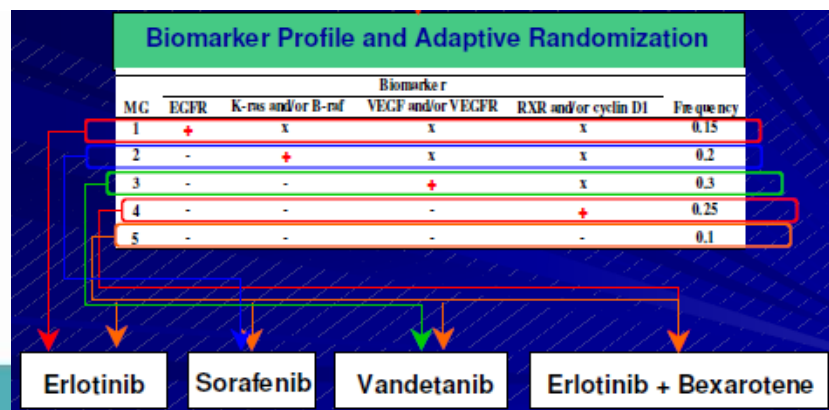
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Adaptive Randomization
N = 158

Erlotinib	Vandetanib	Erlotinib + Bexarotene	Sorafenib
N = 34 N eval = 33	N = 31 N eval = 29	N = 16 N eval = 15	N = 77 N eval = 72

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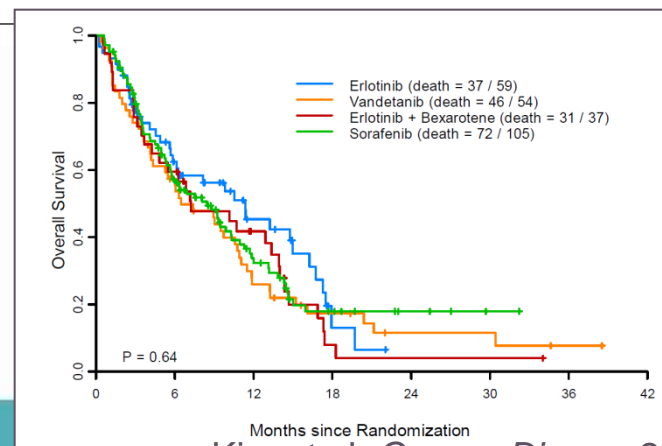
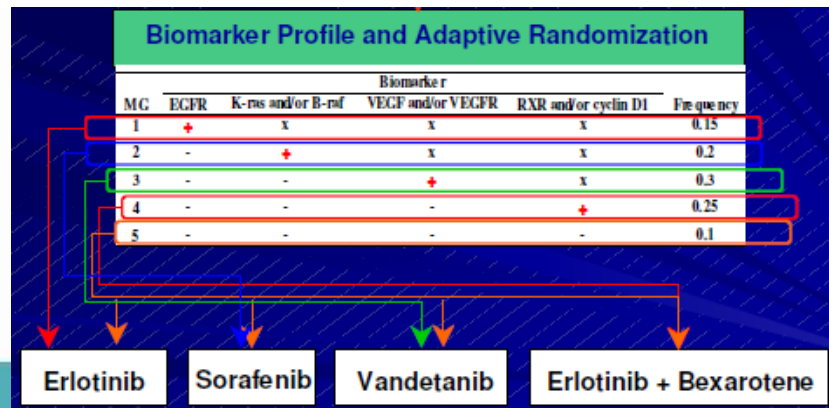
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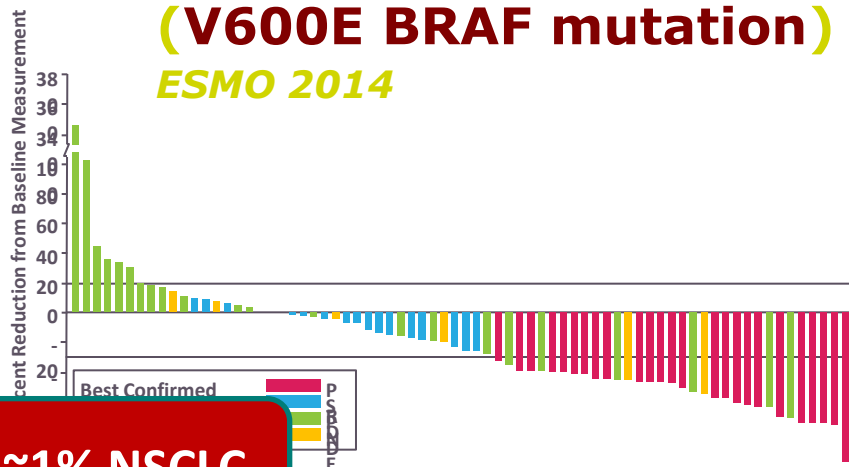
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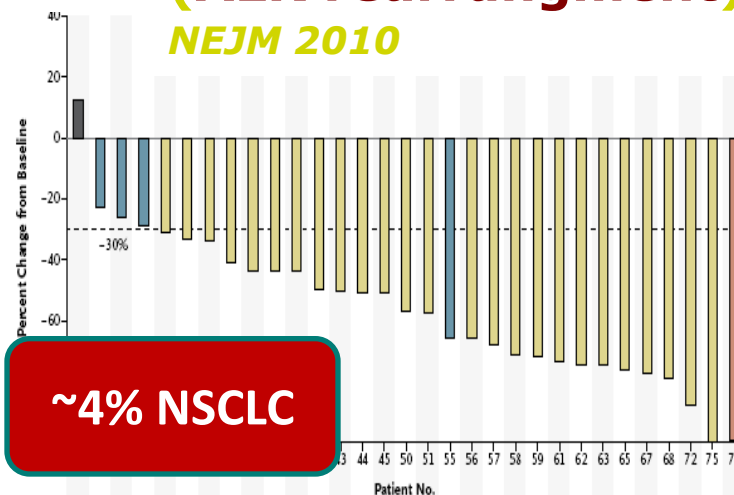
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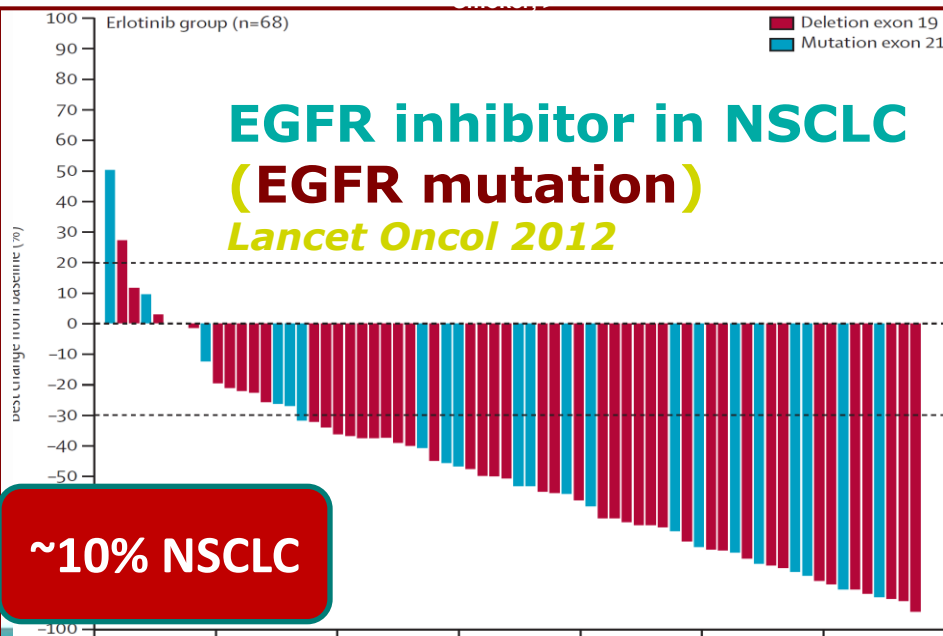
B-RAF inhibitor in NSCLC (V600E BRAF mutation) *ESMO 2014*



