Kanker: Nieuwe Medicamenteuze behandelingen

20 juni 2019

Dr. Vroman Philippe - Medische Oncologie - AZ West

Nieuwe Medicamenteuze Behandelingen

- Enkele opmerkelijke recente ontwikkelingen met belangrijke impact op survival en in de routine therapie (practice changing)
  - Immunotherapie oa bij melanoom
  - Cycline inhibitoren bij borstkanker
  - Parp-inhibitoren bij ovariumkanker
  - TDM-1 (Kadcyla) (chemoconjugaat) bij borstkanker

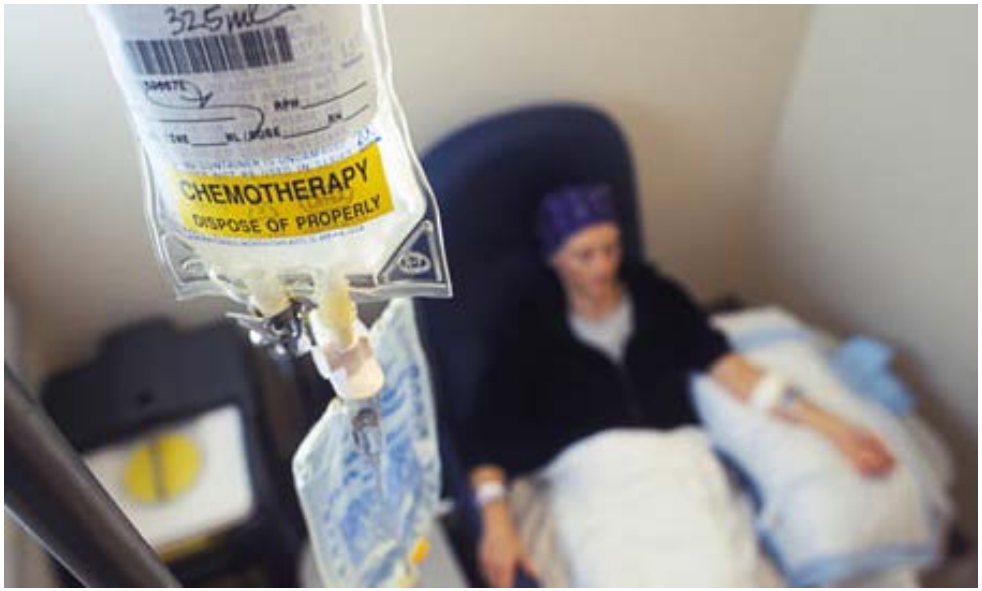
Behandeling van Kanker

- Heelkunde
- Radiotherapie
- Chemotherapie
  - Klassieke cytostatica
  - chemoconjugaten
- Hormonale behandelingen
- Immunotherapie:
  - Gerichte therapie (targeted)
  - immunotherapie

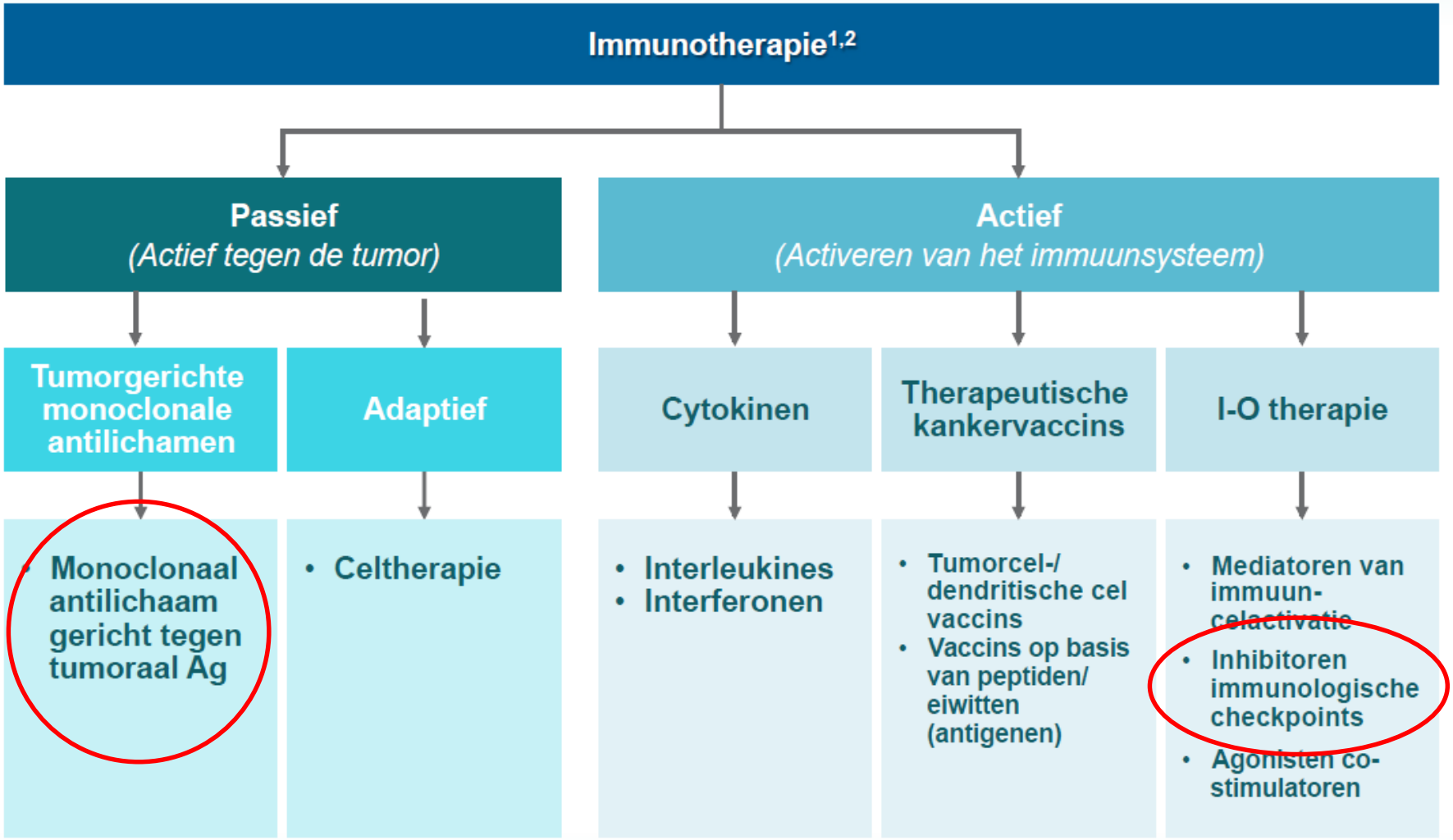
REVOLUTIE ?

Klassieke cytostatica

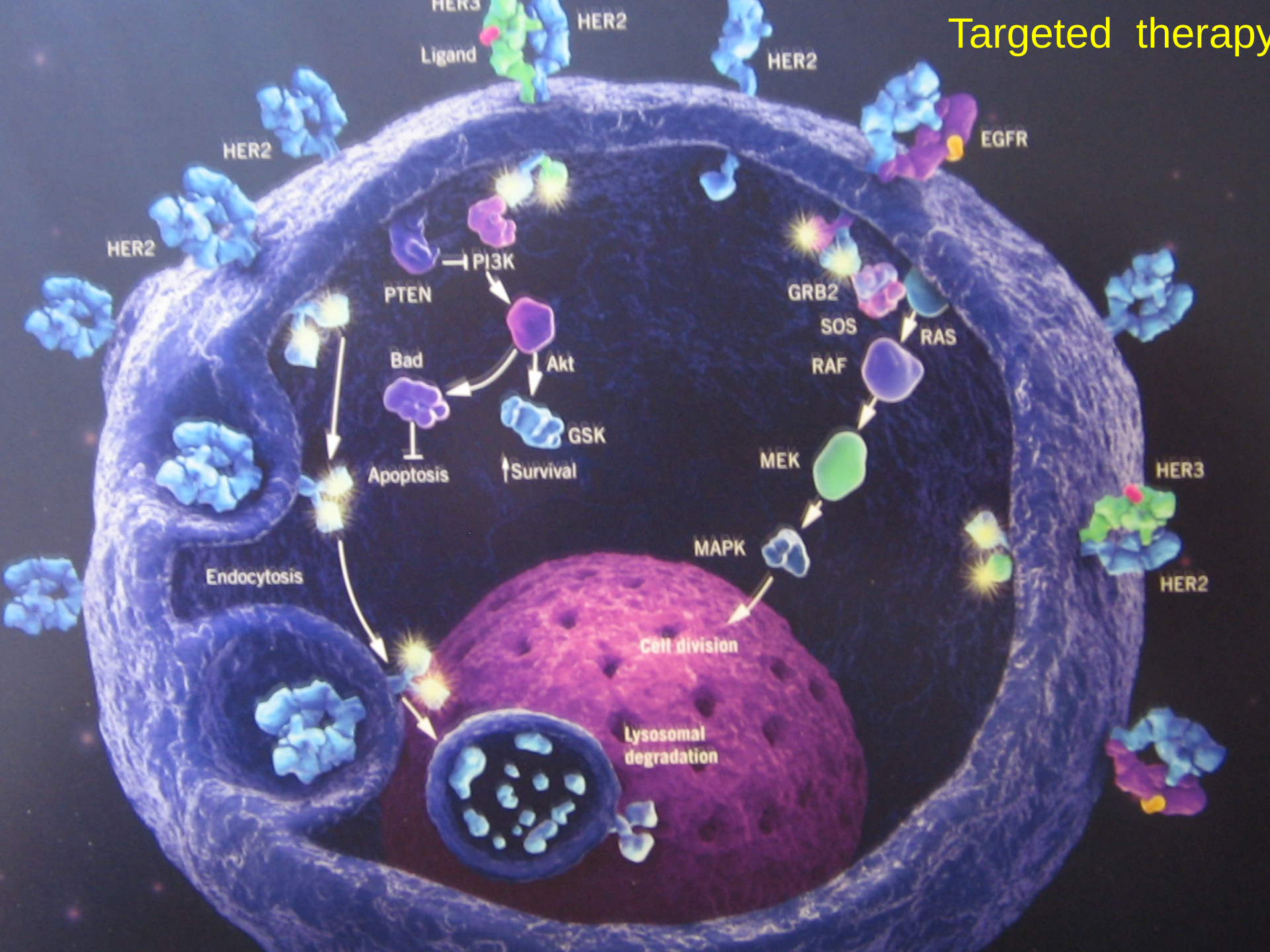
- Actieve middelen
- Nieuwe middelen, nieuwe combinaties
- Betere tolerantie
- Chemotherapie blijft hoeksteen in vele indicaties, zowel in adjuvante (curatief) als palliatieve (niet curatieve) setting



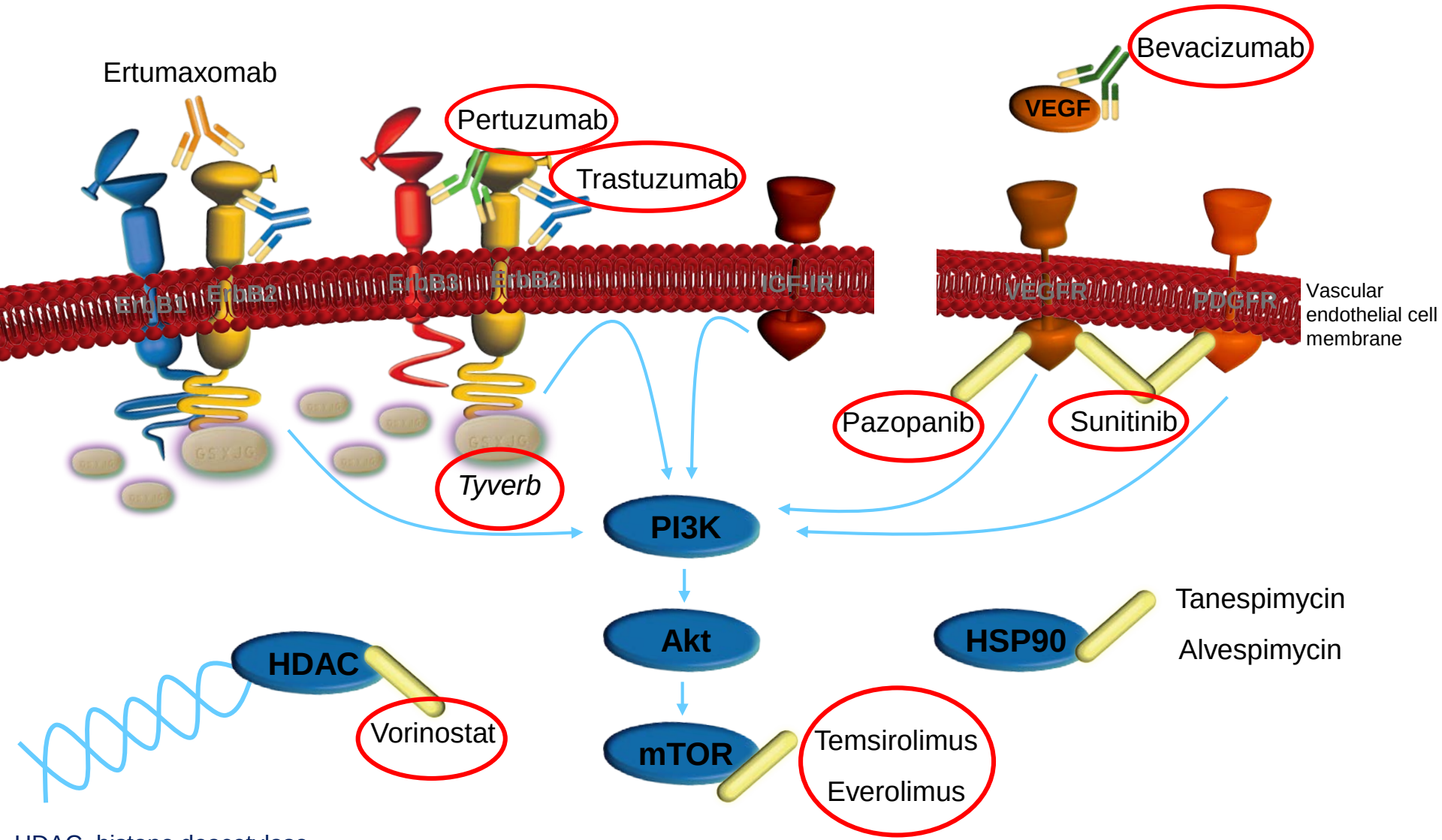
Immunotherapie: een waaier van mogelijkheden



