Optimal use of systemic therapy in the palliative setting

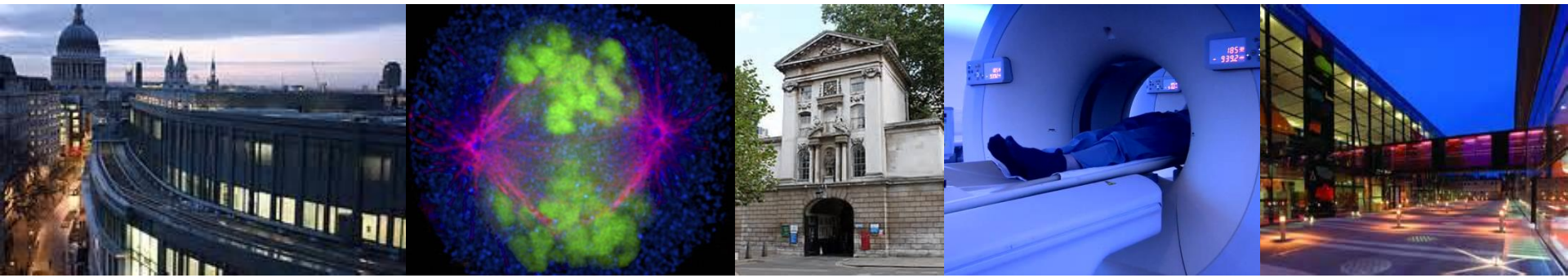
Trials and tribulations: Lifetime experiences of a medical oncologist on chemotherapy intensification

Professor Peter Schmid, MD PhD FRCP

Lead, Centre for Experimental Cancer Medicine

Barts Cancer Institute, St Bartholomew's Hospital

Queen Mary University of London



Chemotherapy Intensification in the Palliative Setting

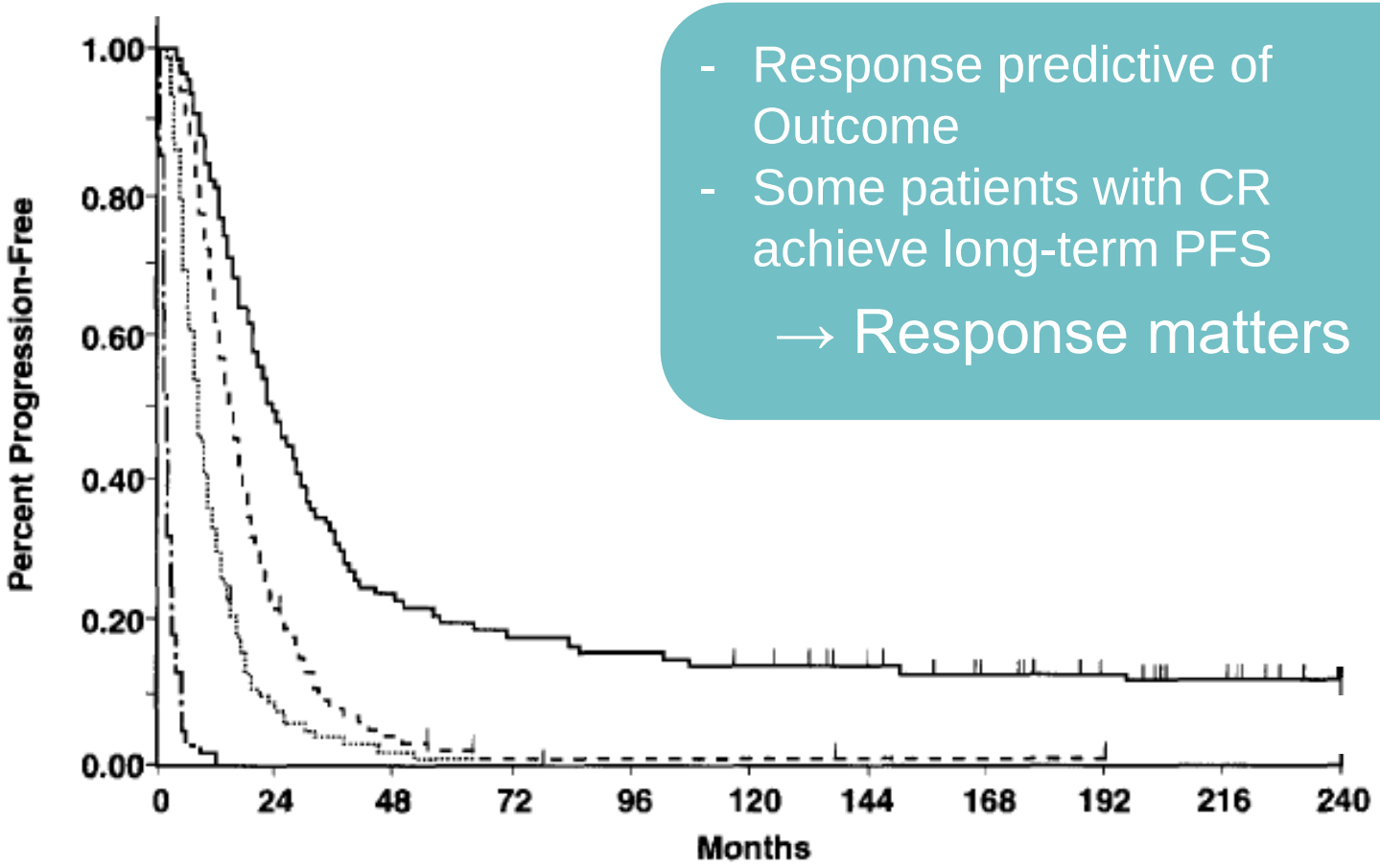
Outline

- Why intensify chemotherapy?
- Is more better?
- Can we better define who might benefit from chemotherapy intensification?
- Is intensification of chemotherapy still the best way forward?

Why intensify chemotherapy?

Metastatic Breast Cancer

Can we achieve long-term remission?



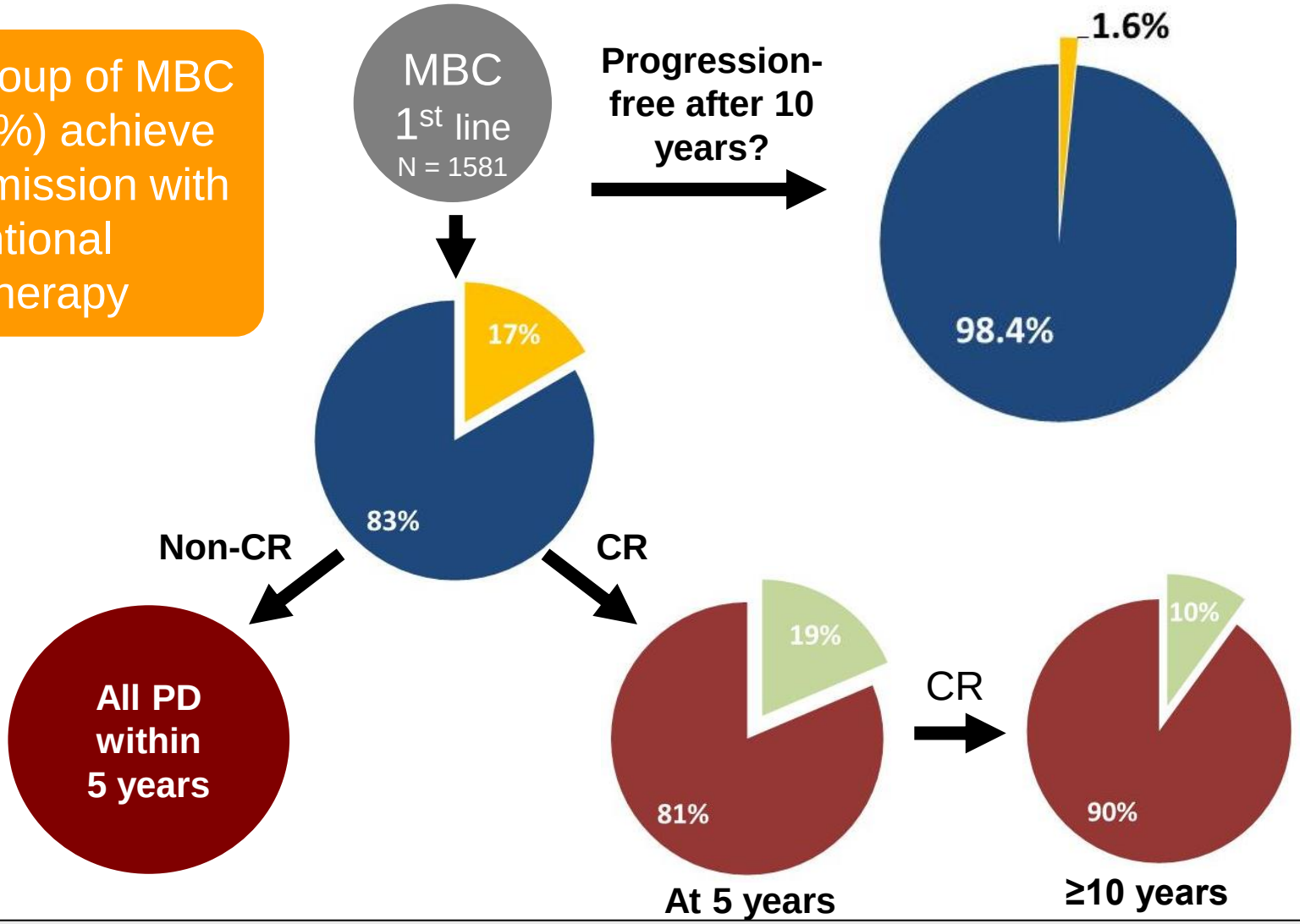
- Response predictive of Outcome
- Some patients with CR achieve long-term PFS