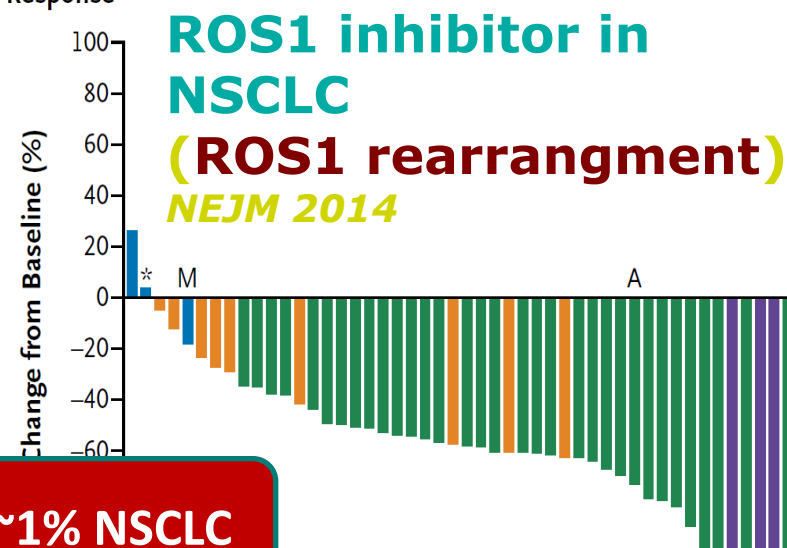
ALK inhibitor in NSCLC (ALK rearrangement) *NEJM 2010*