Targeted therapy

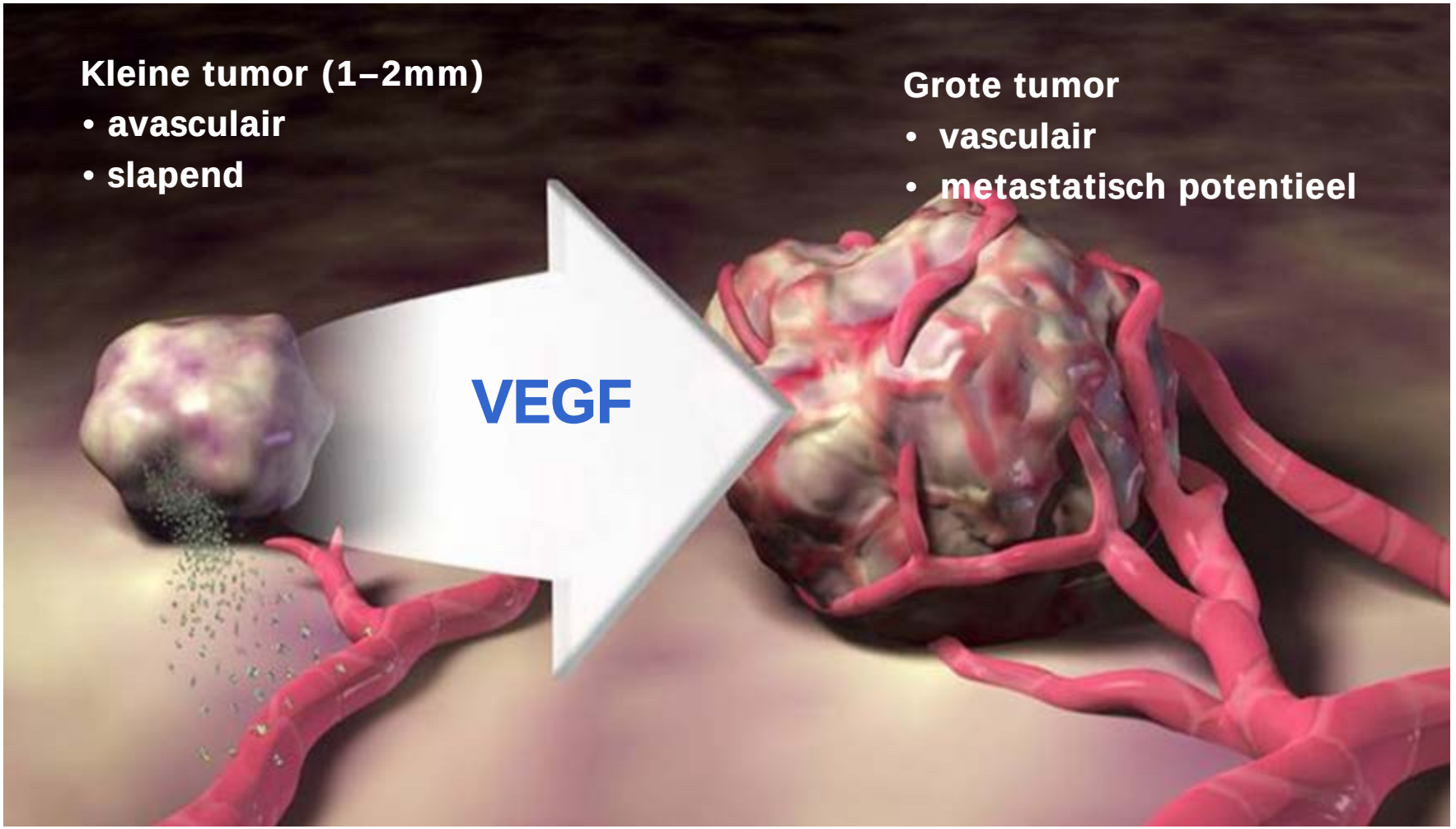


Targets and bullets in cancer



HDAC=histone deacetylase

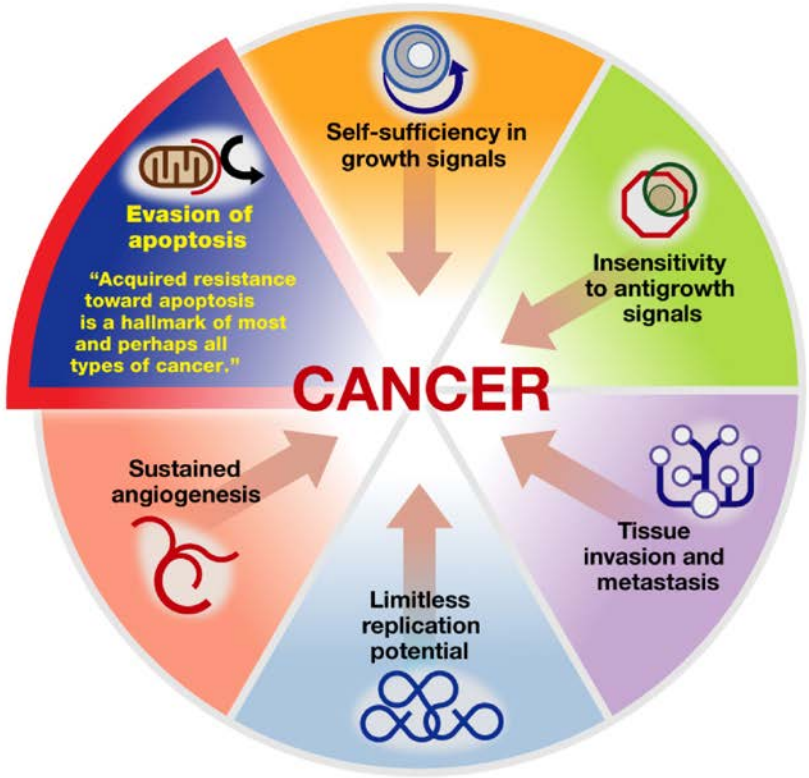
Angiogenese



Gerichte immunotherapie

Voordelen:

- Efficient voorzover target (pathway) uitgeschakeld wordt
- Vaak snelle werking



Nadelen:

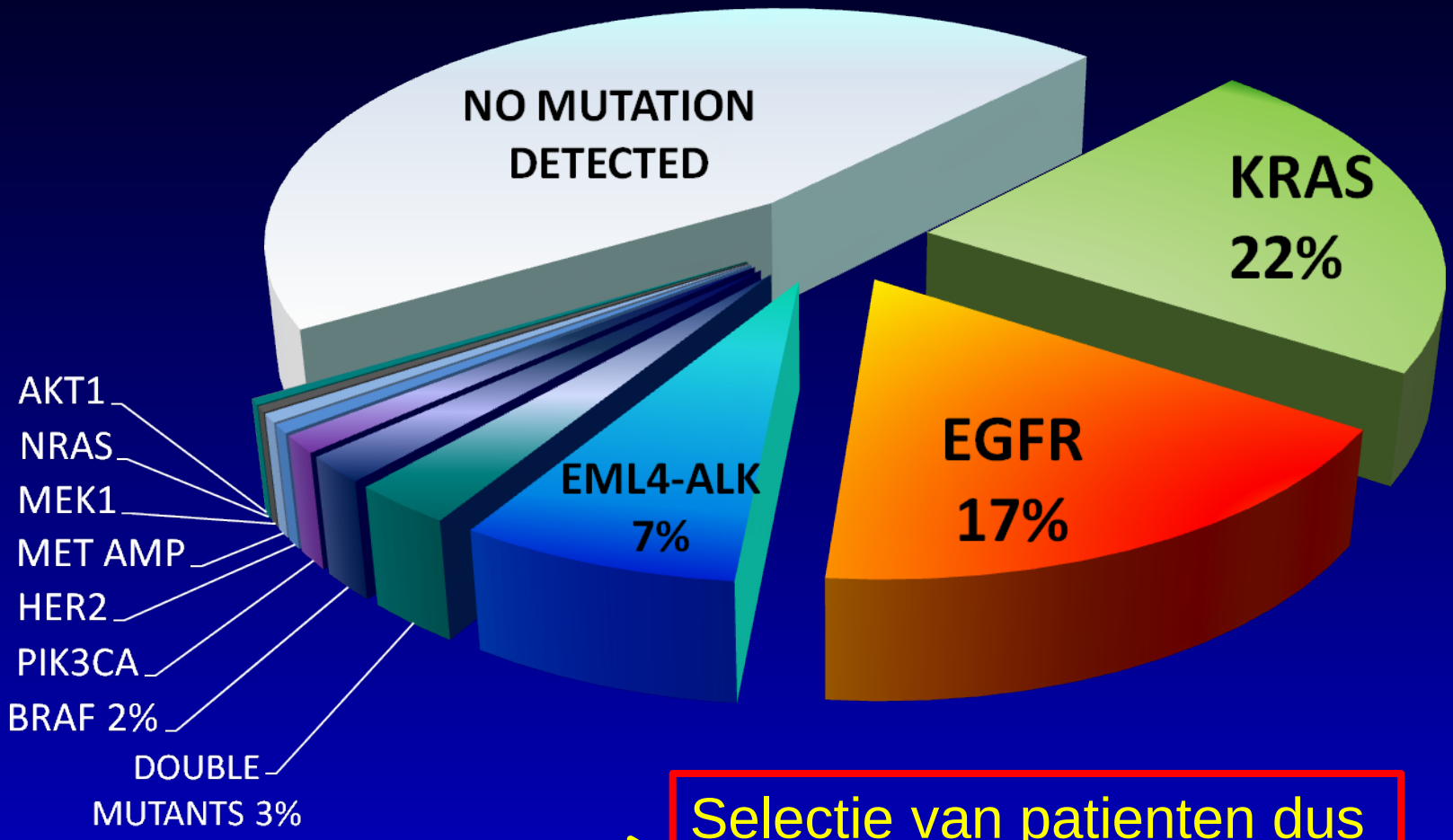
- Complexe engineering
- Even efficient als mate waarin tumor afhankelijk is van geblokkeerde pathway
- Toxiciteit
- Selectieve werking

Speciaal ontworpen lichaamsvreemde vernuftige AL ontworpen via complexe bioengineering om de kankercel in één of meerdere werkingsmechanismen te treffen, waarbij geen gebruik wordt gemaakt van ons eigen natuurlijk afweersysteem

Hanahan, Weinberg, *Cell*, 2000;100:57-70

Lung Cancer Mutation Consortium

Incidence of Single Driver Mutations



→ Selectie van patienten dus PRIMORDIAAL!!