→ Response matters

Greenberg et al., JCO 1996

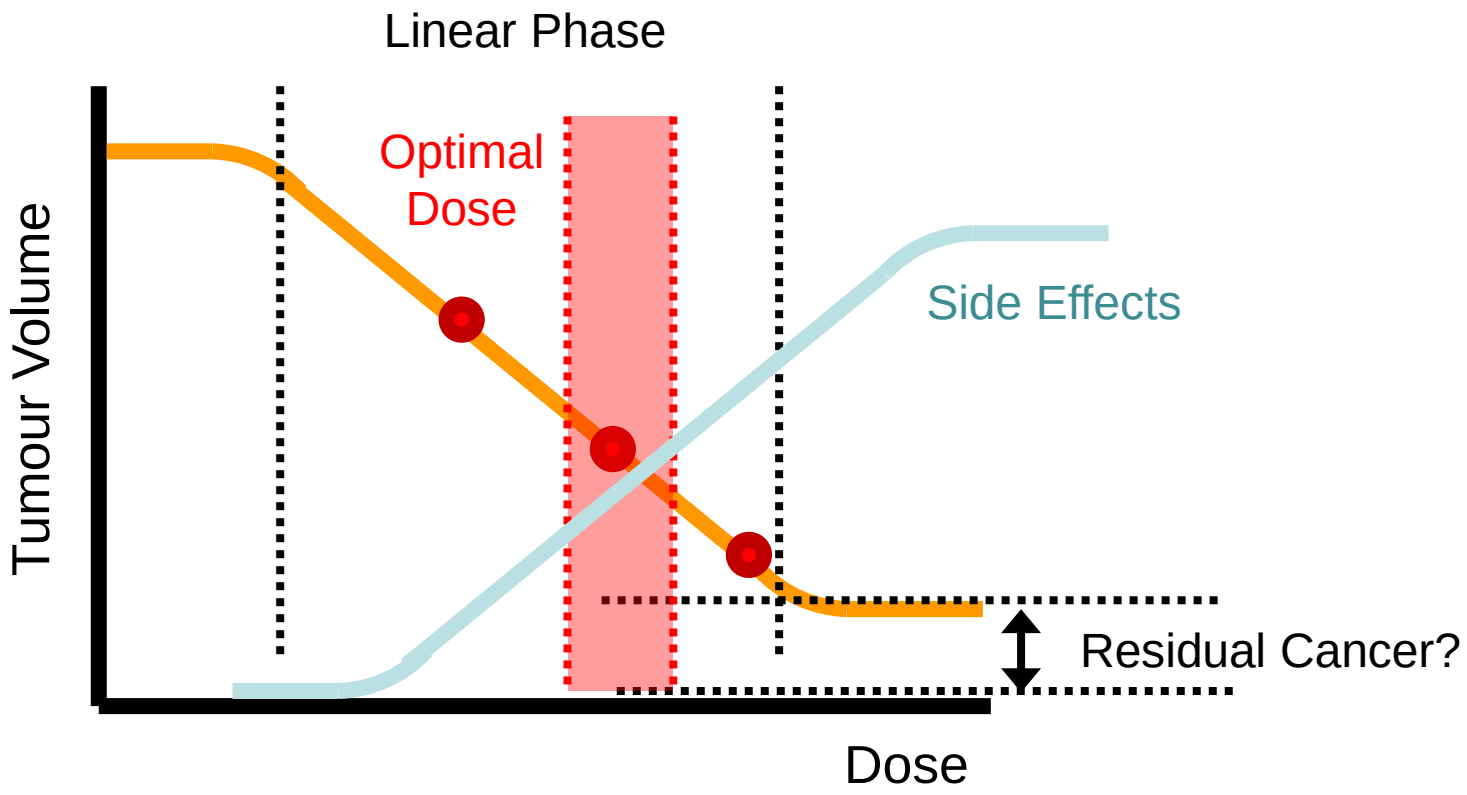
Metastatic Breast Cancer
Can we achieve long-term remission?

Very small group of MBC patients (<2%) achieve long-term remission with conventional chemotherapy

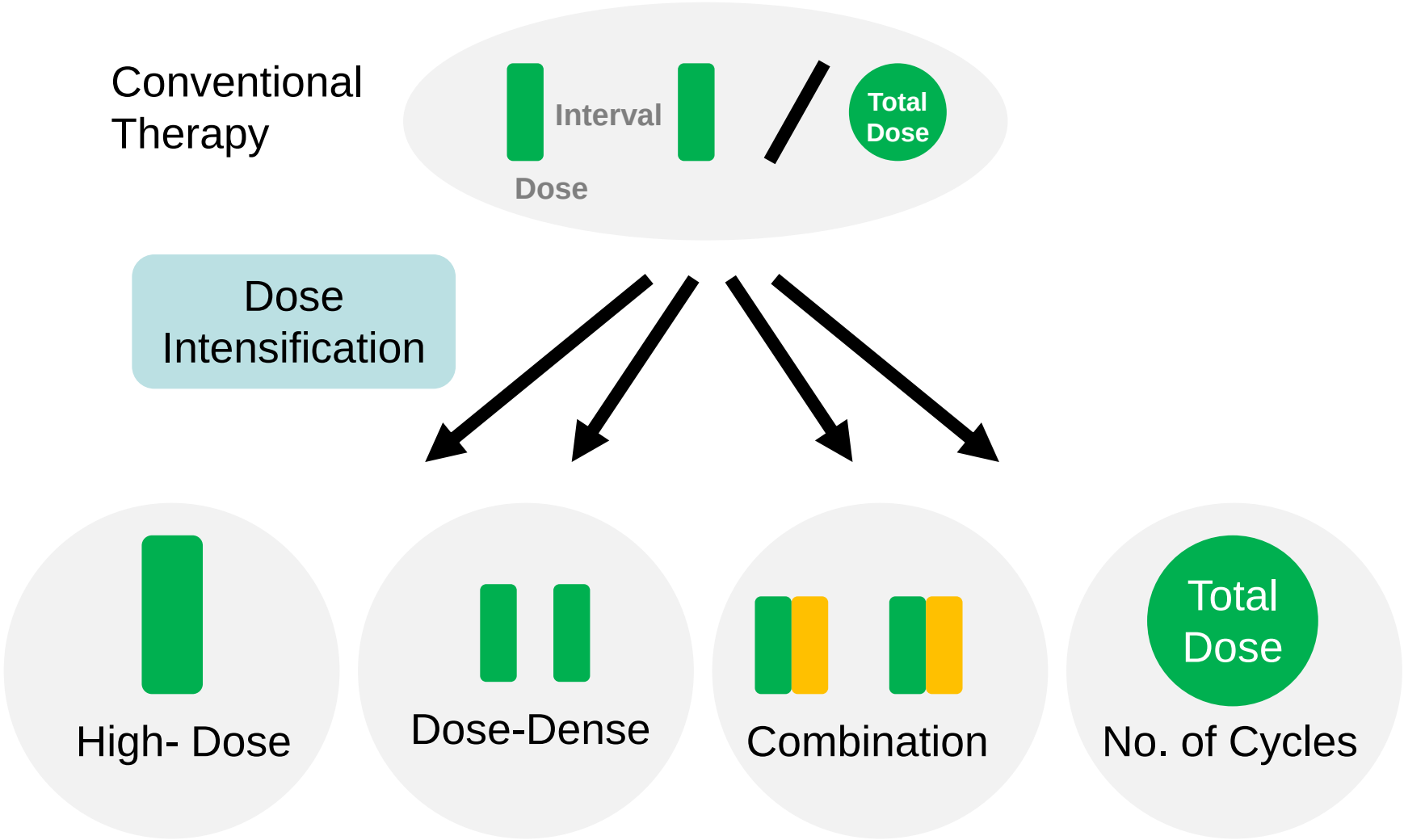


Greenberg et al., JCO 1996

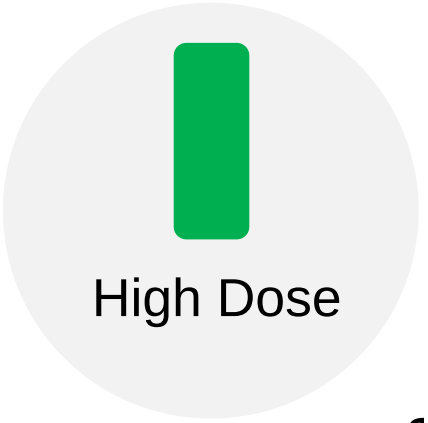
Chemo-Intensification
Basic Considerations (I)

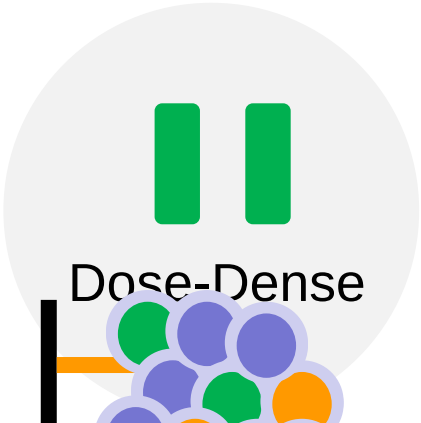


Chemo-Intensification
Basic Considerations (II)



Chemo Intensification - Rationale
High-Dose Chemotherapy

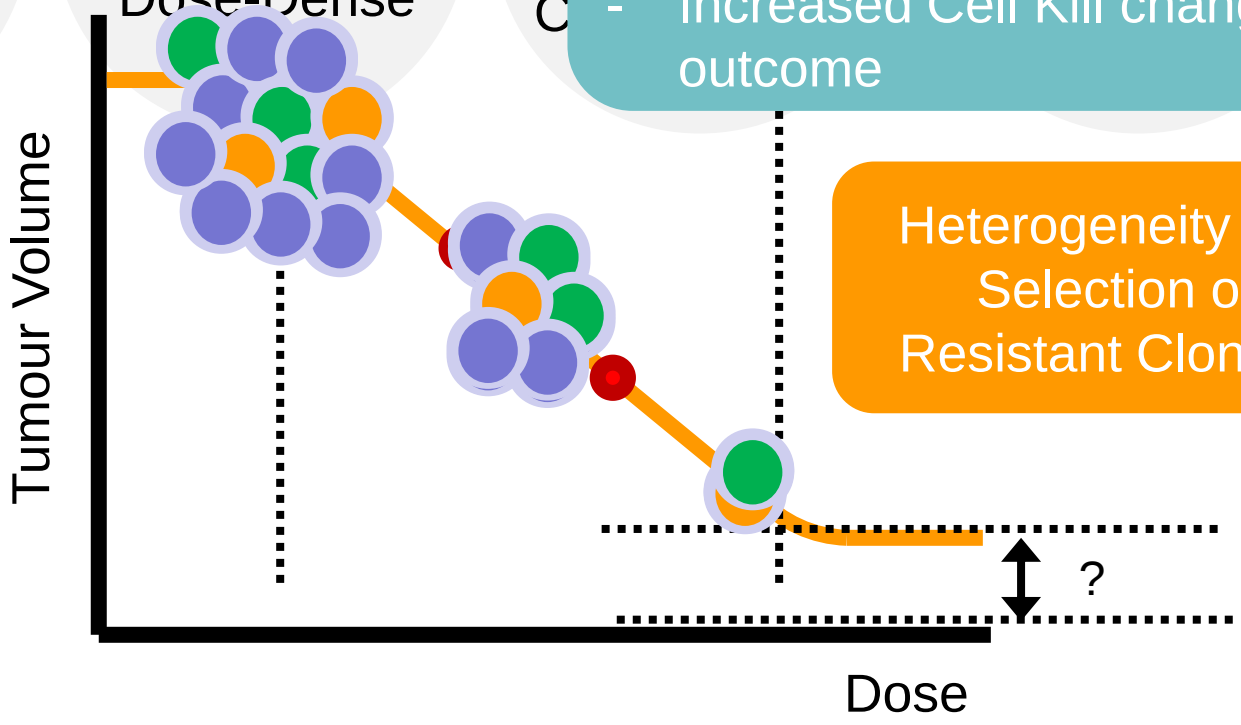




Key assumptions

- Max. Cell Kill not reached
- Haem. Toxicity Dose-limiting
- Increased Cell Kill changes outcome

Heterogeneity and Selection of Resistant Clones?