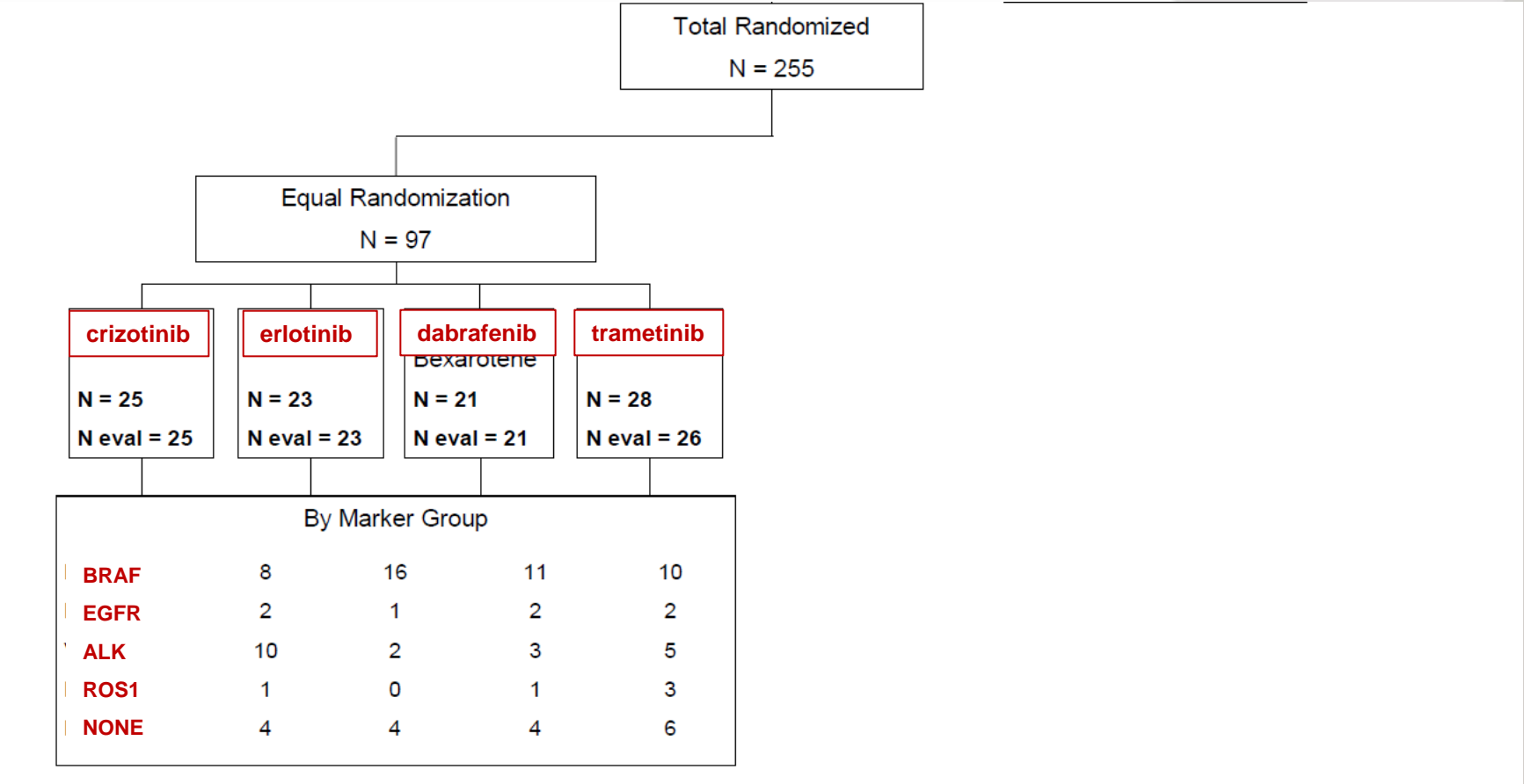
EGFR inhibitor in NSCLC (EGFR mutation) *Lancet Oncol 2012*



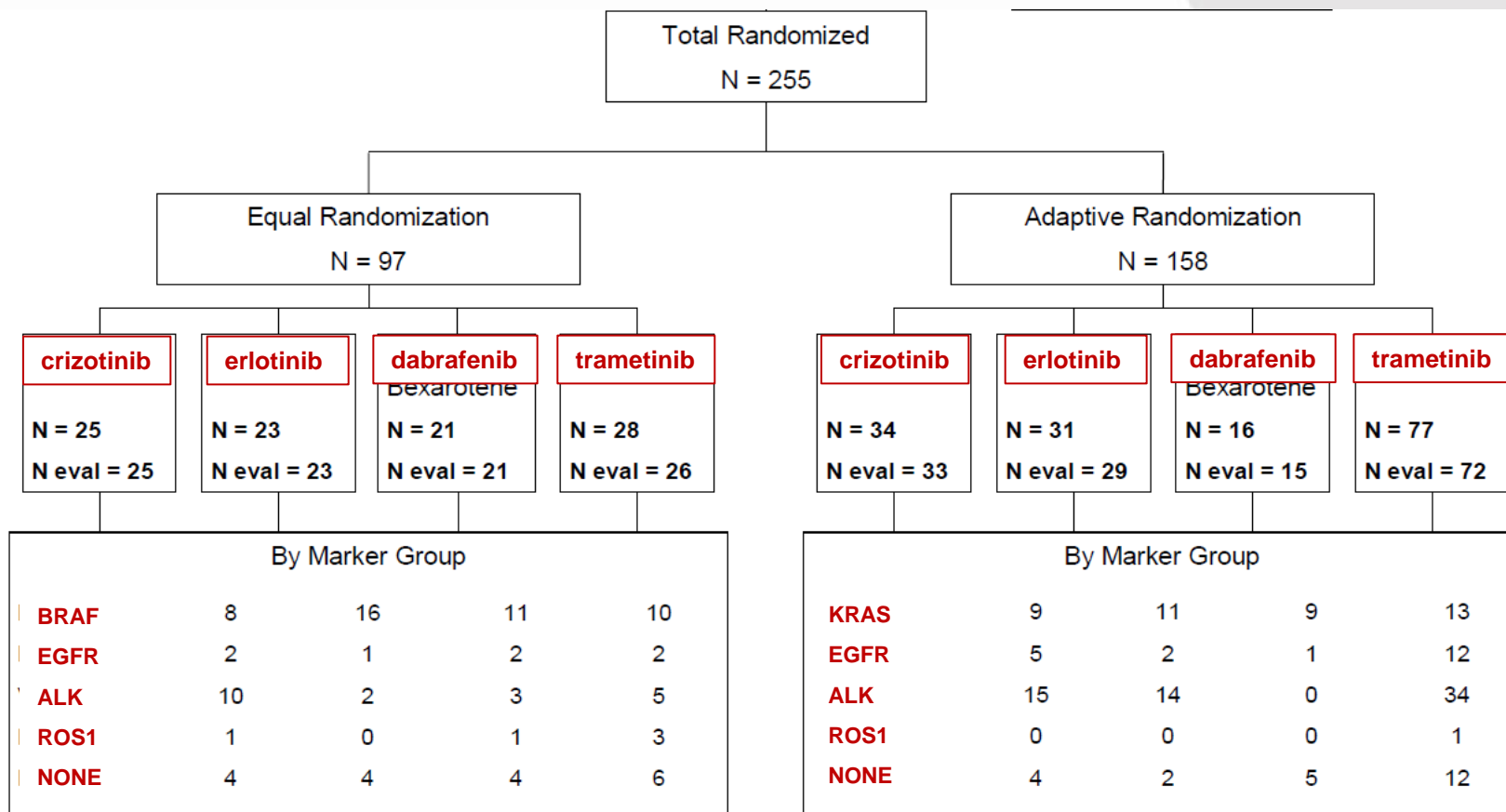
Best Response



FIGHT (Finding Great Human Treatment)