Kris et al. *ASCO* 2011

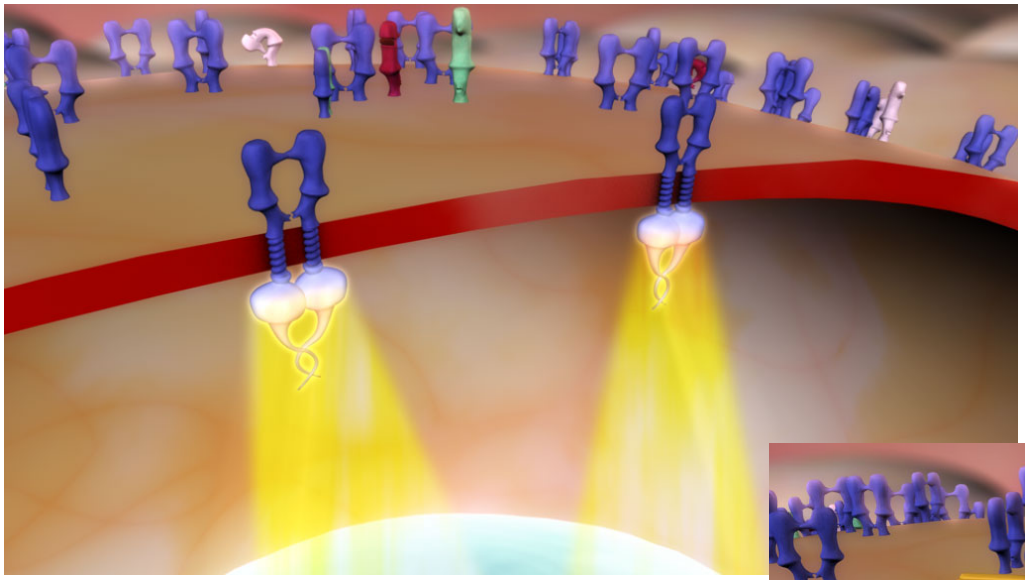
Gerichte (targeted) immunotherapie

- Herceptin, Perjeta
- Sutent, Nexavar, Votrient
- Tarceva, Afatinib
- Erbitux, Vectibix
- Tafinlar, Mekinist
- …

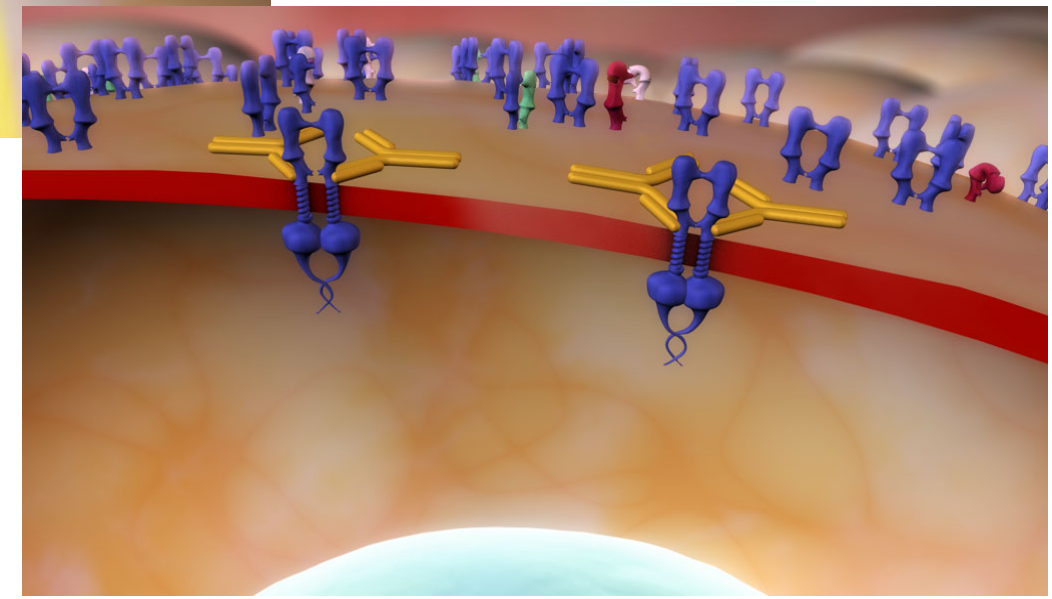
Borstkanker
Gerichte Immunotherapie

- Herceptin (trastuzumab) = antilichaam gericht tegen celmembraan-gebonden (Her-2) receptor
- Alleen zinvol bij overexpressie van de Her-2 receptor! (20-30%)
- Routine therapie in curatieve (adjuvante) en palliatieve setting

Trastuzumab blocks HER2-activated cell proliferation



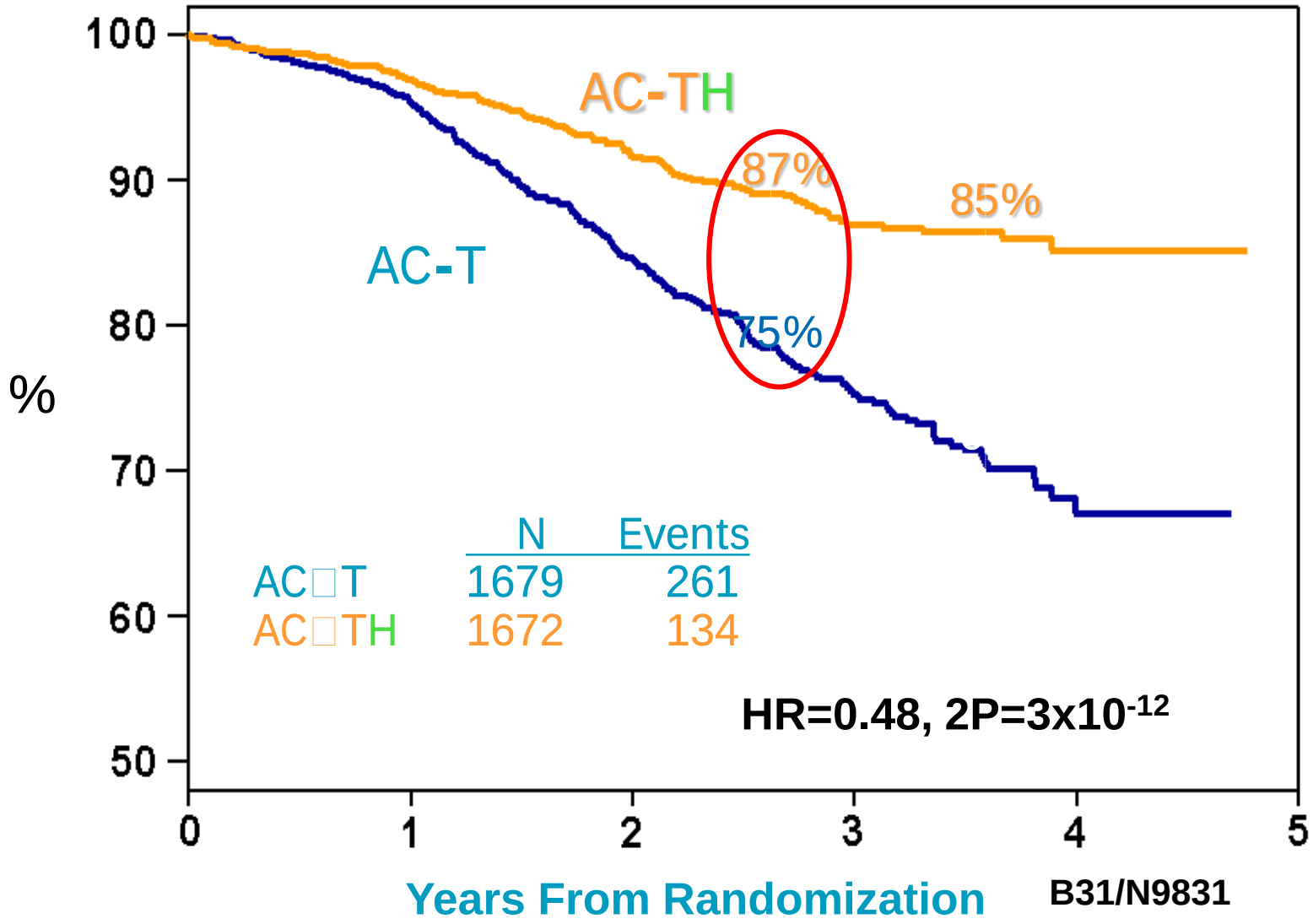
HER2 signalling induces cell proliferation