Chemo Intensification - Rationale
Dose-dense Chemotherapy

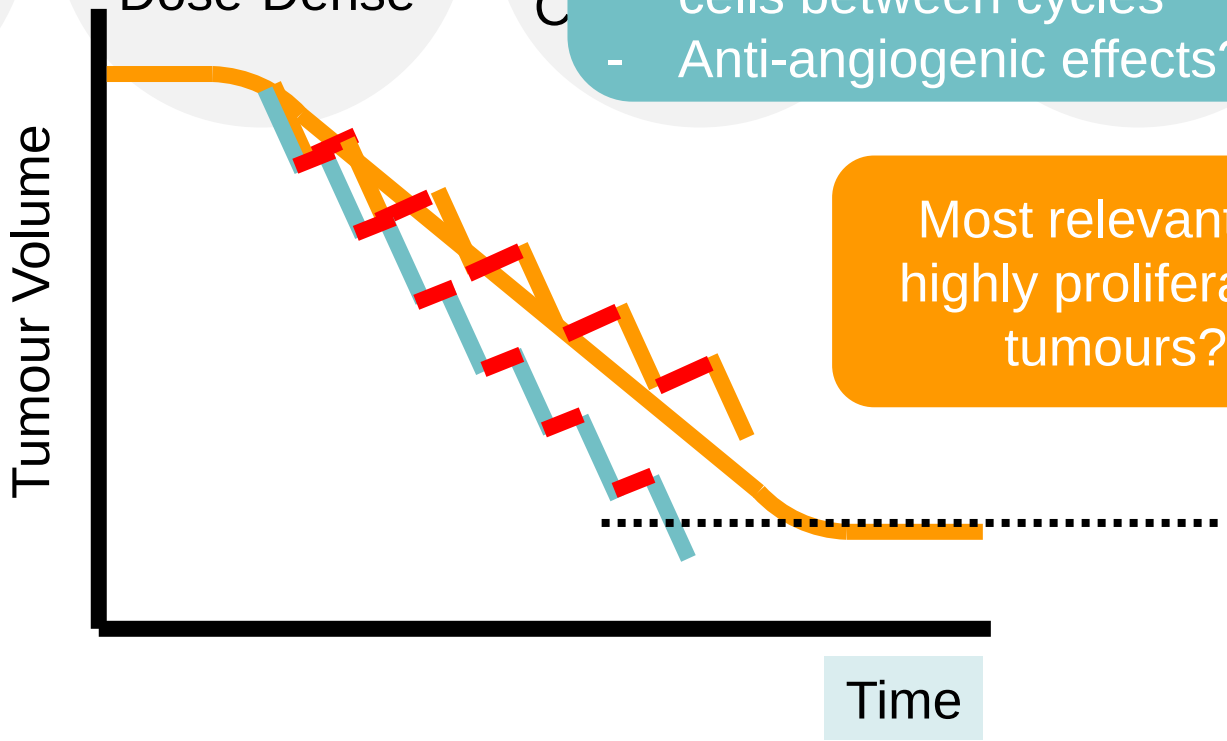
High- Dose

Dose-Dense

C

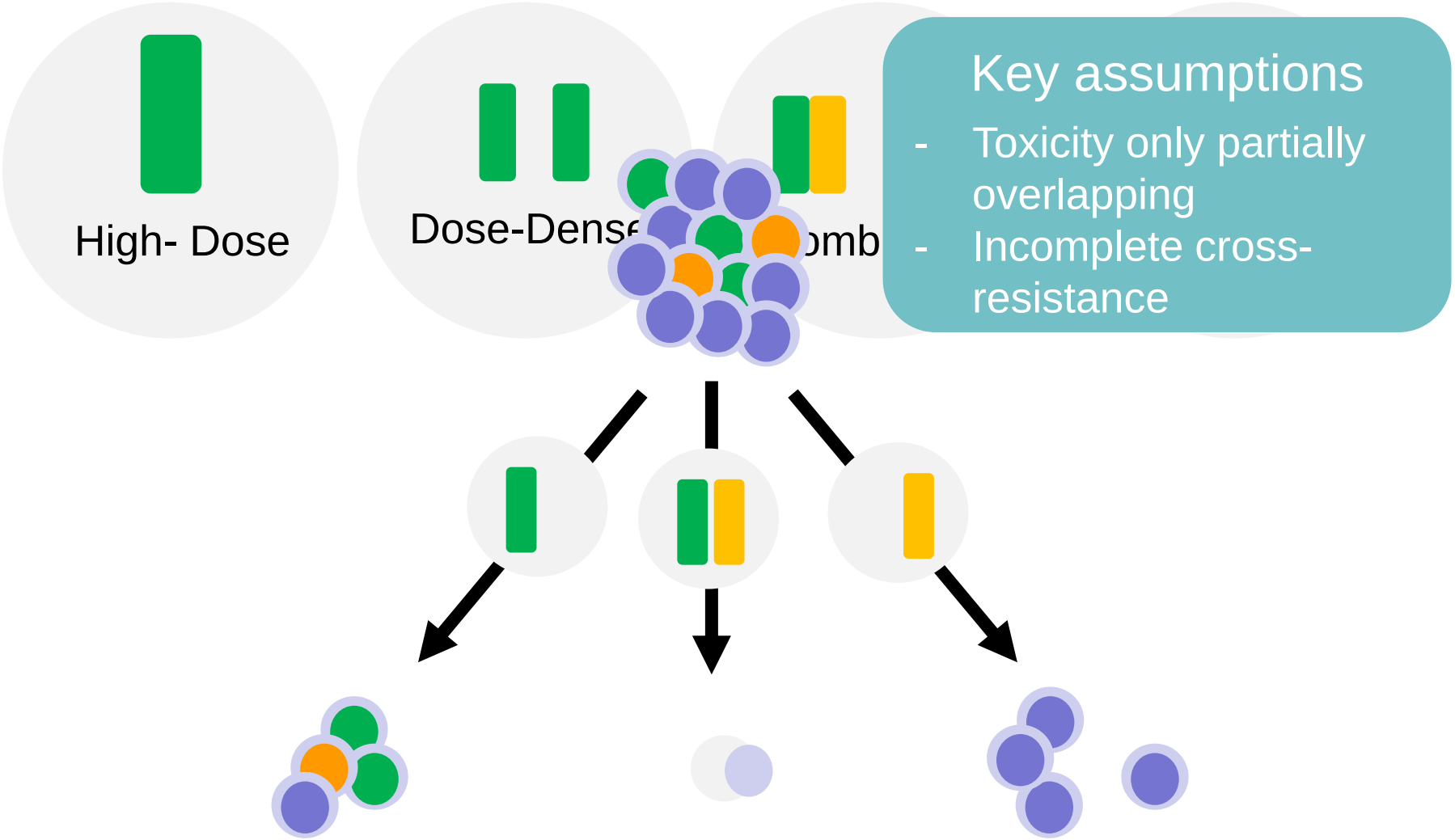
Key assumptions

- Haem. Toxicity Dose-limiting
- “Repopulation” of tumour cells between cycles
- Anti-angiogenic effects?



Most relevant for highly proliferating tumours?

Chemo Intensification - Rationale
Combination Chemotherapy



Chemo-Intensification

Does disease setting matter?

Early Disease

- Microscopic Disease
- Sensitive Disease
- Heterogeneity?
- Vascularisation?

Advanced Disease

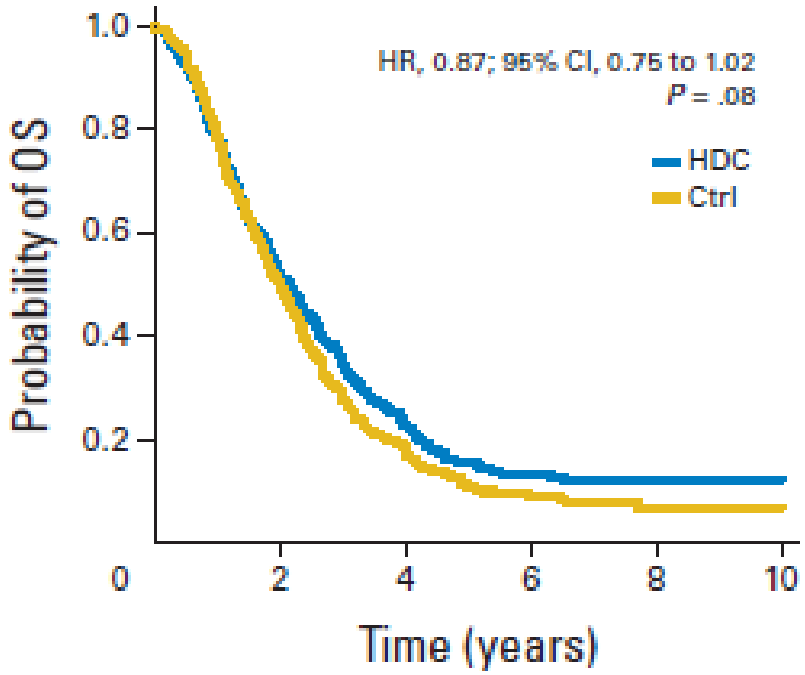
- Macroscopic Disease
- Resistance ↑
- Heterogeneity↑
- Vasculature established

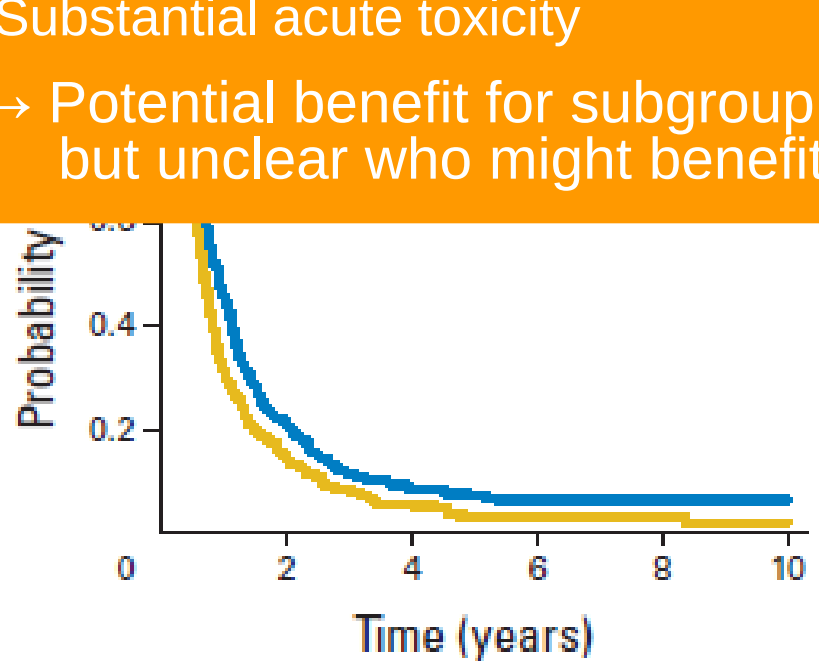
Is more better?