FIGHT (Finding Great Human Treatment)

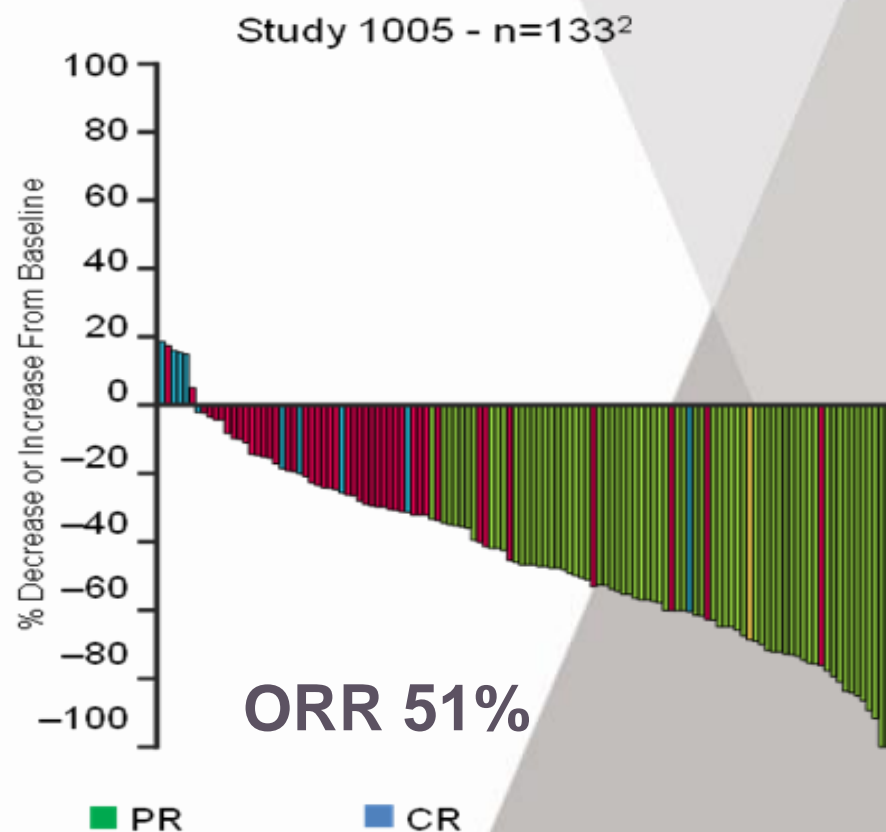
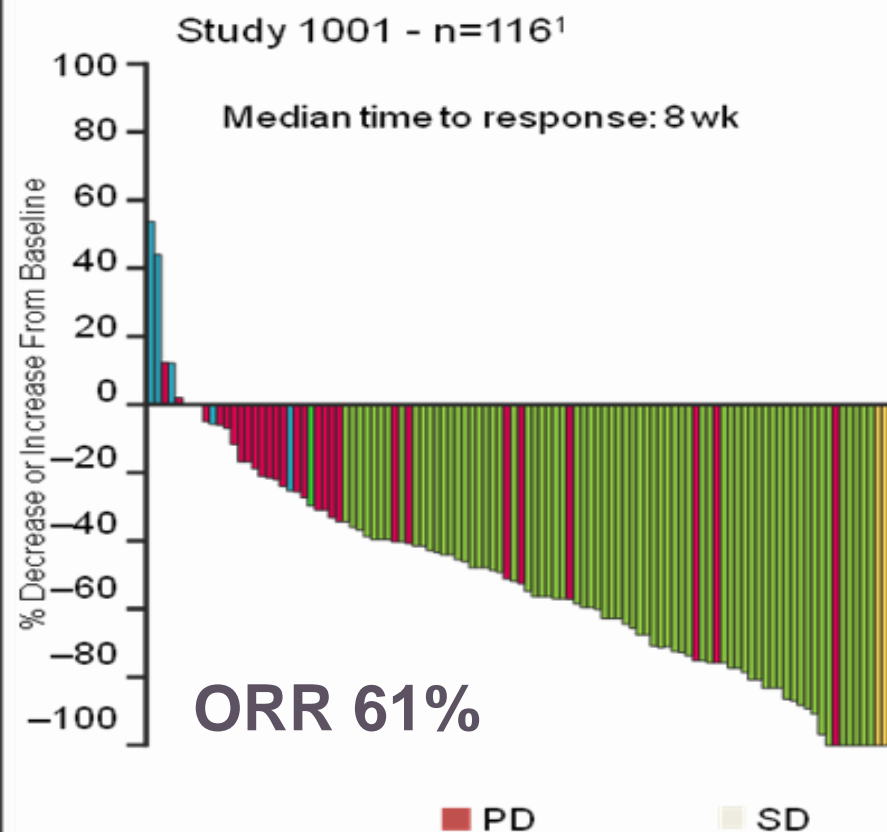


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Response rates to crizotinib in Phase I & II trials ALK+ NSCLC Pts



¹Camidge DR, oral presentation at ASCO 2011; abstract 2501

²Riely GJ, oral presentation at WCLC 2011; abstract 1618

PROFILE 1007 – 2nd line ALK+ NSCLC Pts

PROFILE 1007 – 2nd line

Patients

- Positive for ALK by central laboratory
- 1 prior chemotherapy (platinum-based)

Crizotinib
(250 mg BID)