Trastuzumab interrupts this process

Disease-Free Survival

Adjuvant herceptine
→ Survival benefit



Borstkanker HER-2 overexpressie

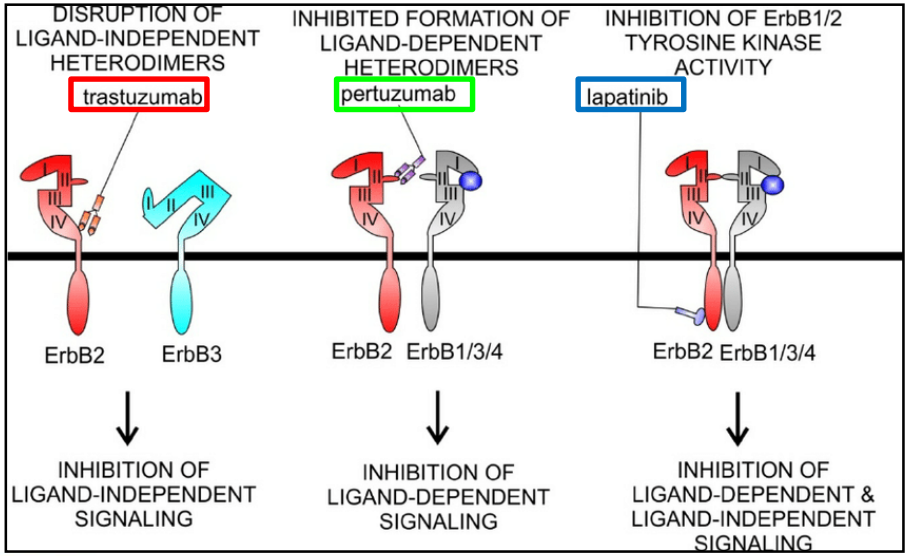
Duale HER-2 blokkade

= trastuzumab + pertuzumab/lapatinib

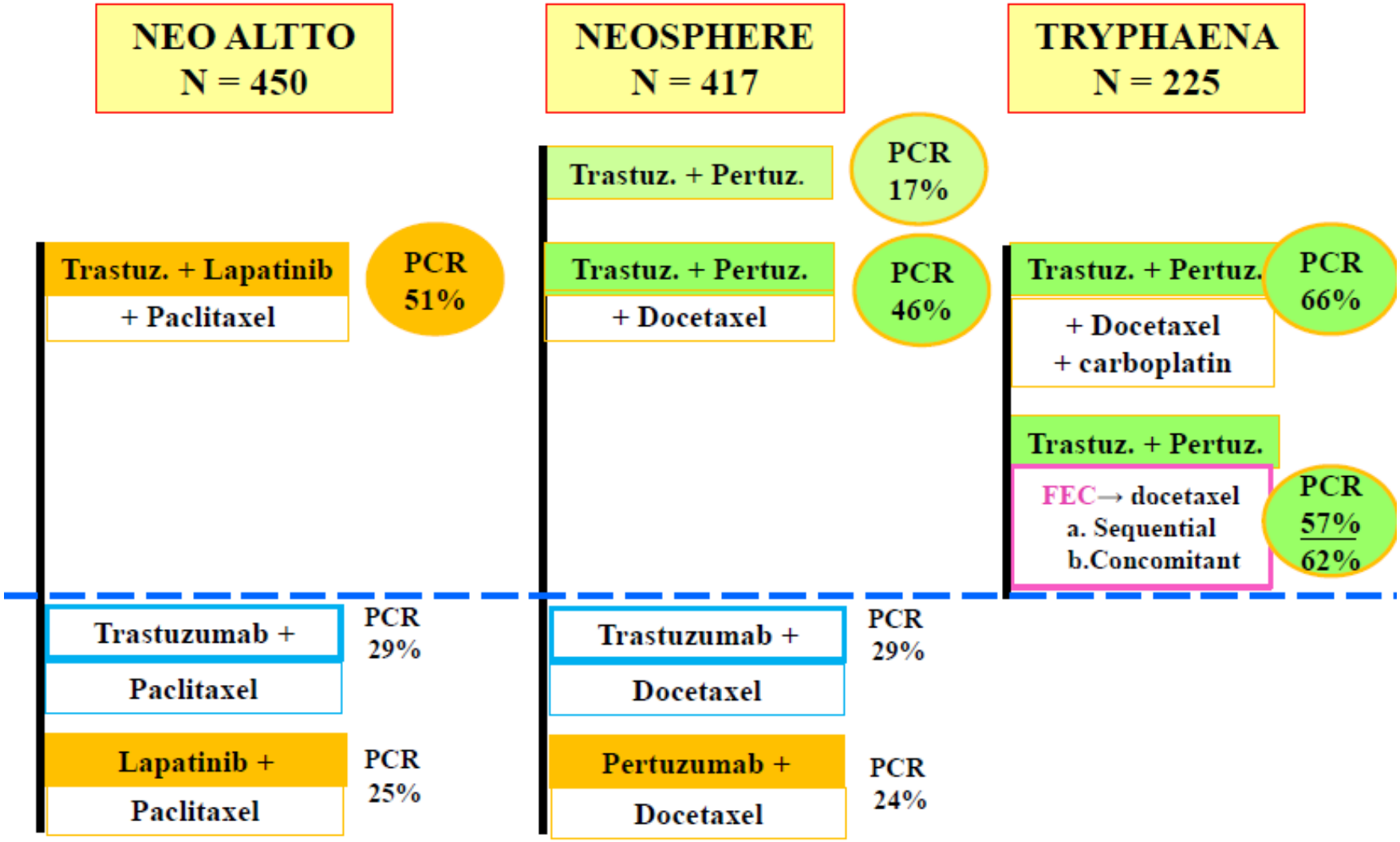
→ Hogere respons rate

Adjuvant

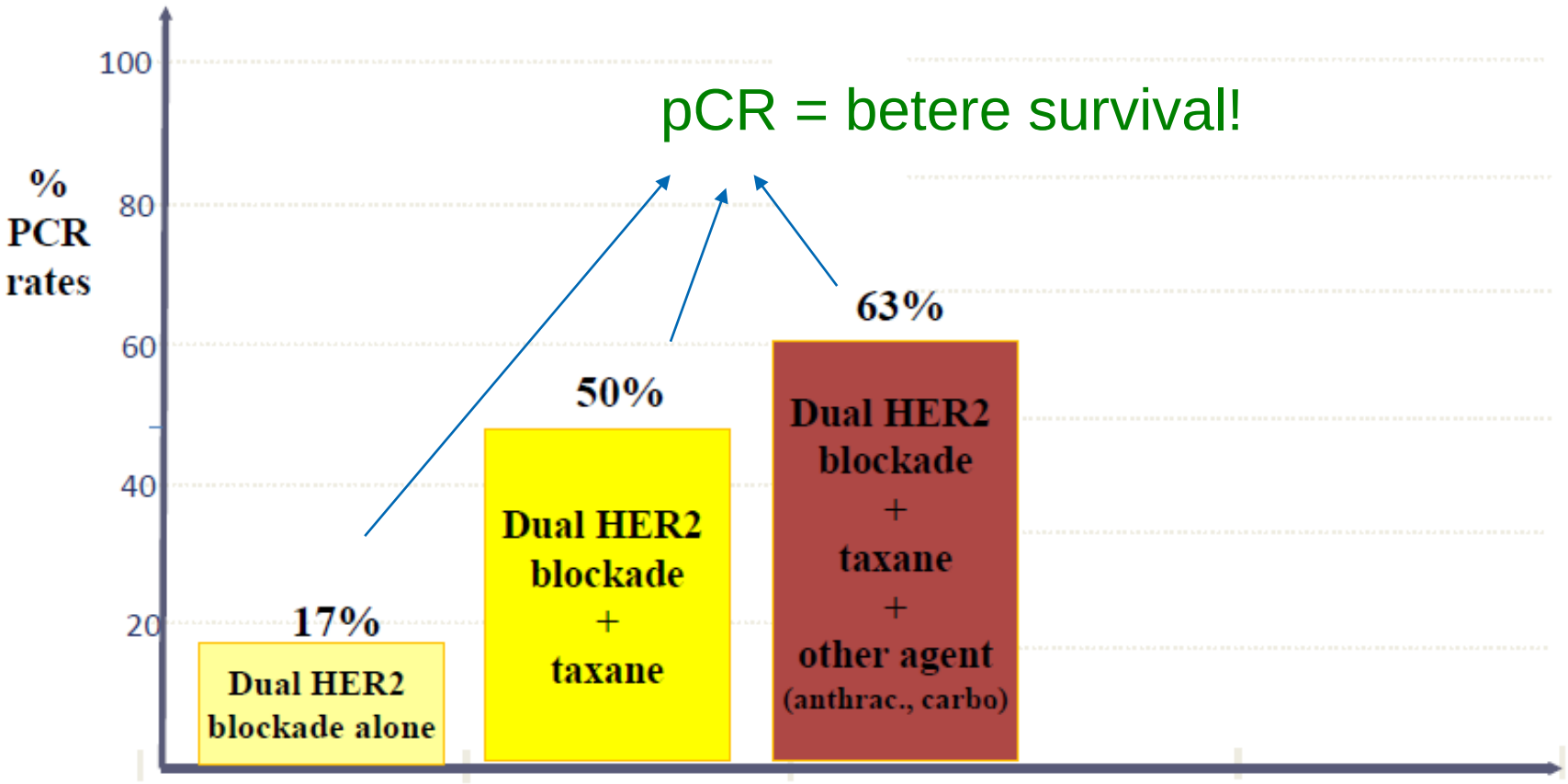
Neo-adjuvant



Lessons learned from neoadjuvant trials investigating dual HER2 blockade



Results obtained with dual HER2 blockade alone or with chemotherapy



Based on NeoSphere, NeoAltto, Tryphaena

POST San Antonio meeting
februari 2019

Praktisch

- Op heden MNP voor pertuzumab ADJUVANT bij N+ (maar we willen natuurlijk liever neo-adjuvant behandelen)
- Binnen enkele maanden : terugbetaling pertuzumab neo-adjuvant en adjuvant bij N+

Chemo-immunotherapie (conjugates)

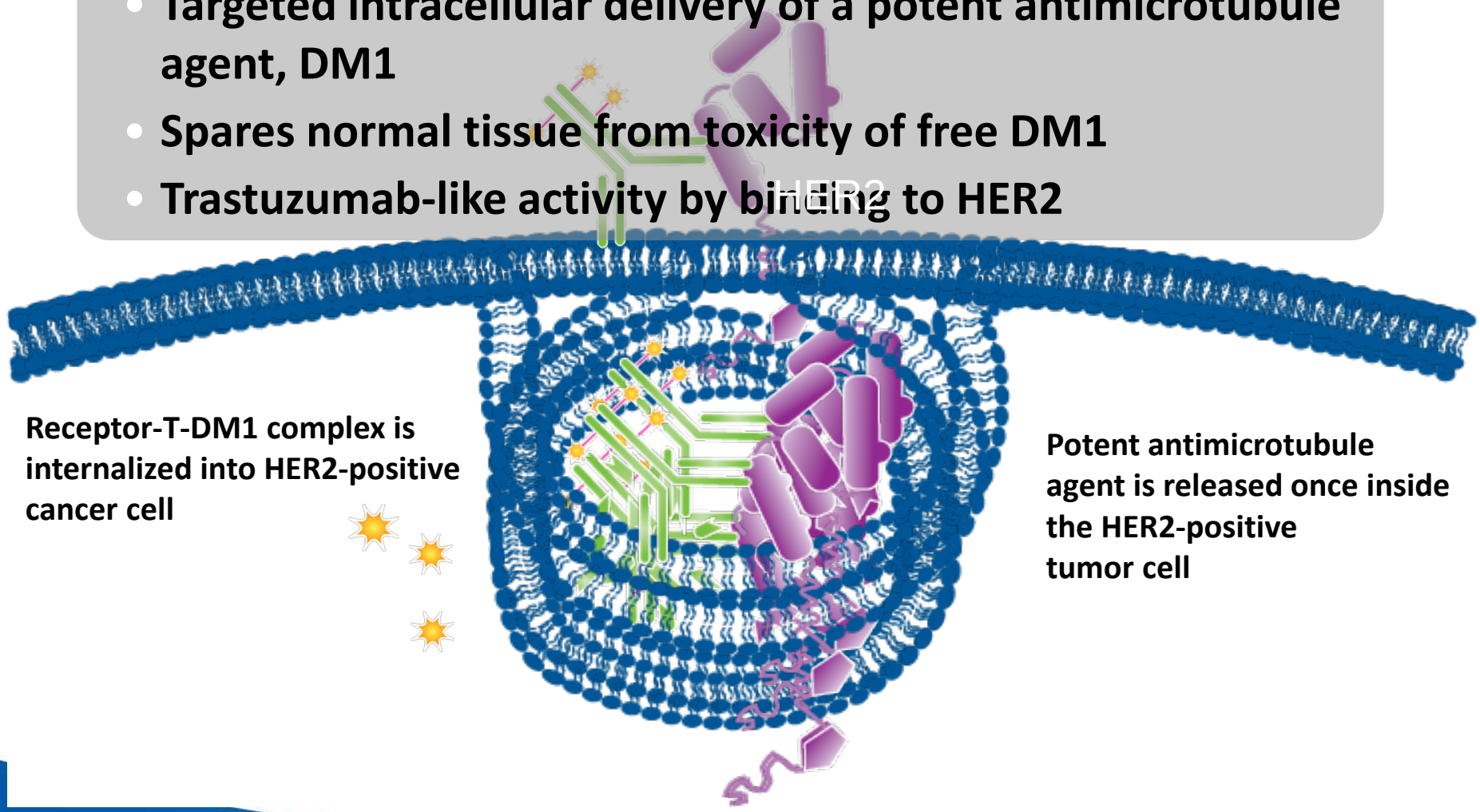
TDM-1 (Kadcyla)

Combinatie van Herceptin met chemotherapie in dezelfde molecule (chemoconjugaat)

→beste van de 2 werelden

T-DM1 selectively delivers DM1 to HER2-positive tumor cells

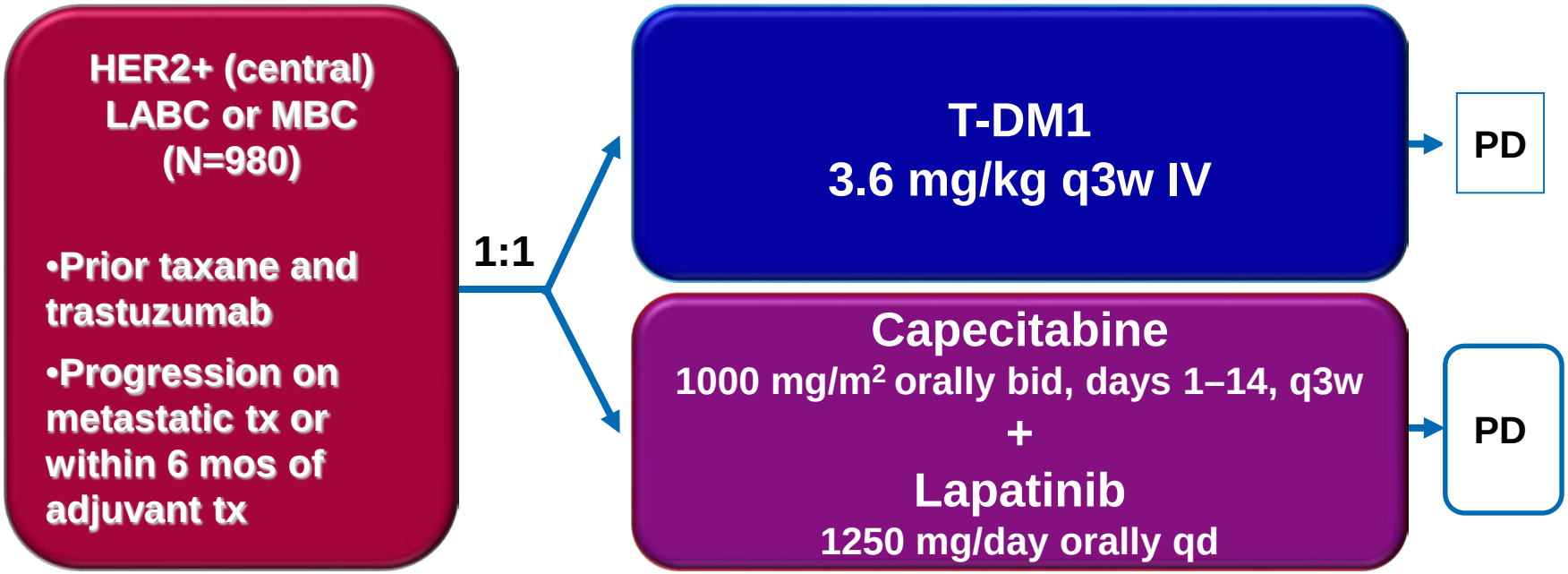
- Targeted intracellular delivery of a potent antimicrotubule agent, DM1
- Spares normal tissue from toxicity of free DM1
- Trastuzumab-like activity by binding to HER2