Metastatic Breast Cancer
High-dose chemotherapy

- Small benefit in PFS but not in OS
- Patients <50 years of age have modest OS benefit
- Biological subtype analysis limited
- Substantial acute toxicity

→ Potential benefit for subgroup but unclear who might benefit





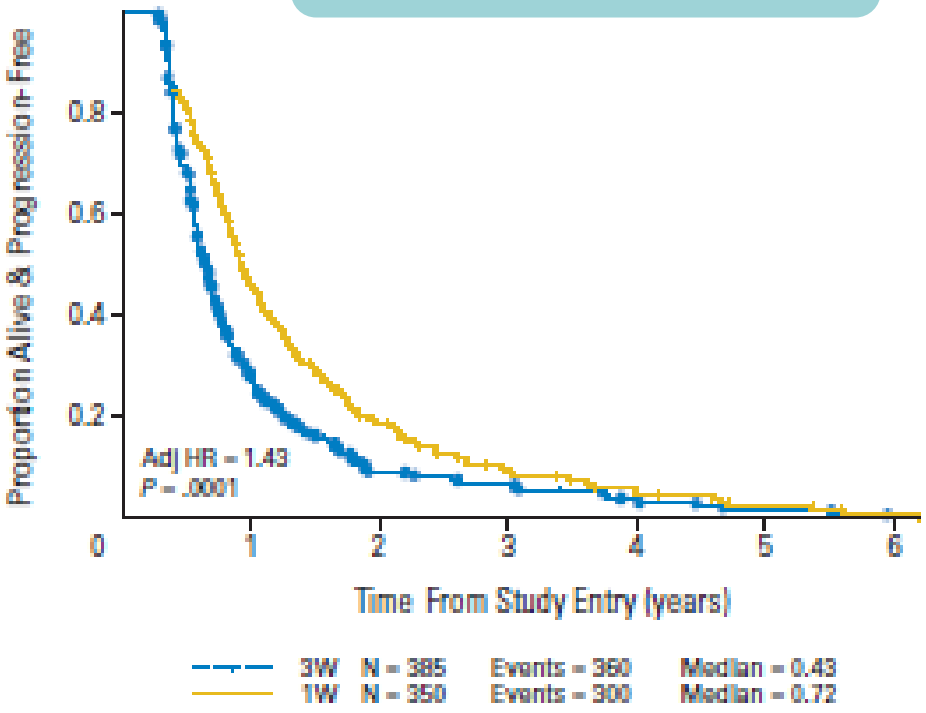
Berry et al., JCO 2011

Metastatic Breast Cancer
Dose-dense chemotherapy

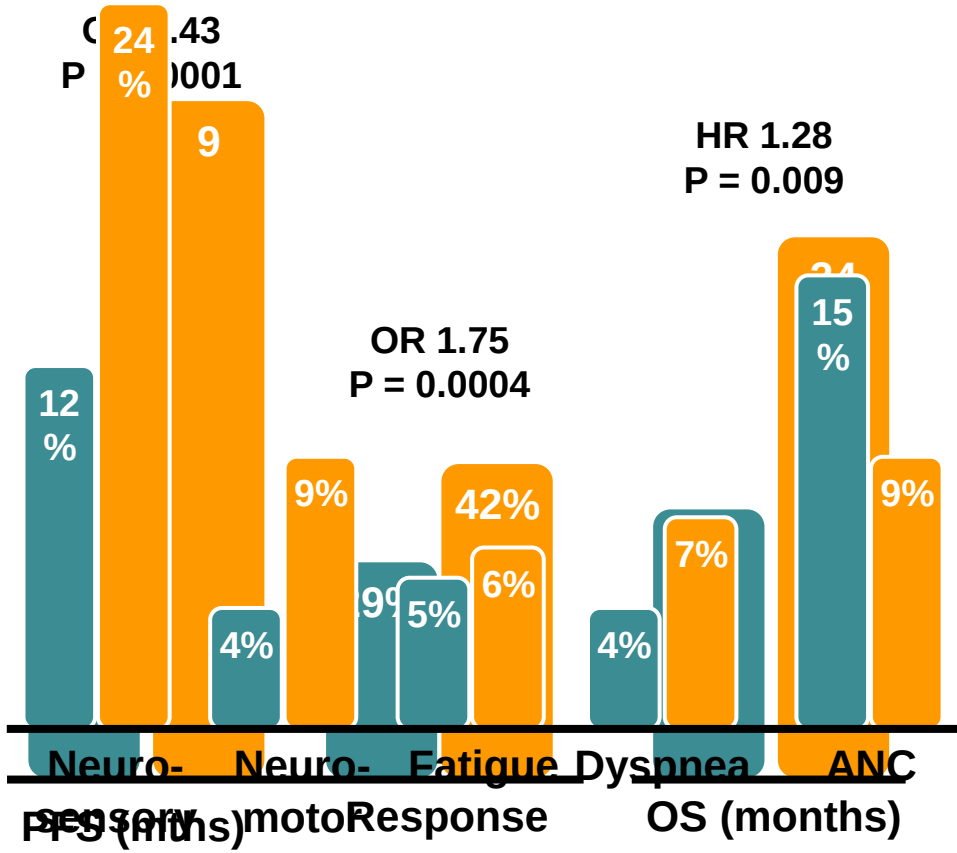
R

Paclitaxel, 80 mg/m² weekly

Paclitaxel, 175 mg/m² q3 wks

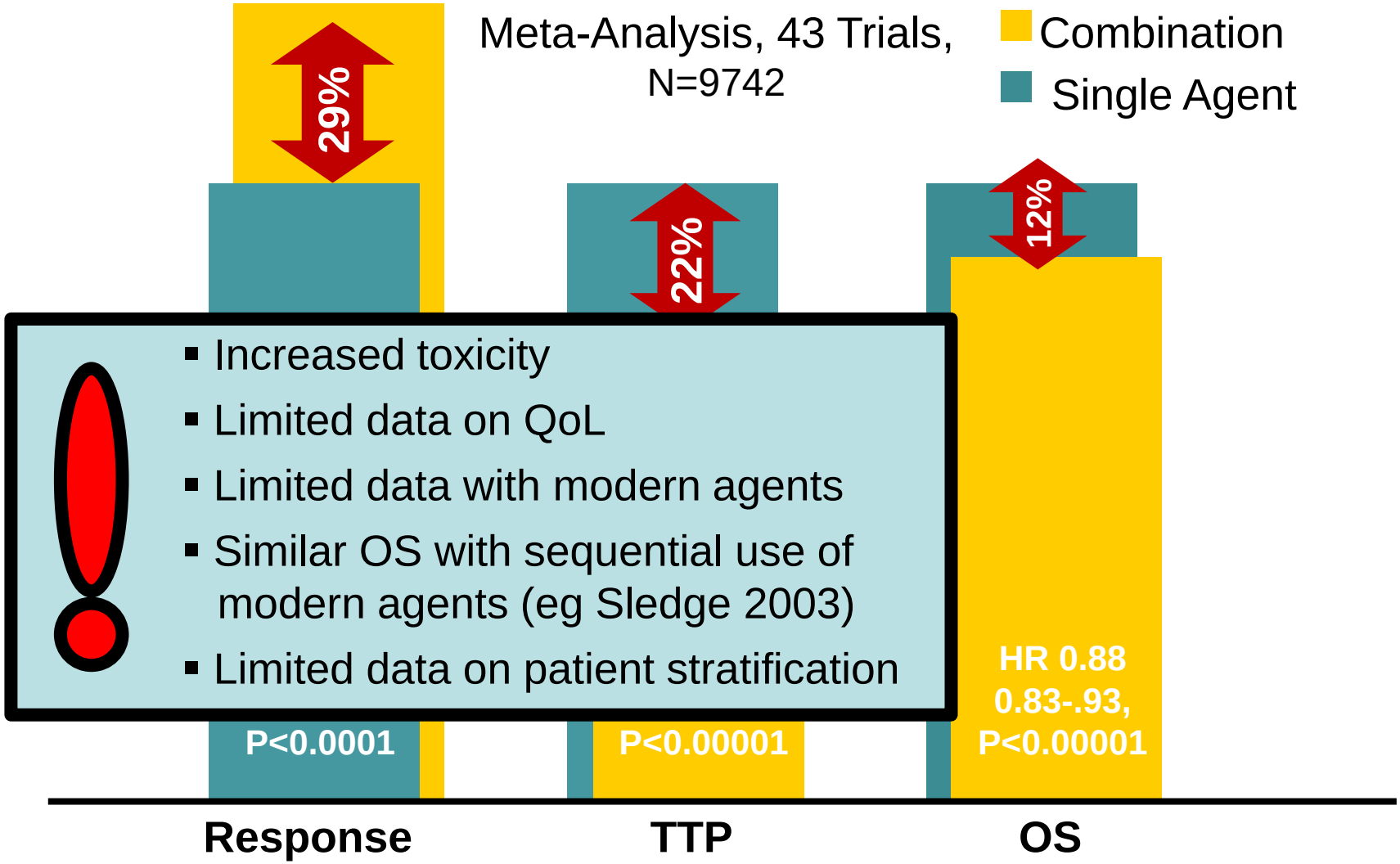


Dose dense, but also dose intensity 1.37 x higher



Seidman et al., JCO 2008

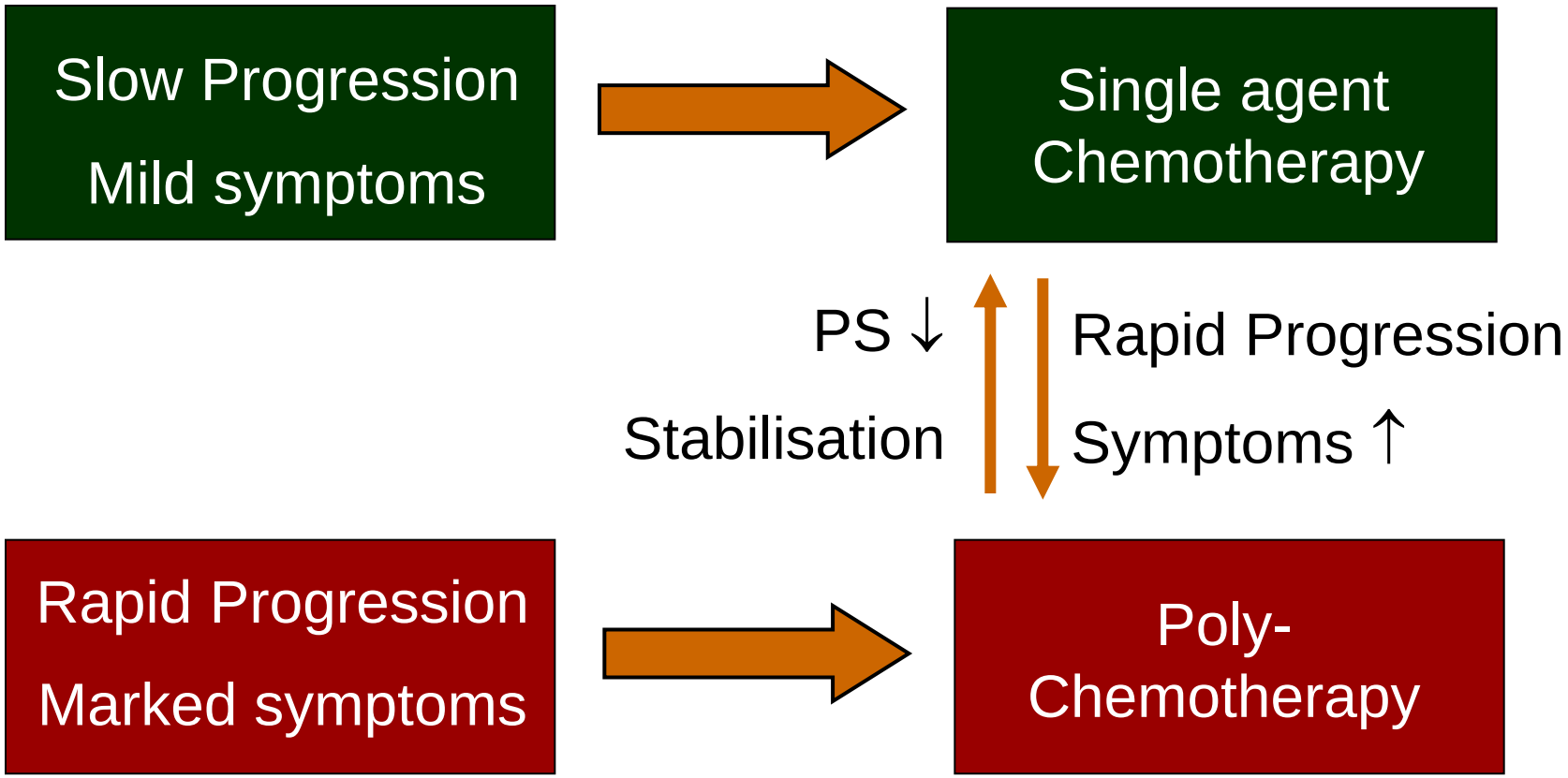