Pemetrexed
500 mg/m² or
docetaxel
75 mg/m²
3 weekly cycle

N=318



PROFILE 1007 – 2nd line ALK+ NSCLC Pts

PROFILE 1007 – 2nd line

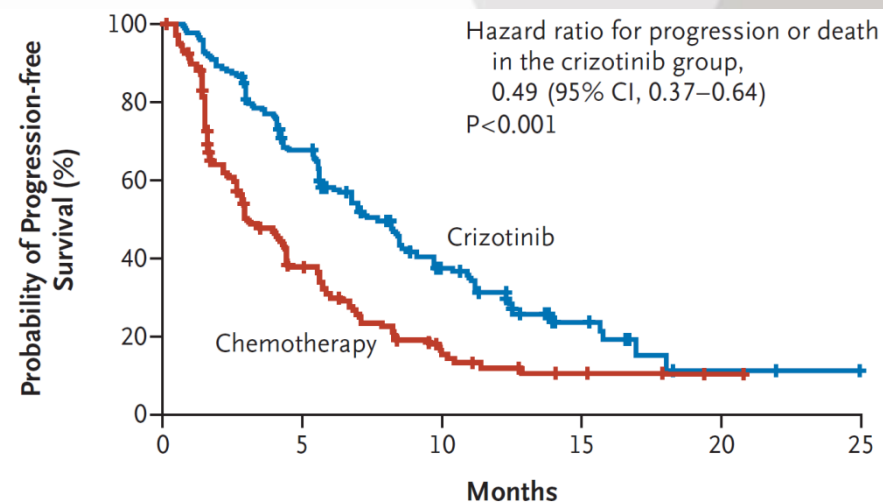
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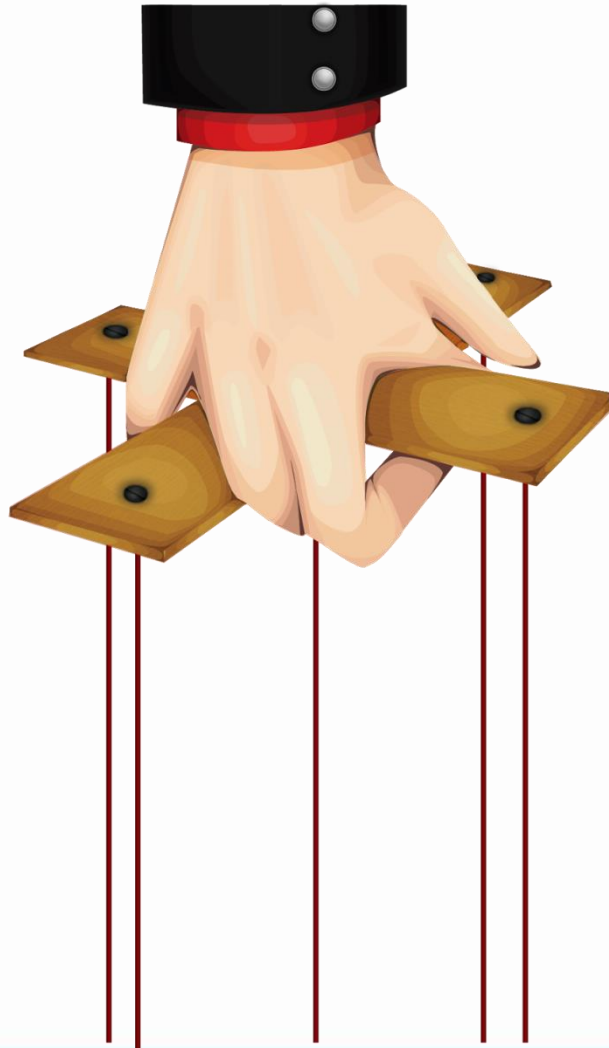
N=318



No. at Risk

Crizotinib	173	93	38	11	2	0
Chemotherapy	174	49	15	4	1	0

FDA/EMA ~~STATS~~



PROFILE 1007 – 2nd line ALK+ NSCLC Pts

- Hypothesis : PFS 7.0 mo vs. 4.5 m
 - 217 events
 - Power 90%, one-sided alpha 0.025. (HR~0.64)
- Observed : PFS 7.7 mo vs 3.0 mo