Receptor-T-DM1 complex is internalized into HER2-positive cancer cell

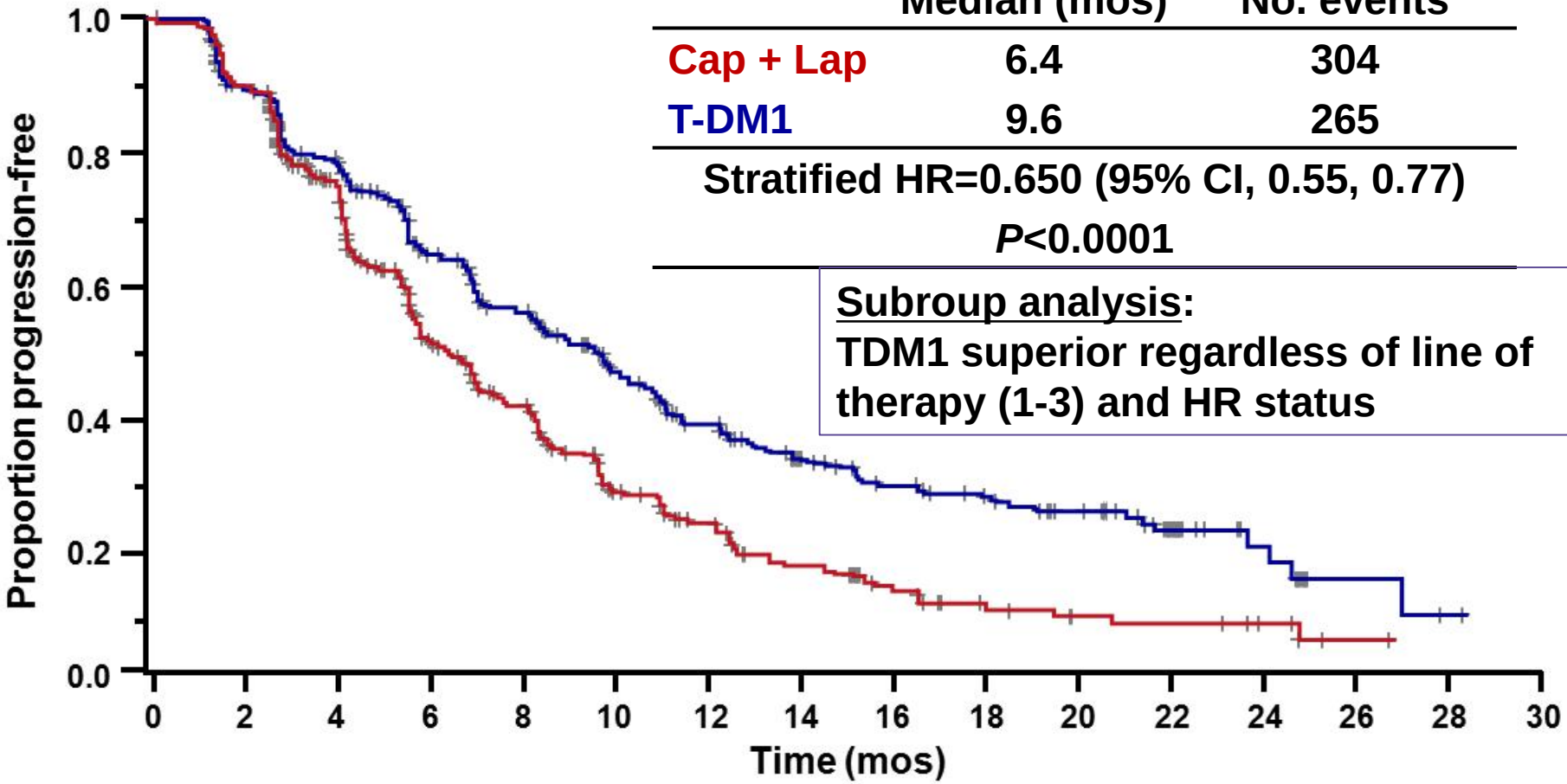
Potent antimicrotubule agent is released once inside the HER2-positive tumor cell

EMILIA Study Design



Blackwell et al, ASCO 2011

Progression-Free Survival



	Median (mos)	No. events
Cap + Lap	6.4	304
T-DM1	9.6	265

Stratified HR=0.650 (95% CI, 0.55, 0.77)

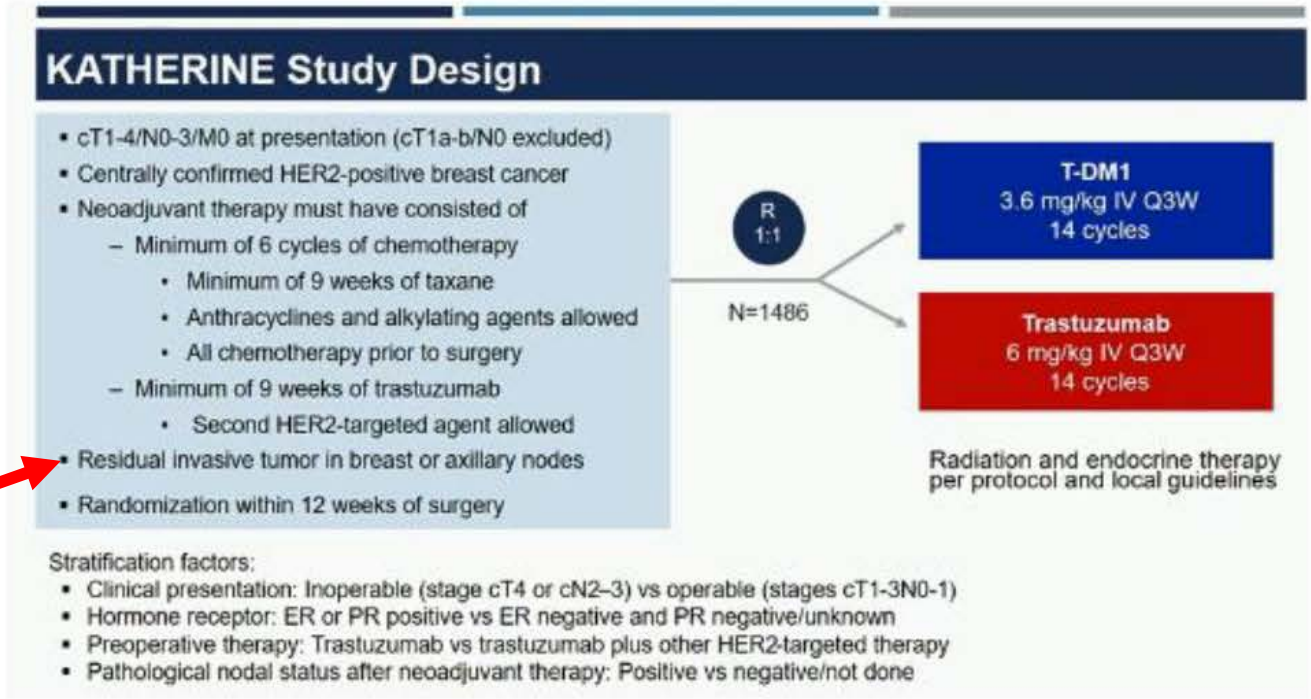
***P*<0.0001**

<u>Subroup analysis</u>:
TDM1 superior regardless of line of therapy (1-3) and HR status

TDM-1: Gunstig tolerantie profiel!

SAN ANTONIO Breast cancer dec 2018:

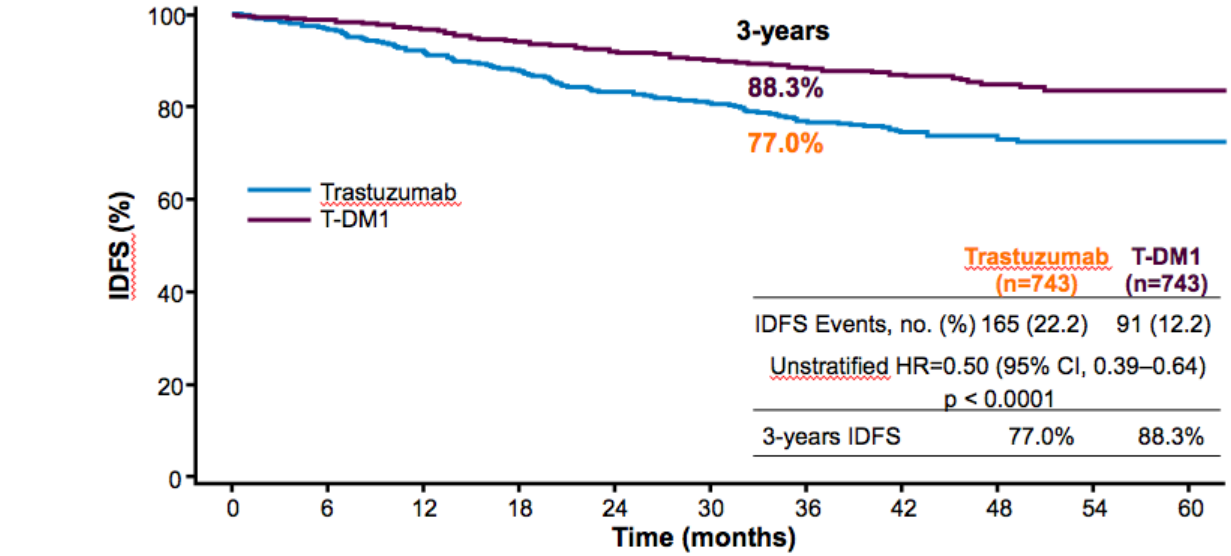
KATHERINE Study Design



KATHERINE study:
adjuvant TDM-1 (Kadcyla)

(SAN ANTONIO Breast cancer dec 2018)

Results: invasive disease-free survival



No. at Risk

Trastuzumab	743	676	635	594	555	501	342	220	119	38	4
T-DM1	743	707	681	658	633	561	409	255	142	44	4

Besluit : Adjuvant Kadcyla

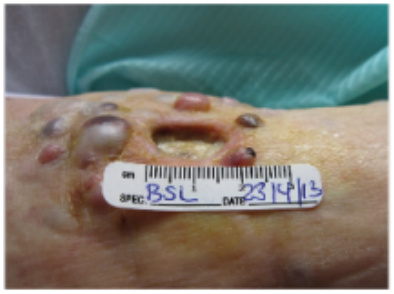
- Adjuvante behandeling met Kadcyla heeft een statistisch significant en klinisch relevant voordeel tov adjuvant trastuzumab (**na 3j 88,3% vd pten ziektevrij tov 77%)**
- Voordeel van Kadcyla werd gezien bij **alle subgroepen**, ongeacht HR status, uitgebreidheid van residuele ziekte en of er neo-adjuvant enkel trastuzumab of ook bijkomende anti-HER2 therapie toegediend werd
- Aanvaardbare toxiciteit
- OS data nog niet matuur

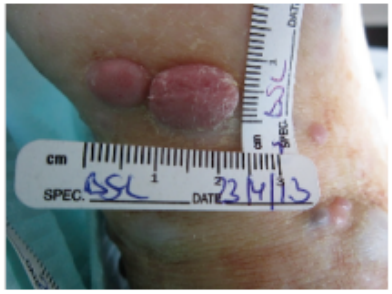
→ Sterk argument **PRO neo-adjuvante** therapie bij **HER2+ mammacarcinoom**! Belangrijke therapeutsche consequenties!

Praktisch

- EMA approval wordt verwacht eind 2019, dus terugbetaling in België eind 2020
- Firma werkt aan stalenprogramma, maar op dit moment nog niet ter beschikking