Metastatic Breast Cancer
Combination vs single agent therapy?



Carrick et al., Cochrane Library 2009

Breast Cancer: Agressive vs non-agressive therapy?

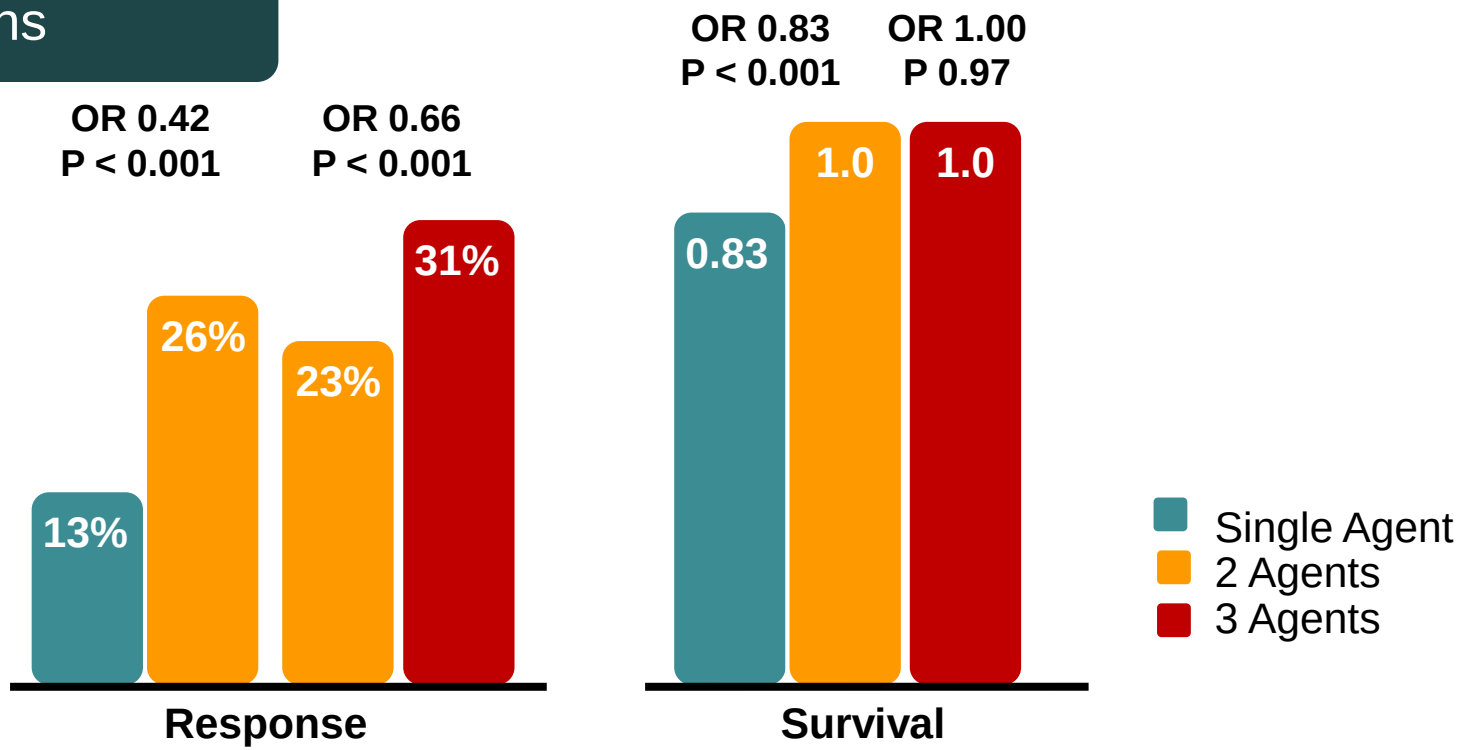
Patient Stratification



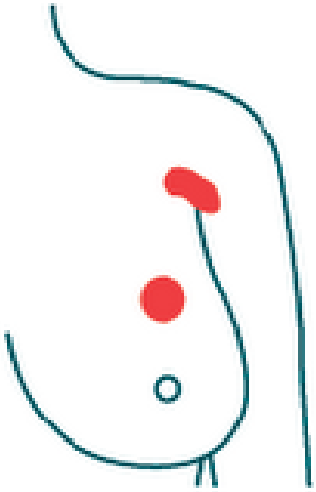
Advanced NSCLC
Combination vs Single Agent Therapy?

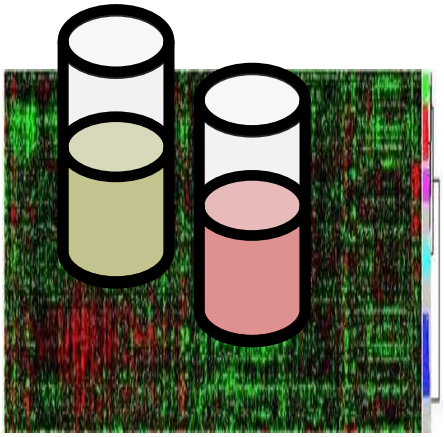
- Doublet combination standard
- No benefit for triplet combinations

ysis: 65 Trials (1980-2001, n = 13,601)



Delbaldo et al. JAMA 2004

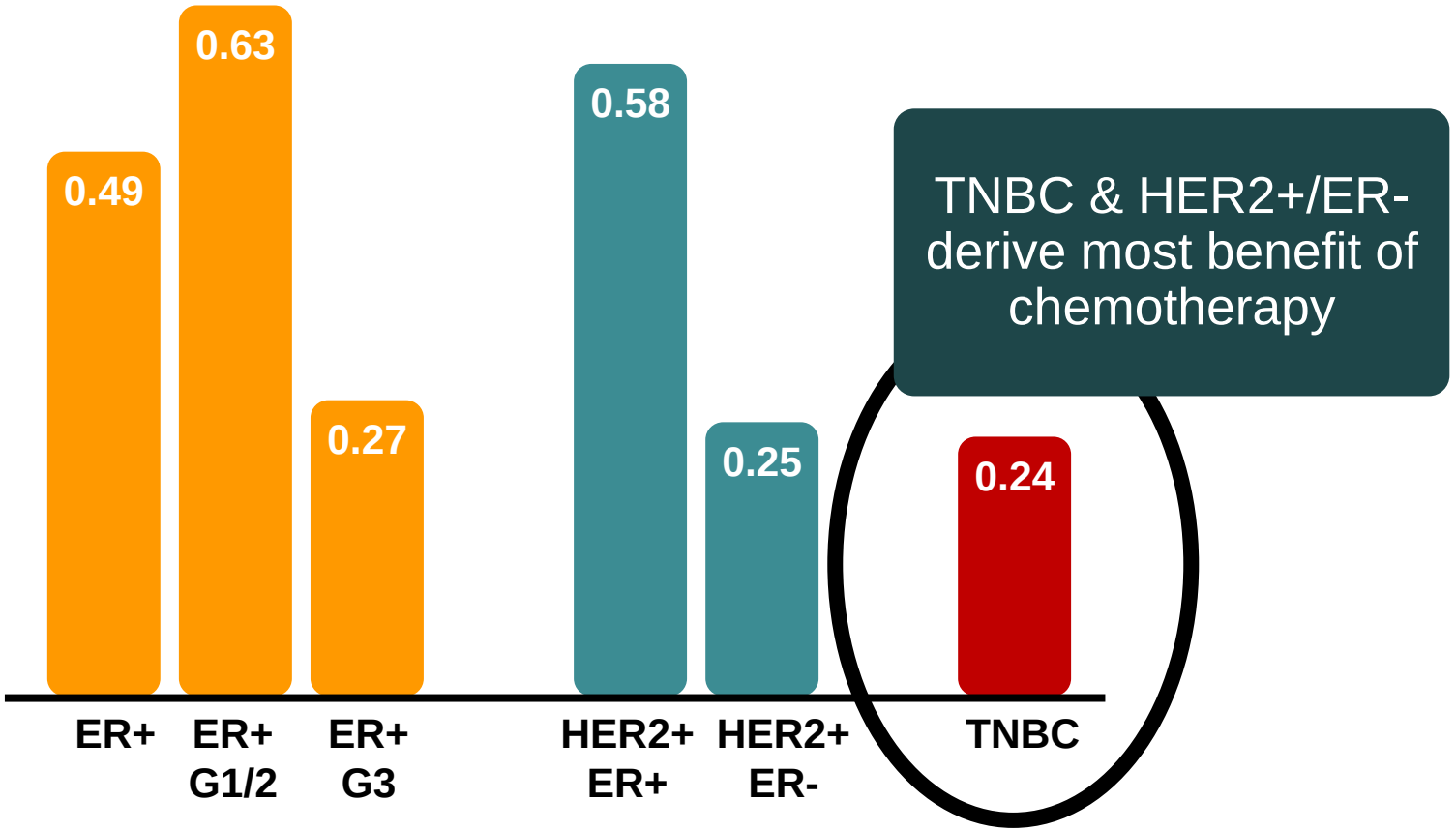




Can we better define who might benefit from chemotherapy intensification?