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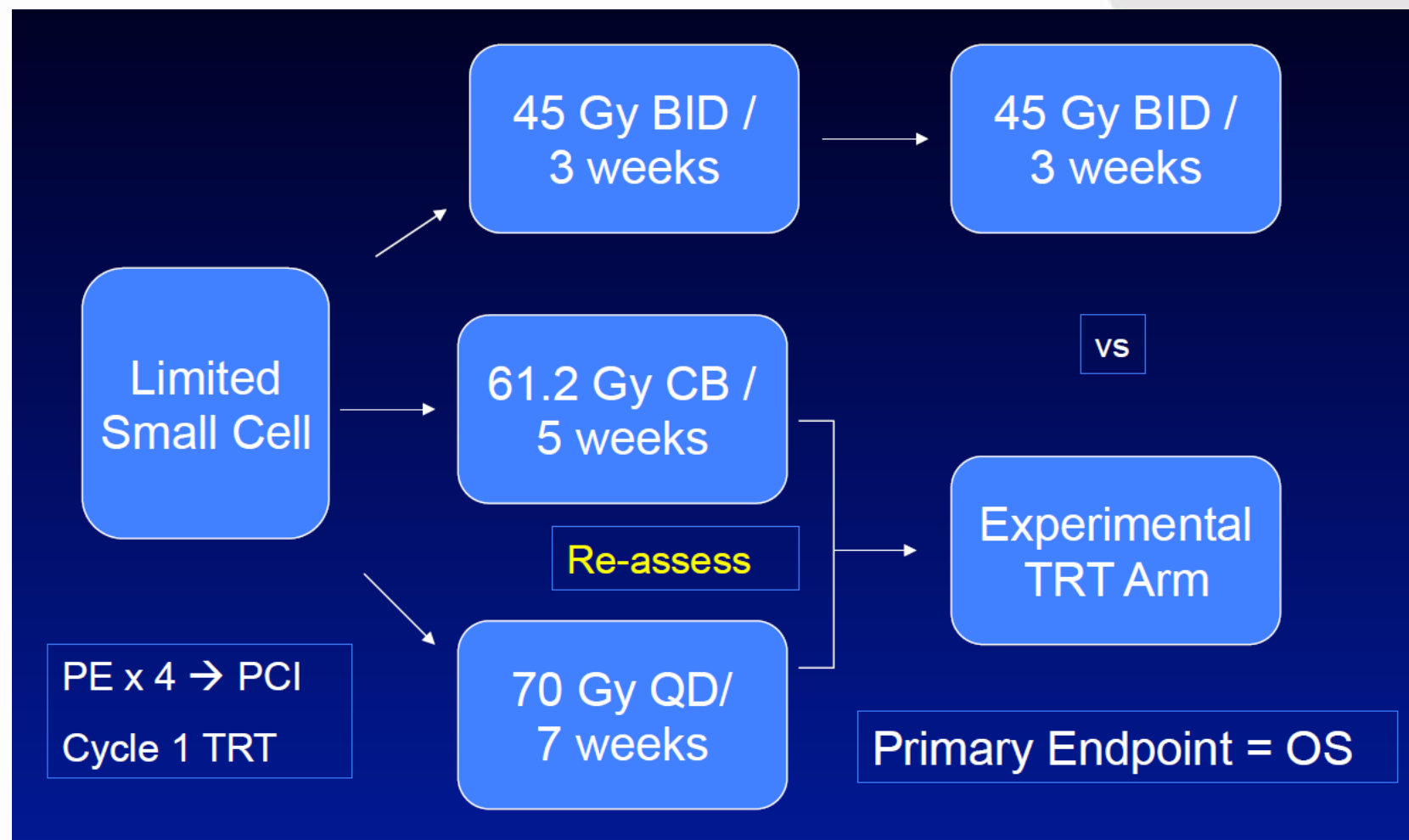
- **Interim analysis**
 - Same efficacy
 - With 50% information
 - 24 events
 - on 60 patients
- **New sample size**
 - 48 events
- **N=70 vs 318**
- **250 Patients 'saved' !**

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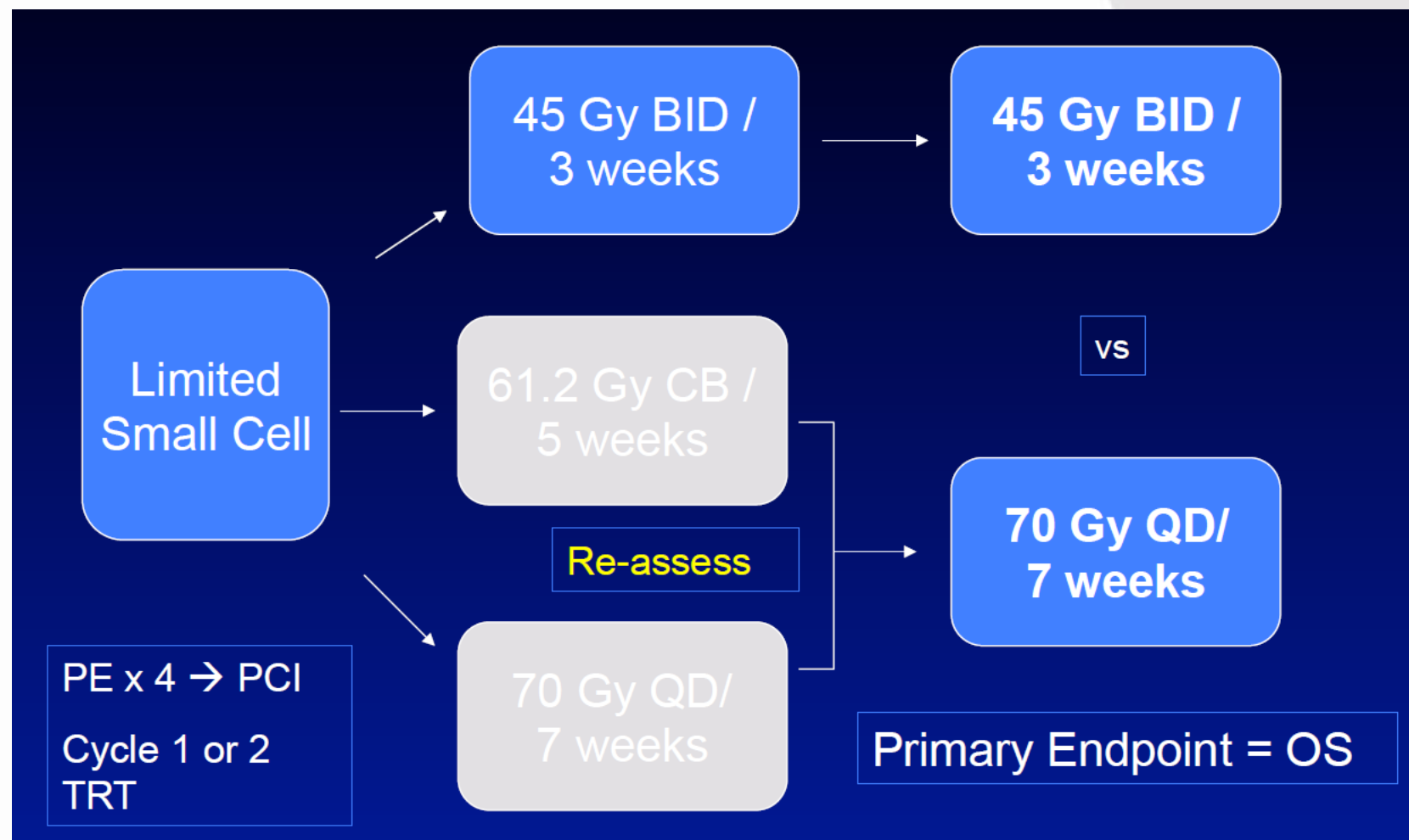