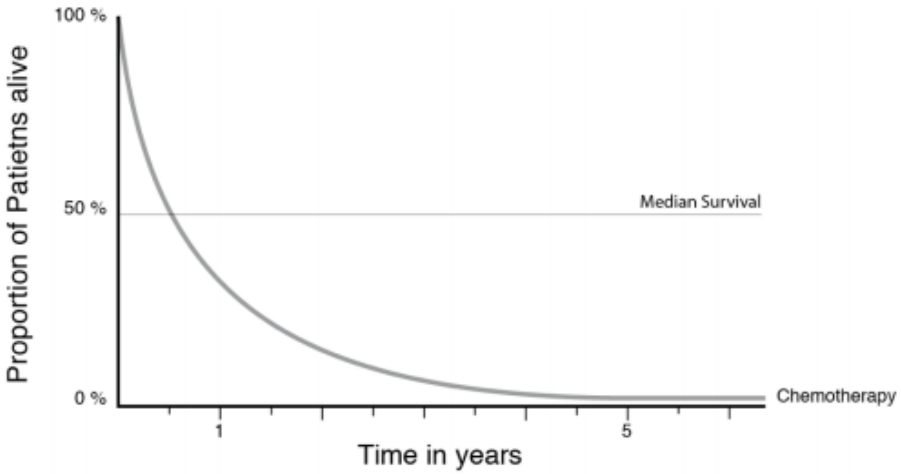
Melanoma : a perfect model for research





Easy to obtain a tumour biopsy

Good candidate for deriving cell lines



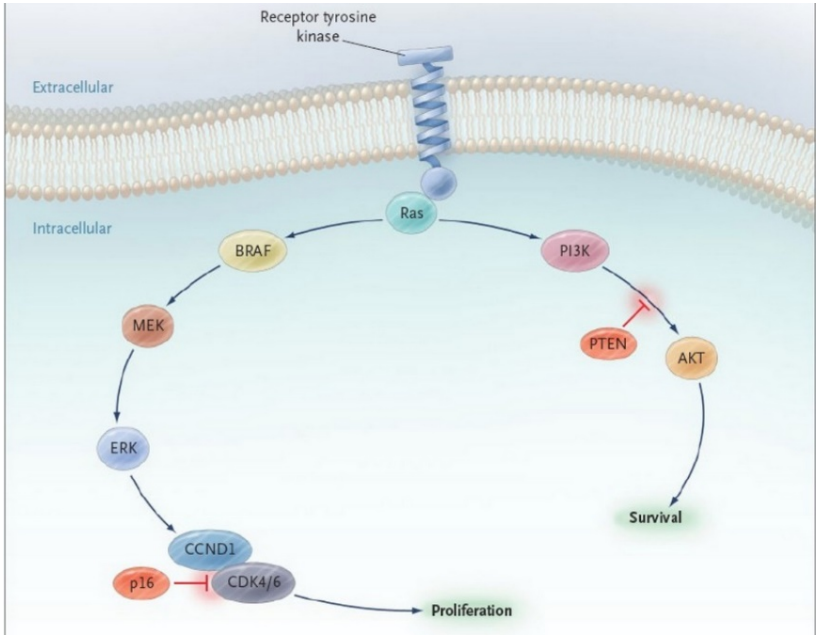
No effective treatment

Two great advances

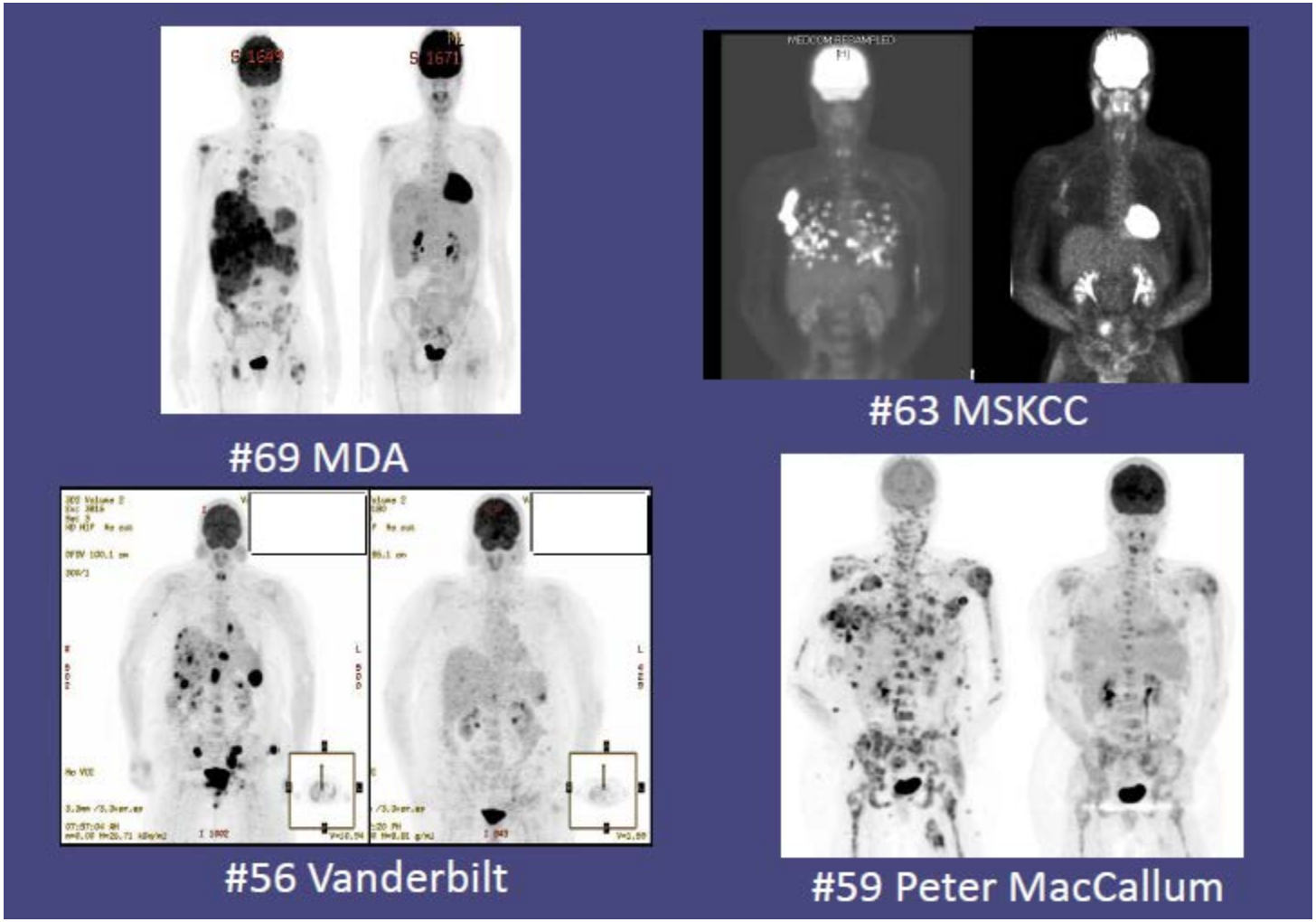
Targeted therapies
Immunotherapy

Metastatic Melanoma and Mutant B-Raf

- B-Raf kinase mutations occur in ≈ 60% of melanoma cases:
  - Most are V600E point mutations (> 90%).



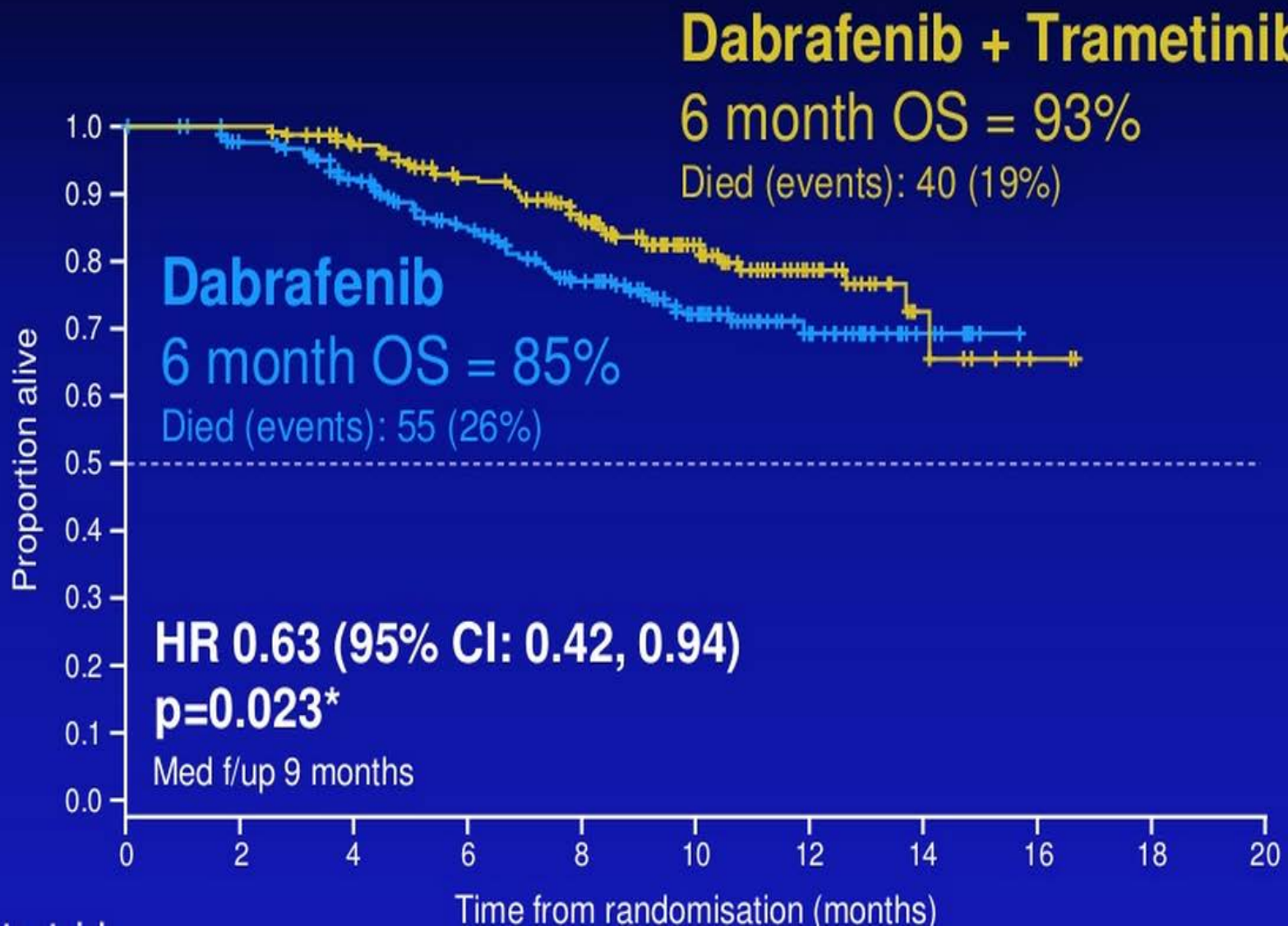
PET Scans at Baseline and Day 15 after PLX4032 (VEMURAFENIB)



ORR = 48%

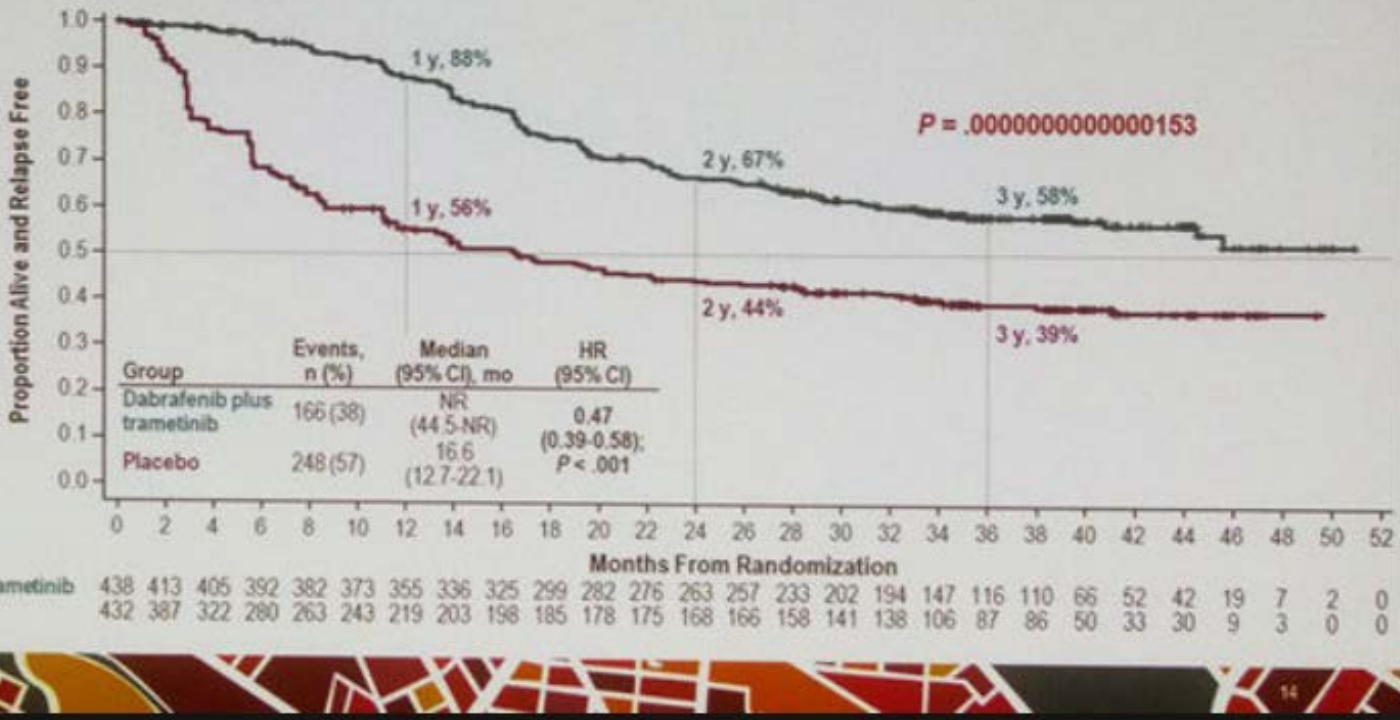
COMBI-d: Overall Survival

Data cut August 2013



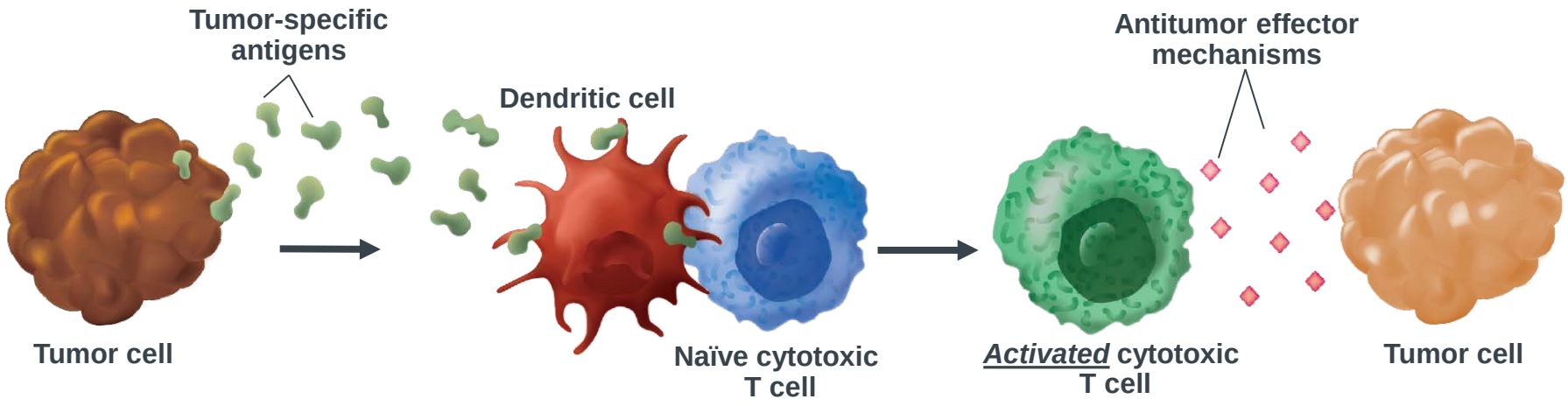
RELAPSE-FREE SURVIVAL (PRIMARY ENDPOINT)