Breast Cancer: Who benefits most from chemotherapy?
Response to Chemo in Subtypes

Association between pCR and event-free survival, by breast cancer subtype

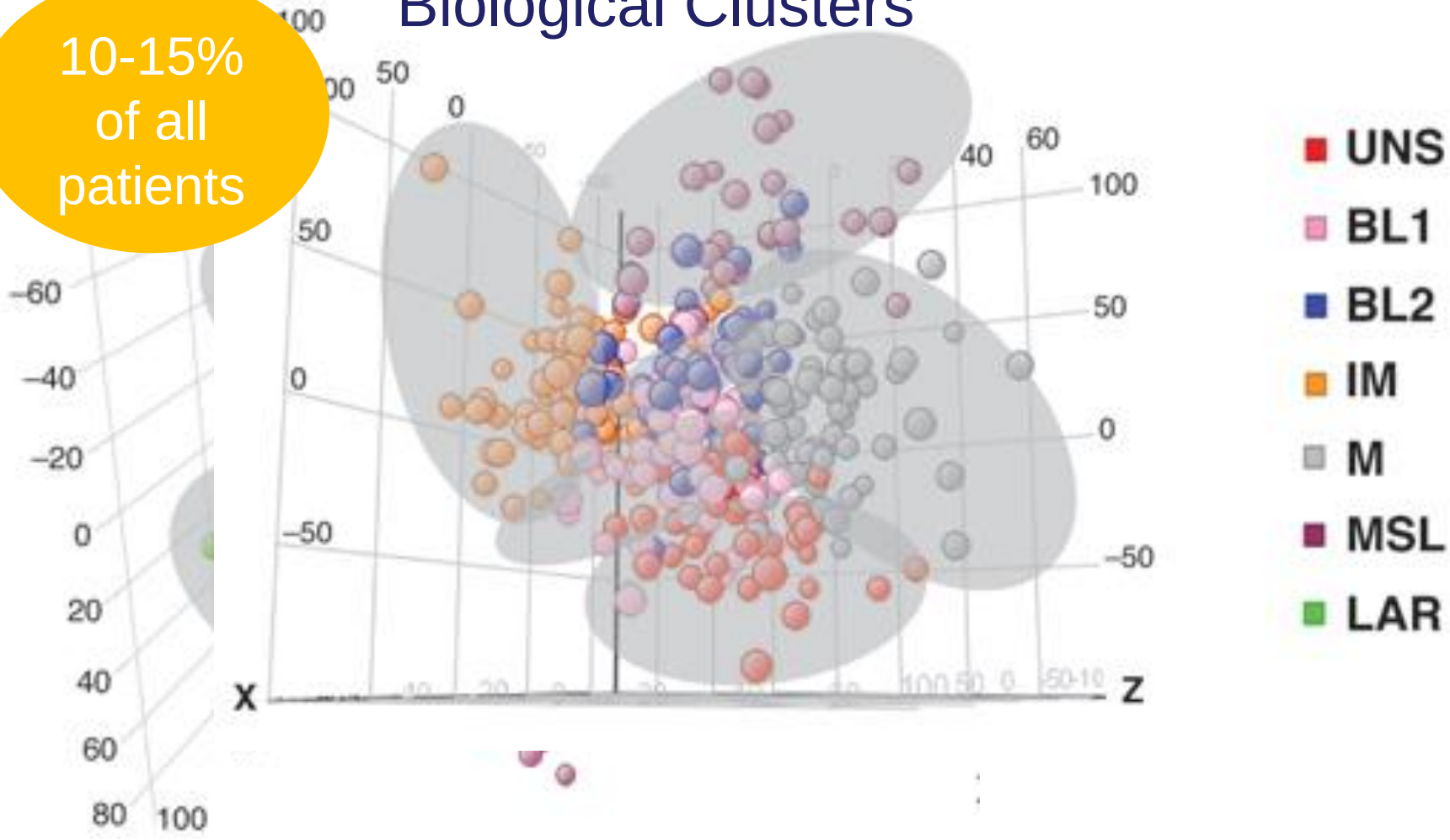


[1] Cortazar, Lancet 2014

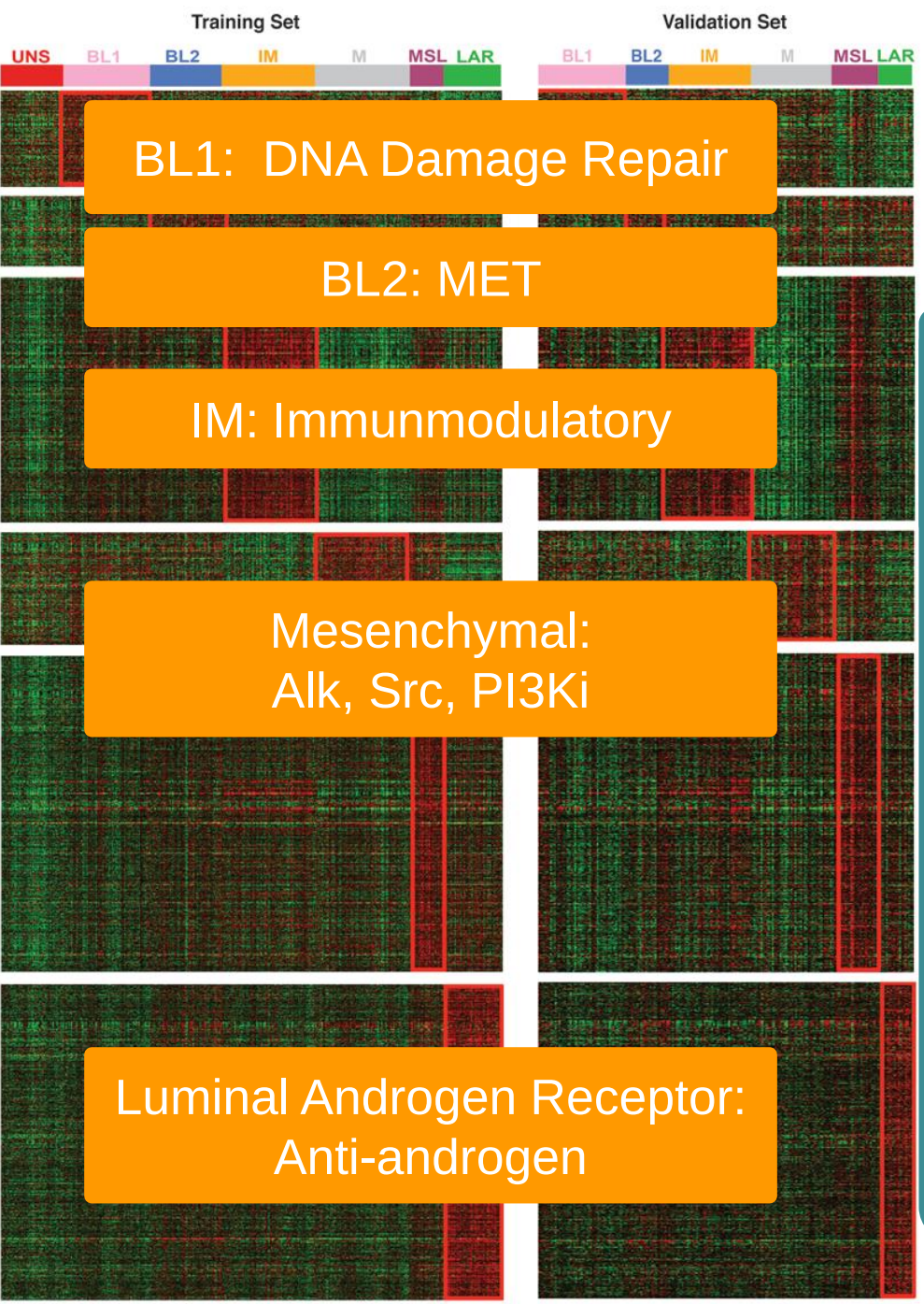
Triple-negative Breast Cancer
Heterogeneity requires different strategies

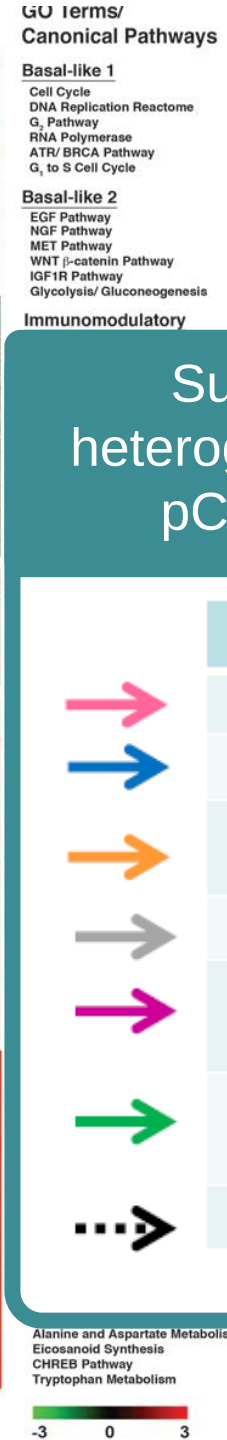
10-15% of all patients

Biological Clusters



Lehmann et al, JCI 2011





Different Targets for Biological Clusters

Subtyping also reveals heterogeneity in probabilities of pCR to neoadjuvant CT

	pCR
Basal-like 1	++
Basal-like 2	-
Immunomodulatory	+(+)
Mesenchymal-like	+(+)
Mesenchymal stem-like	±
Luminal androgen-receptor	±
Unclassified	+(+)