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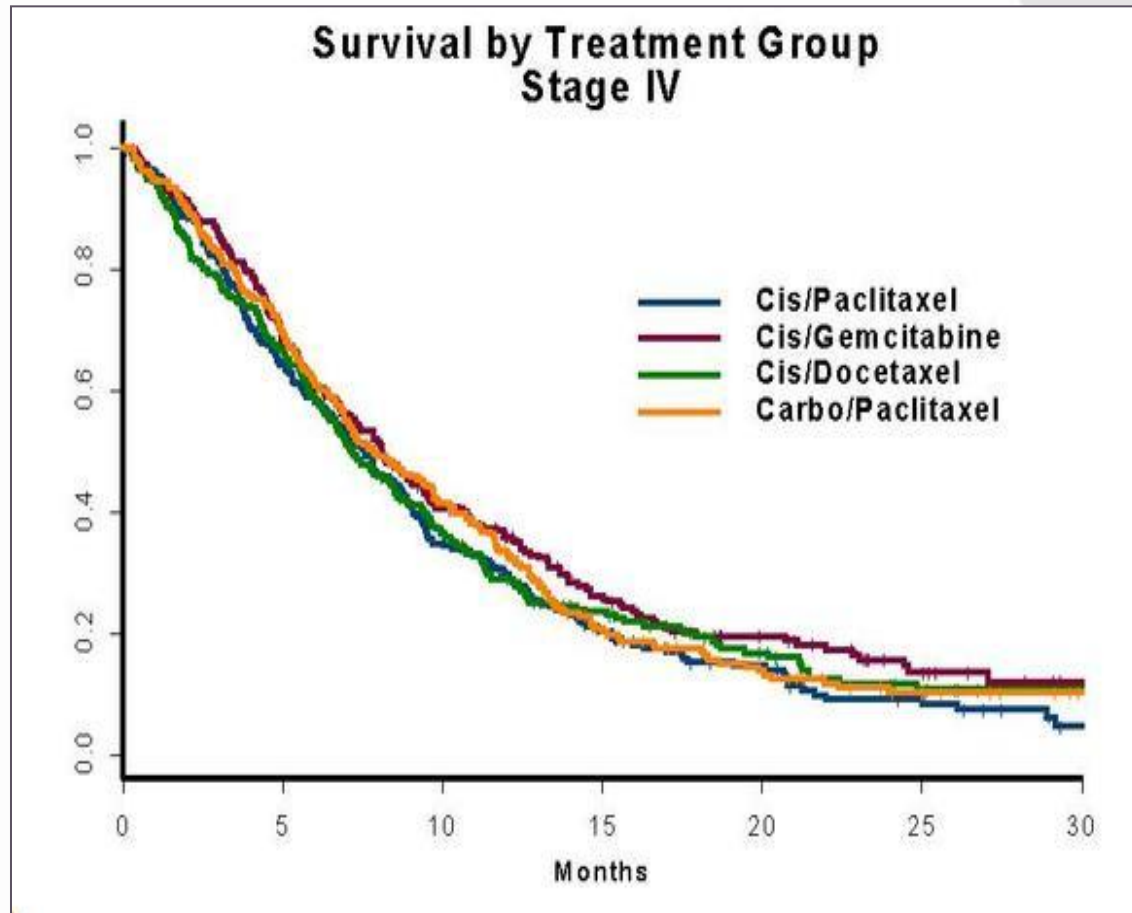
CALGB 30610 / RTOG 0538



CALGB 30610 / RTOG 0538



If « drop the loser » was borned...