MADRID 2017 ESMO congress



Antitumor Immune Response door “manipulatie” van EIGEN afweer

T-cell–mediated immune response[1,2]



- The body’s immune response can detect and destroy tumor cells through activated T cells and other mechanisms[1]
- Tumor cells express multiple antigens that are not expressed in normal tissue[2]

NSCLC = non–small cell lung cancer.
Image adapted from Chen DS et al. *Immunity*. 2013;39(1):1–10. Reprinted with permission from Elsevier.

1. May KF Jr et al. In: Prendergast GC et al. *Cancer Immunotherapy*. 2nd ed. Philadelphia, PA: Elsevier; 2013:101–113.
2. Chen DS et al. *Immunity*. 2013;39(1):1–10.

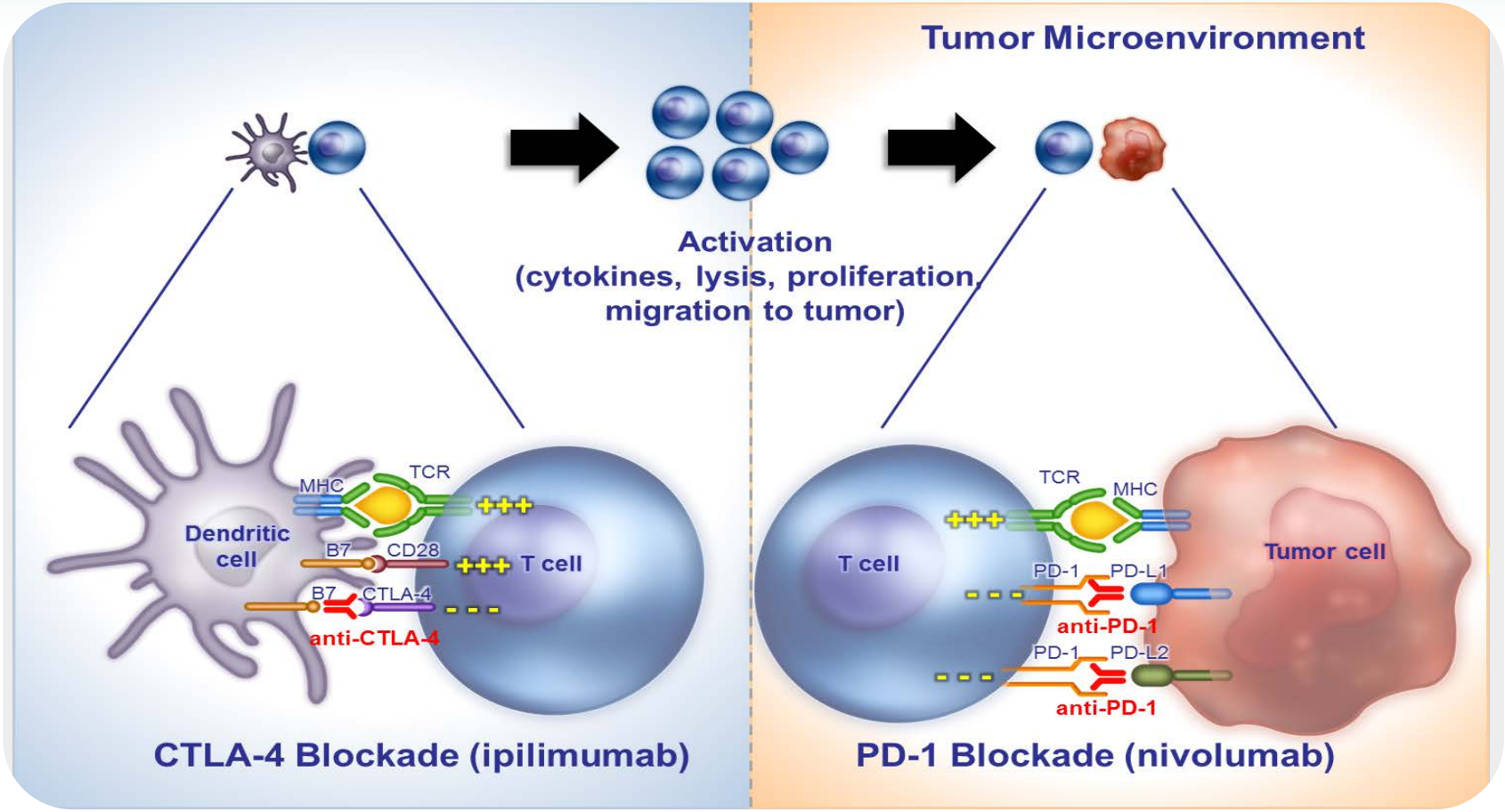
Immune System Inhibitory Pathways

- autoregulatie mechanisme om immuunrespons te stoppen wanneer “vijand” overwonnen is
- Zoniet blootstelling aan ernstige auto-immuun gerelateerde neveneffecten
- Voorbeeld: griep overwonnen: afweersysteem mag gaan rusten
- Is handig bij griep, minder bij tumoren…

→ Bedoeling is autoregulatie te blokkeren en afweersyteem (tegen de tumor) aan te houden

“INHIBIT the INHIBITOR”

CTLA-4 and PD-L1: Distinct Immune Checkpoint Pathways[1]



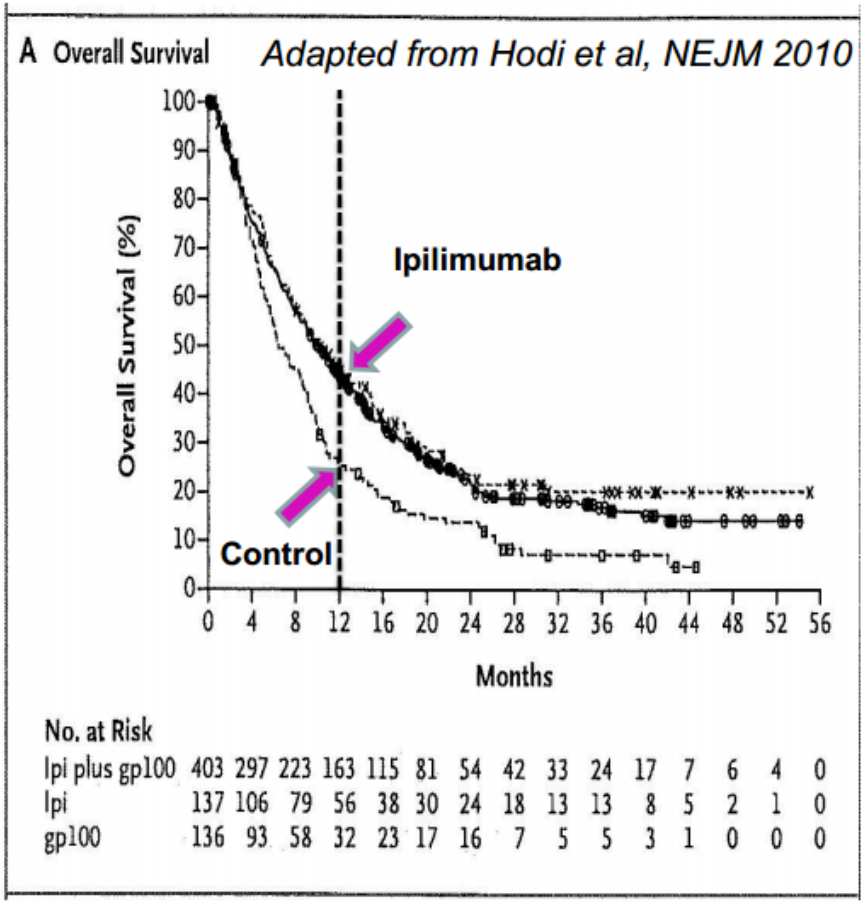
- Data suggest certain combinations may overcome the limitations of monotherapy[2]
  - For example, anti-CTLA-4 appears to drive T cells into tumors and this may, in turn, induce PD-L1 expression in the tumor microenvironment

1. Weber J S, Kahler K C, Hauschild A. JCO 2012;2691-2697 2. Sharma P, et al. *Science*. 2015;348:56-61.

Advances in Immunotherapy 2011

Anti-CTLA-4 (ipilimumab) was approved for treating metastatic melanoma based on improved overall survival in a randomized study.

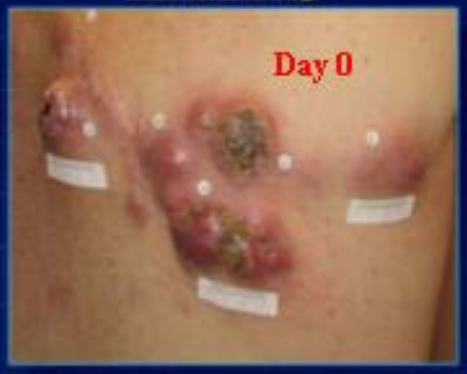
However, the grade 3-4 drug-related toxicity rate approximated the clinical benefit rate