Masuda et al, ASCO 2013

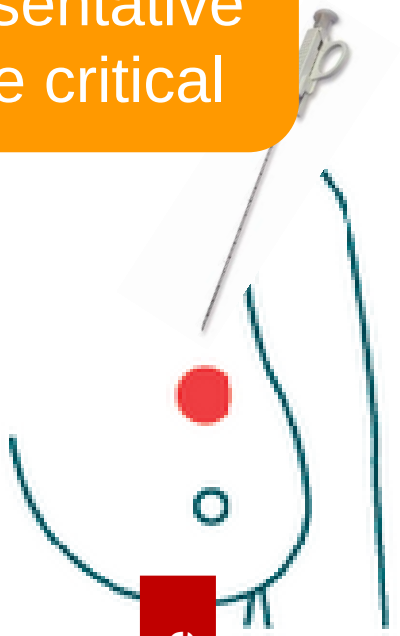
Lehmann et al, JCI 2011

Change of Tumour Biology over Time

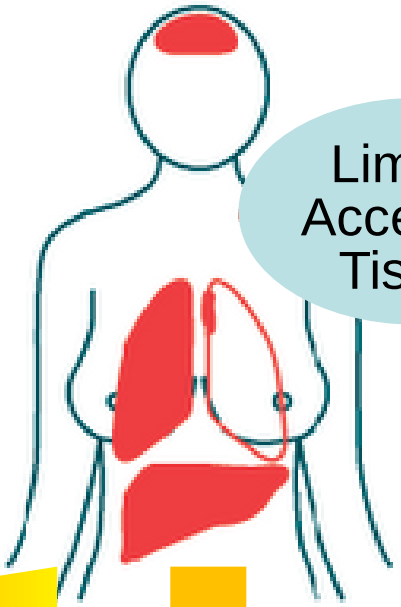
Access to representative tissue critical

ancer

Metastatic Disease



Months to Years



Limited Access to Tissue

Tissue

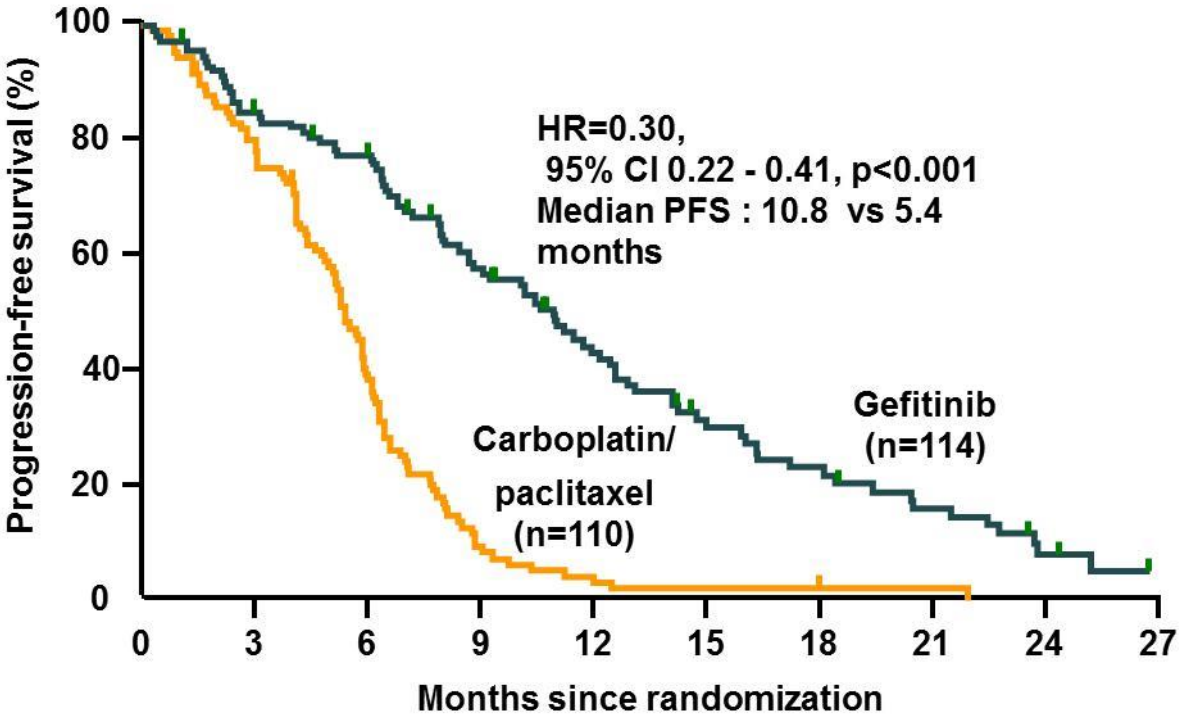
Change in Tumour Biology

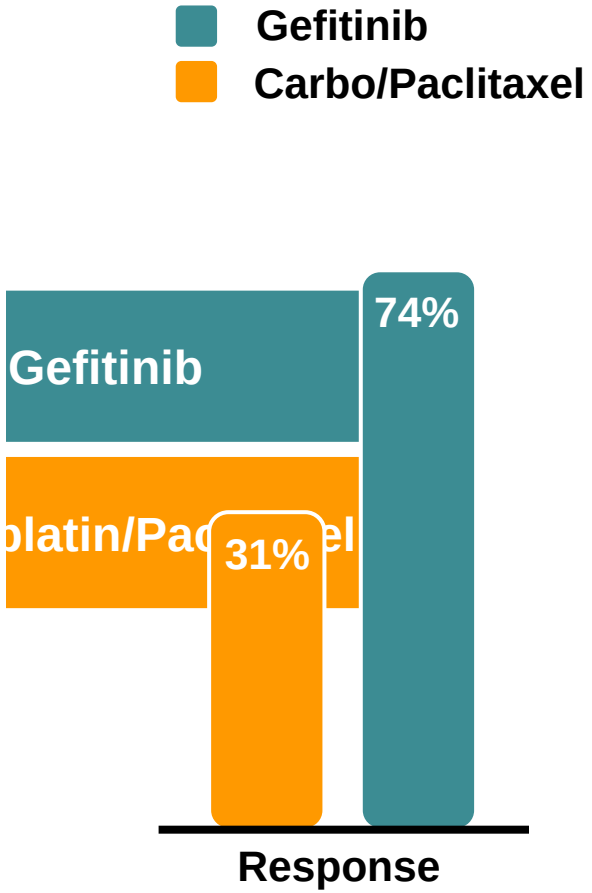
Tissue

Is intensification of chemotherapy still the best way forward?

New Therapeutic Strategies

Combination chemotherapy versus Biologicals
EGFR-Inhibition in EGFR-M+ NSCLC



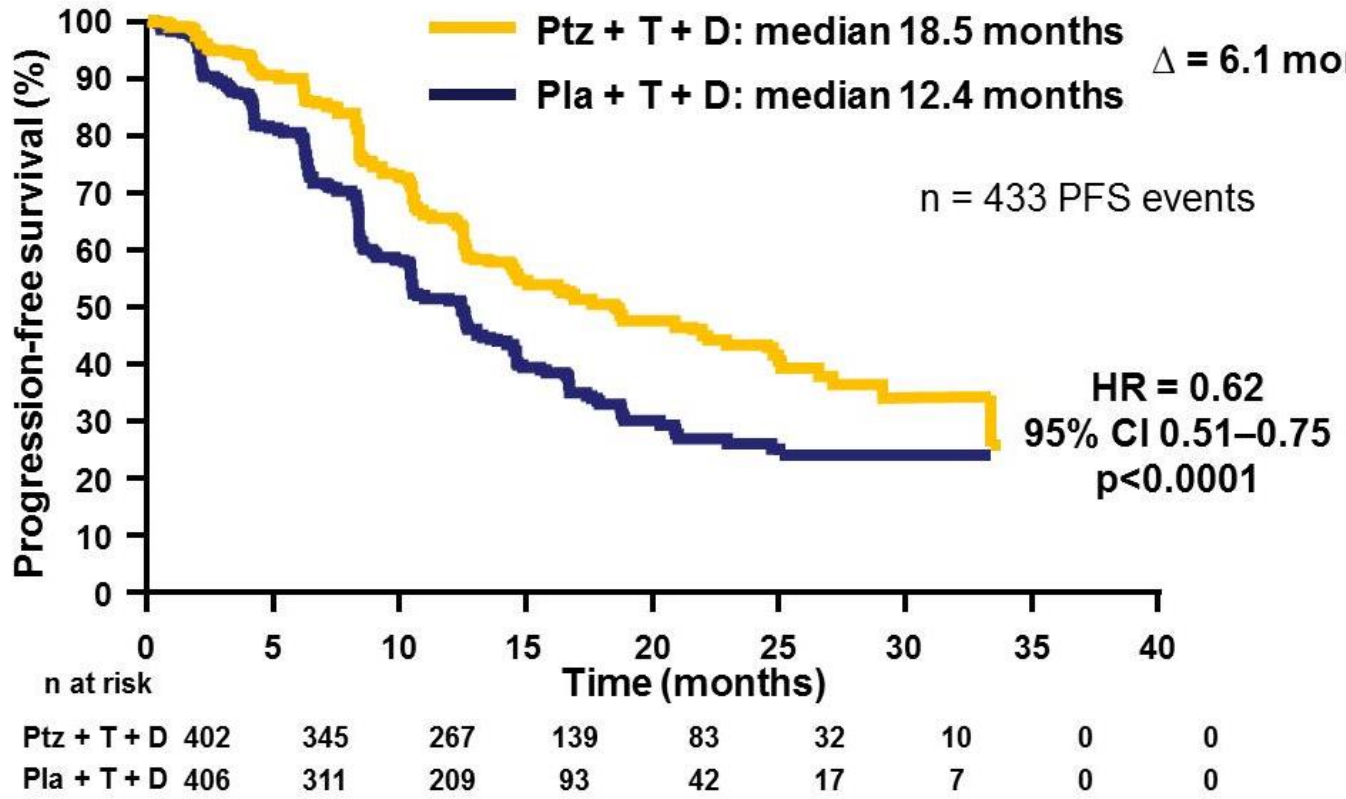


Maemondo et al NEJM 2010

Combination of chemotherapy and Biologicals
Dual vs Single Target Inhibition

Patient
HER2-pos
centrally c
(N =

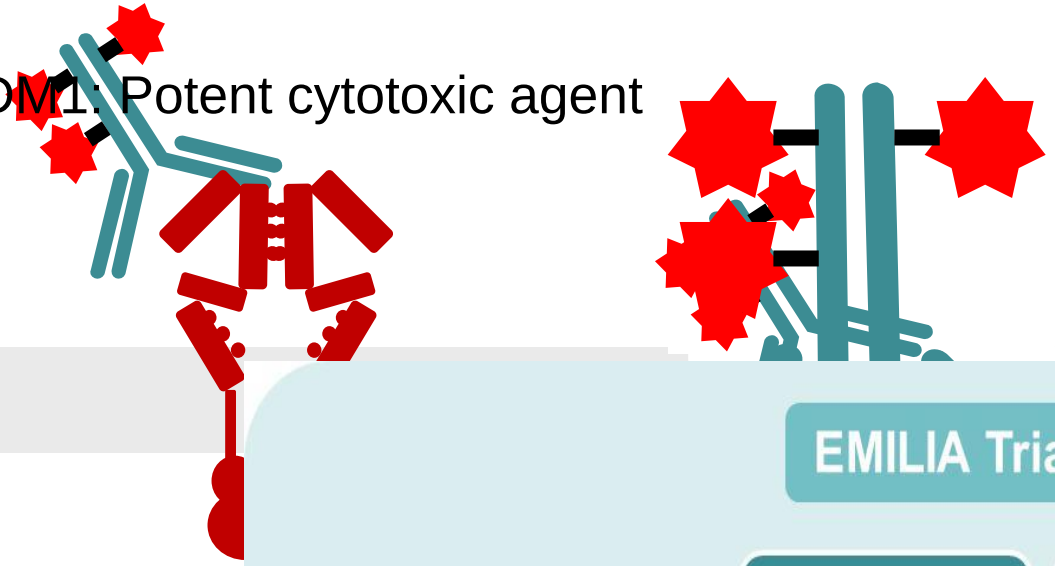
Cleopatra Study (n=808)