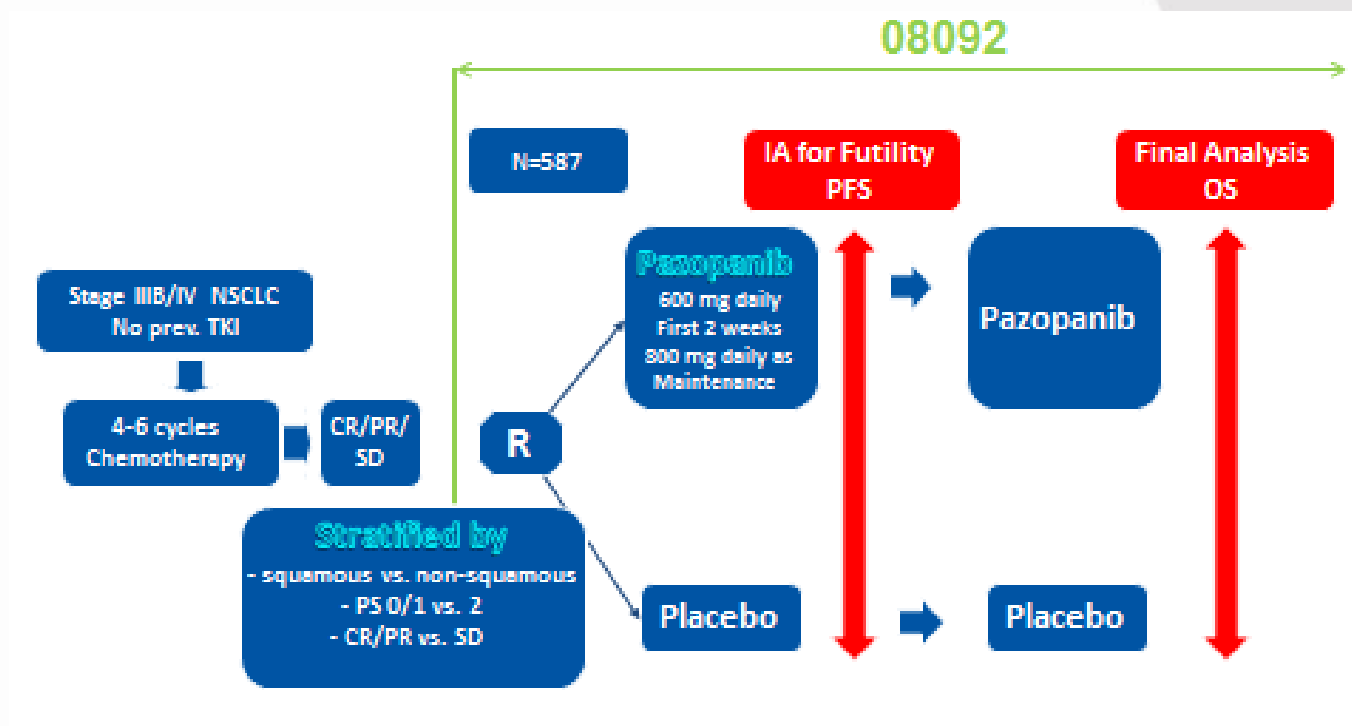
Drop the loser : ~800 pts vs ~1200

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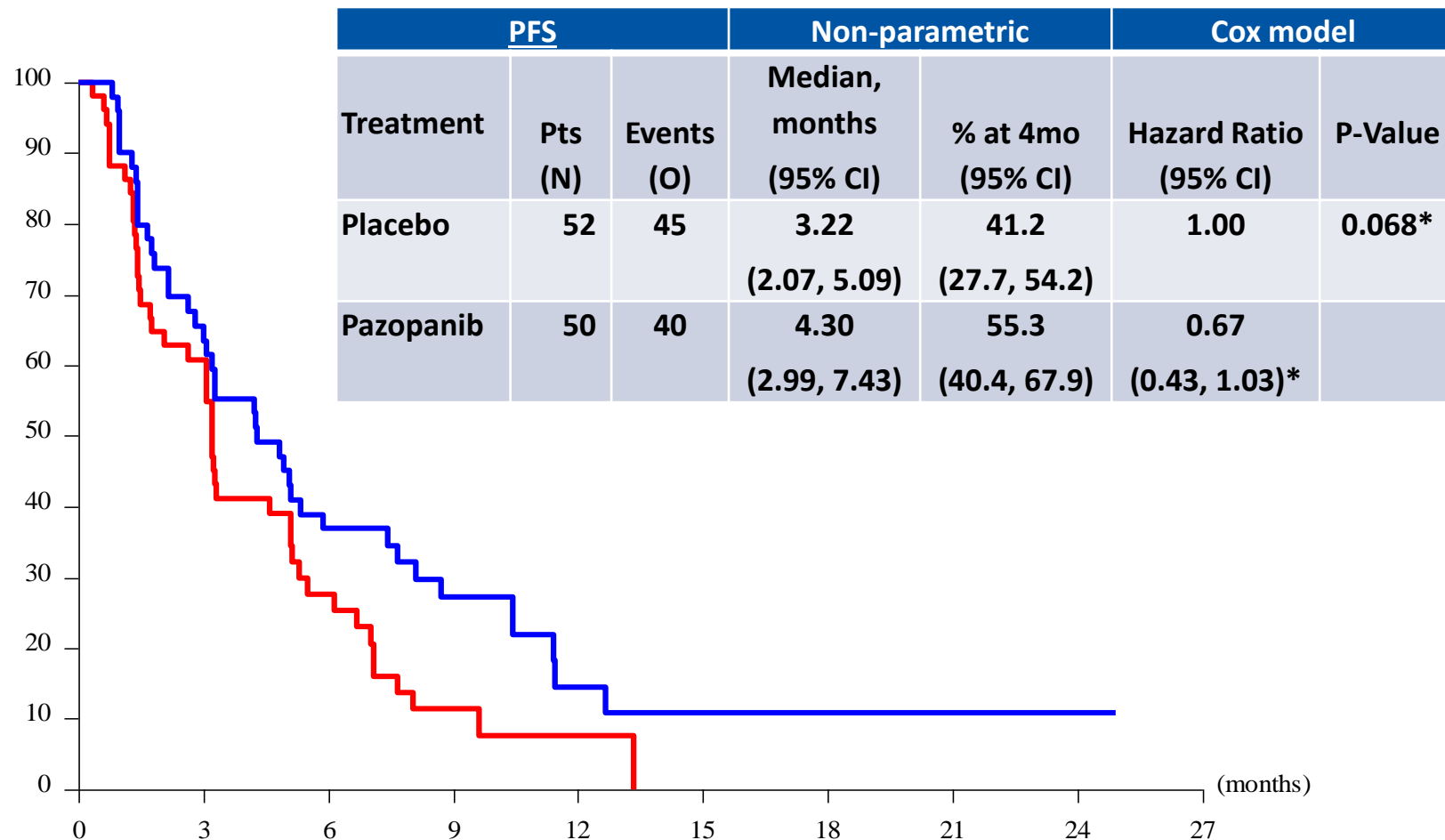
Phase II/III MAPPING



- **Sample Size:**

- 587 patients - OS from 9.7 to 12.7 months.
- 102 patients (63 events) were analyzed in an early IA conducted due to safety and efficacy concerns, though IA was originally planned after 200 patients (150 events).

Endpoint at interim analysis: PFS



Adaptive design allows to...

- **Correct** wrong assumptions made at the beginning

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- **Correct** wrong assumptions made at the beginning
- **Select earlier** the most promising option
- **Use new information** outside of the trial
- **React earlier** to surprises (either + or -)
- **Speed up** the development process

**I used what I learned from my
former patients
to treat my current patients**

Clinicians are adaptive by nature