- Pertuz
- Trastu
- Docetaxel: 75 mg/m^2, escalating to 100 mg/m^2 if tolerated

Increased Local Intensity: Antibody-Drug-Conjugates
Trastuzumab-DM1

DM1: Potent cytotoxic agent



Retains biologic activity of Trastuzumab

Targ
D

- **Mitoti**
- **Low s**
  due to HER2 targeting

EMILIA Trial

Patients with HER2-positive MBC and PD or relapse after Trastuzumab (n = 980)

R

n=496 → **Capecitabine + Lapatinib**

n=495 → **T-DM1**

Time to Progression

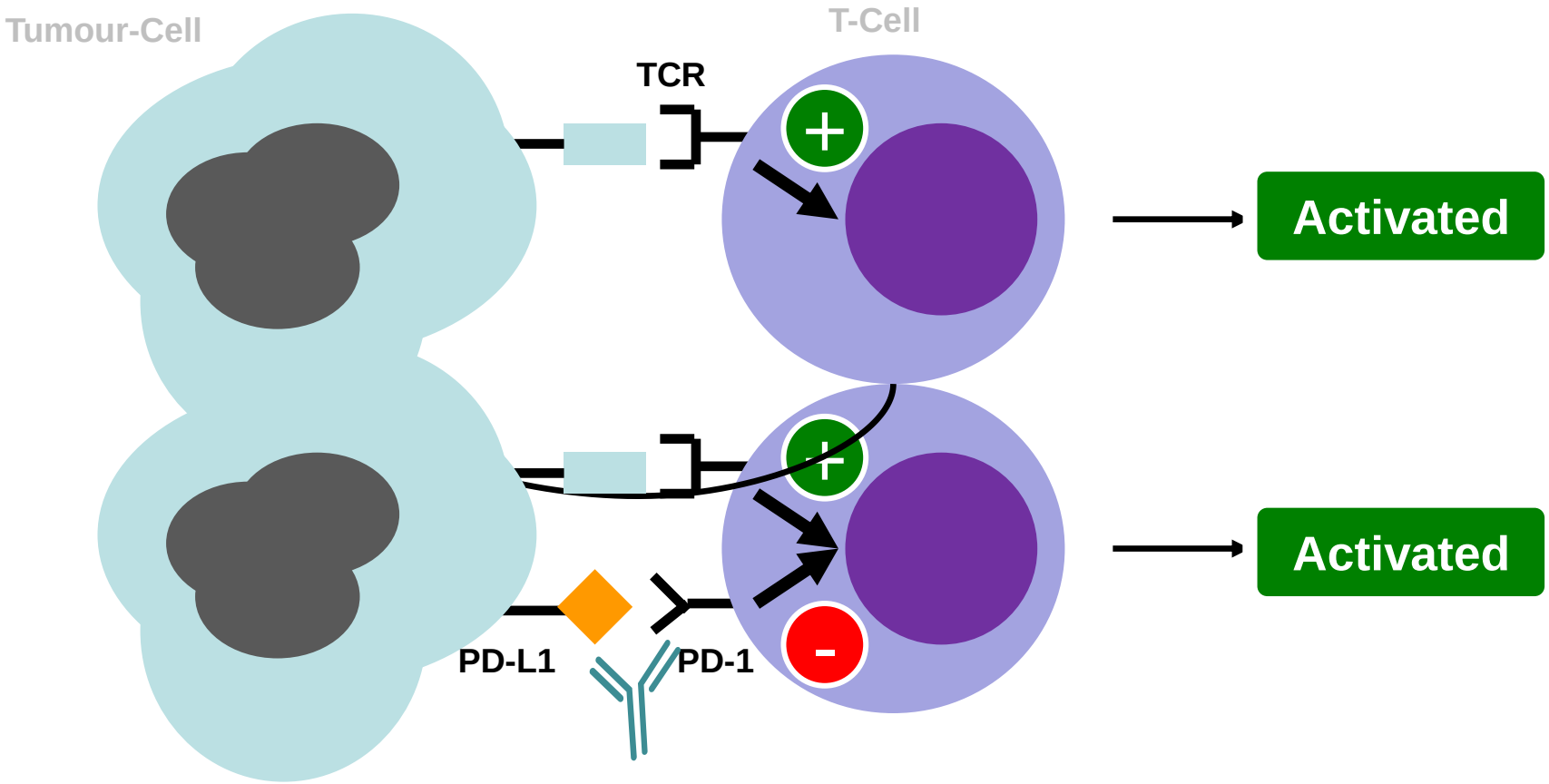
6.4 months

9.6 months

HR = 0.65
95%CI 0.55-0.77
P <0.0001

Konecny, Cancer Res 2006; Scaltriti, Oncogene 2009

Targeting Immune-Checkpoints

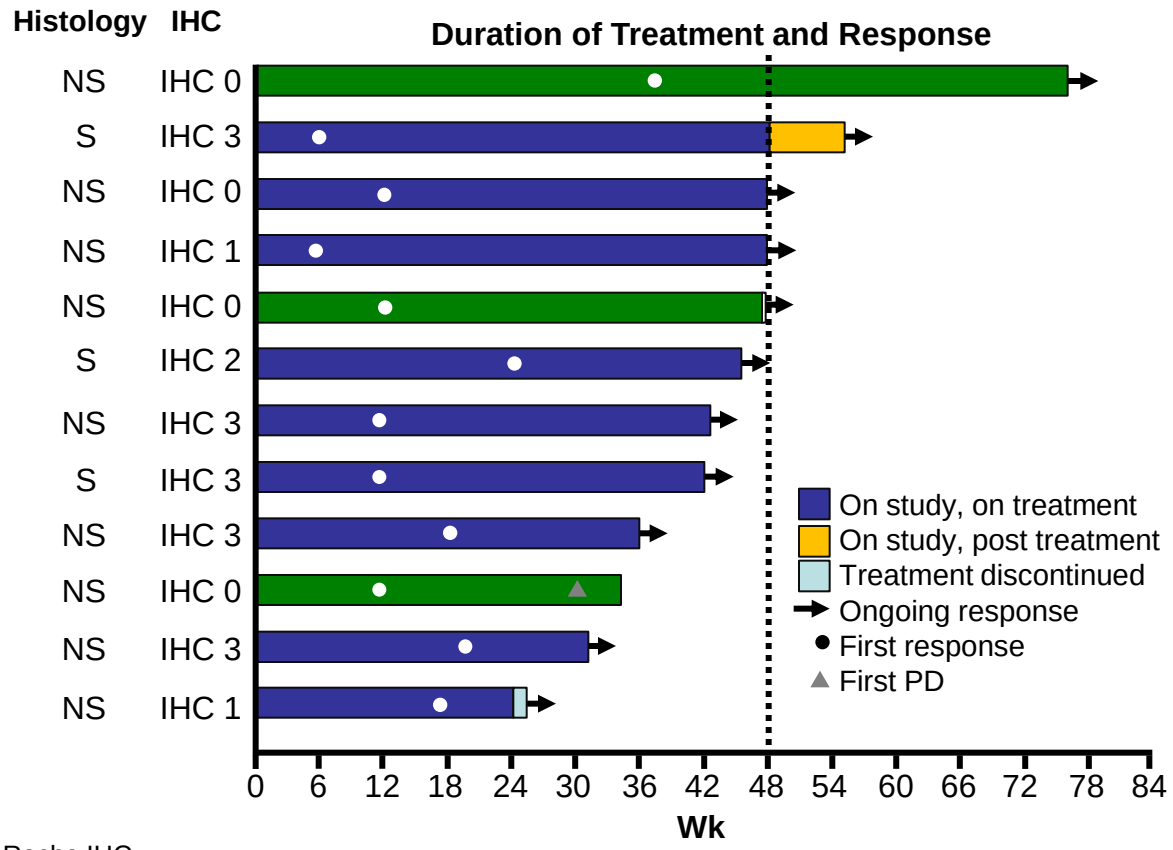


Targeting Immune-Checkpoints in NSCLC

Response in NSCLC by PD-L1 Status

Anti-PD-L1 (MPDL3280A)

PD-L1 Status* (N = 53)	ORR,† %	Pts With PD, %
IHC 3 (n = 6)	83%	17%
IHC 2 & 3 (n = 13)	46%	23%
IHC 1/2/3 (n = 26)	31%	38 %
All patients (N = 53)	23%	40 %



*PD-LI status determined using proprietary Genentech Roche IHC.
†ORR includes investigator-assessed unconfirmed and confirmed (u/c) PR per RECIST 1.1.
Patients first dosed at 1-20 mg/kg by October 1, 2012. Data cutoff April 30, 2013.

Horn L, et al. WCLC 2013. Abstract MO18

Chemotherapy Intensification in the palliative setting
Summary and Conclusions

- Intensification of chemotherapy includes high-dose, dose-dense and combination strategies
- Benefits of intensified strategies might differ between early and advanced disease
- There is an optimal dose and dose intensity for most treatments and for most patients in the palliative setting intensification does NOT have added benefit
- Small subsets might benefit from more intensive approaches; strategies to date have not considered enough the tumour biology
- New developments such as targeted treatments, ADCs or immune therapy are reducing the need for conventional intensification

Optimal use of systemic therapy in the palliative setting

Trials and tribulations: Lifetime experiences of a medical oncologist on chemotherapy intensification

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