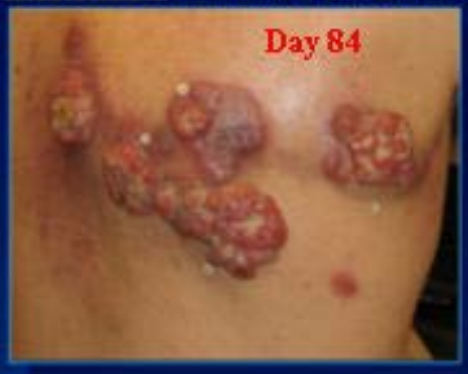
azWest
Zorg op mensenmaat

Ipilimumab: Helping Patients Prevail Over Serious Disease

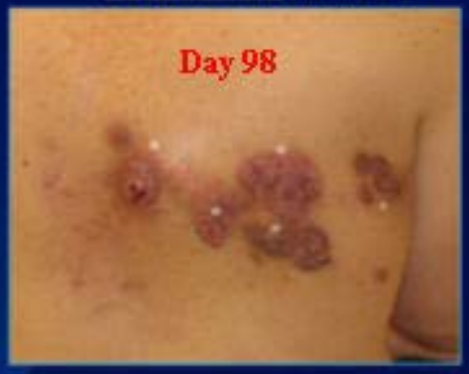
Screening



Week 12: swelling & progression



Week 14: improved



Week 16: continued improvement

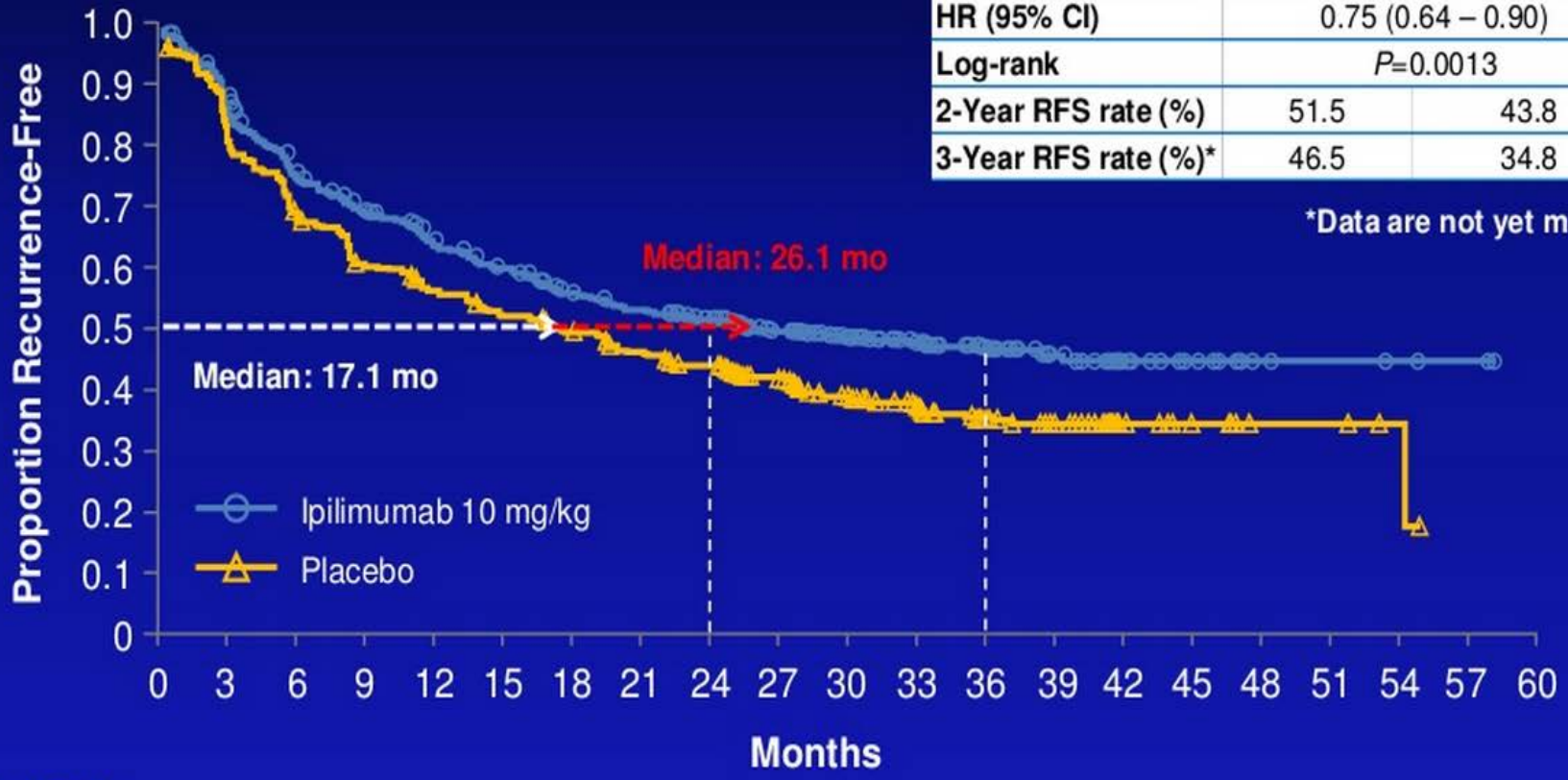
Week 72: complete remission

Week 108: complete remission

Ipilimumab: adjuvant na operatie

	Ipilimumab	Placebo
Events/patients	234/475	294/476
Median RFS, mo	26.1	17.1
HR (95% CI)	0.75 (0.64 – 0.90)	
Log-rank	*P*=0.0013	
2-Year RFS rate (%)	51.5	43.8
3-Year RFS rate (%)*	46.5	34.8

*Data are not yet mature.

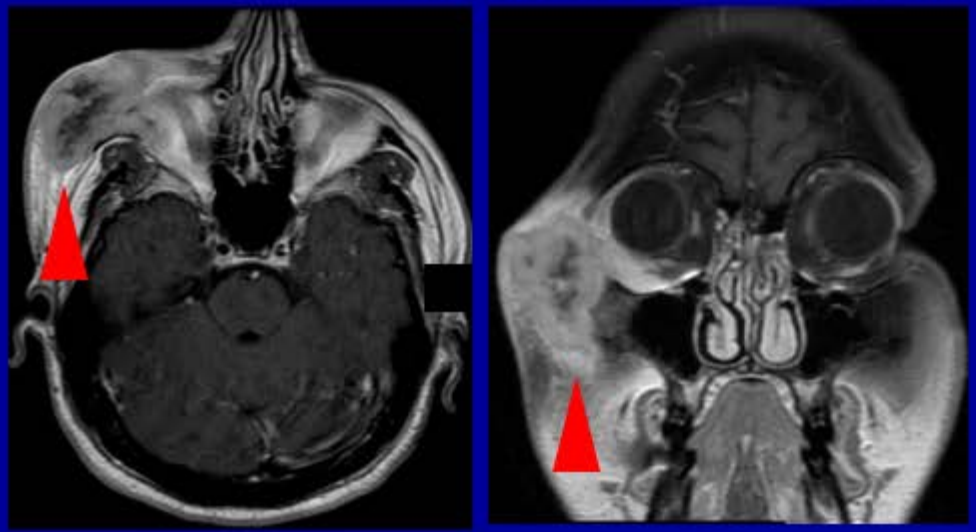


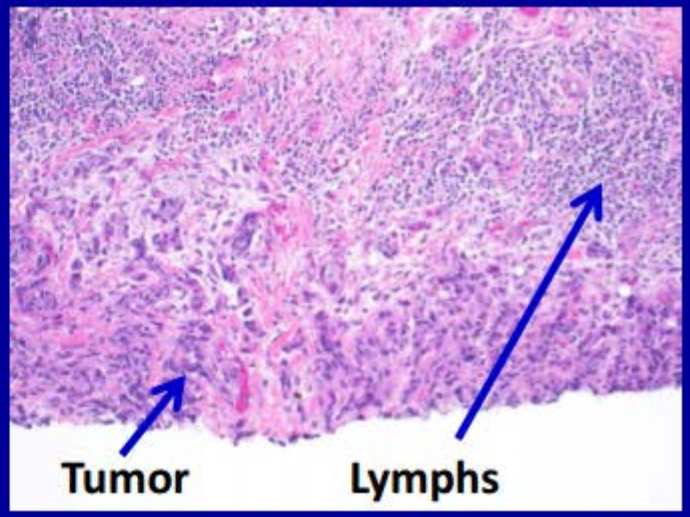
Patients at Risk

Ipilimumab	475	389	338	308	276	258	233	221	205	170	131	98	67	45	23	15	5	4	3	2	0
Placebo	476	376	319	282	260	239	224	207	193	160	119	94	62	42	19	12	4	4	2	0	0

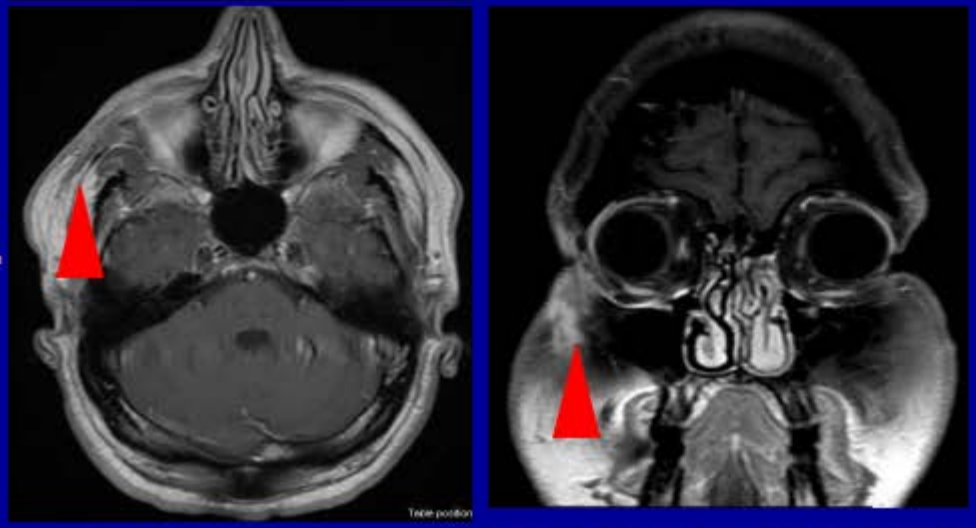
Partial response of locally advanced primary melanoma to anti-PD-1

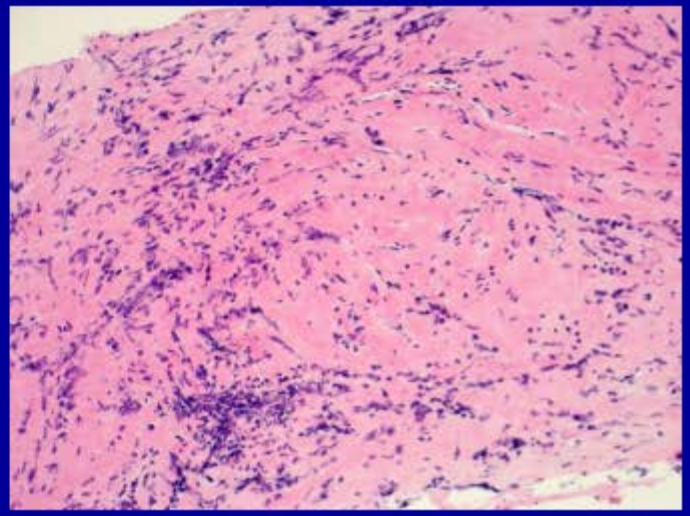
Pre





2 mo.

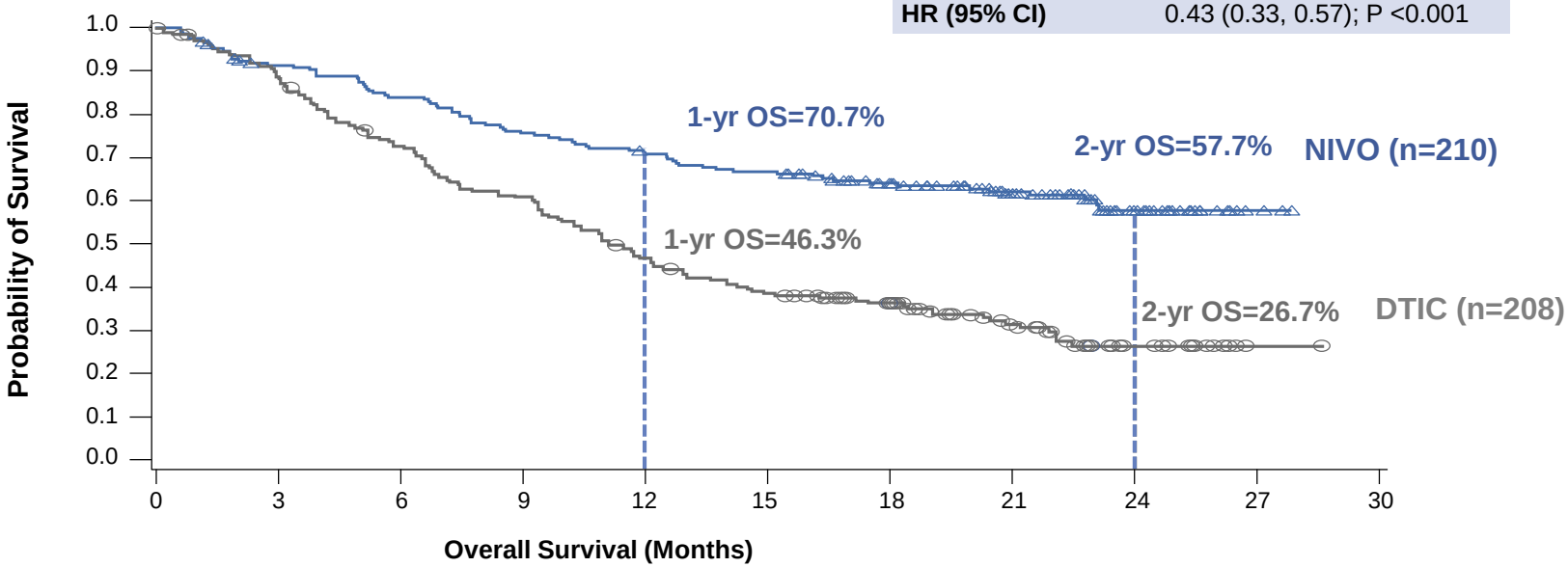




- 35-year-old patient had disease progression after surgery and IL-2.
- Response to anti-PD-1 ongoing at 23 months.

CheckMate 066: Primary Endpoint - Overall Survival
2-year OS update [1,2]

	NIVO	DTIC
Median OS, mo (95% CI)	NR (23.1, NR)	11.2 (9.6, 13.0)
HR (95% CI)	0.43 (0.33, 0.57); P <0.001	



Patients at Risk

Nivolumab	210	186	171	154	143	135	111	81	30	4	0
Dacarbazine	208	179	146	122	92	76	60	38	16	1	0

- Common AEs associated with NIVO included fatigue, pruritus, and nausea.[2] Grade 3–4 treatment-related AEs occurred in 13% of patients in the NIVO arm and 17% of patients in the dacarbazine arm[1]

HR, hazard ratio; NR; not reached.

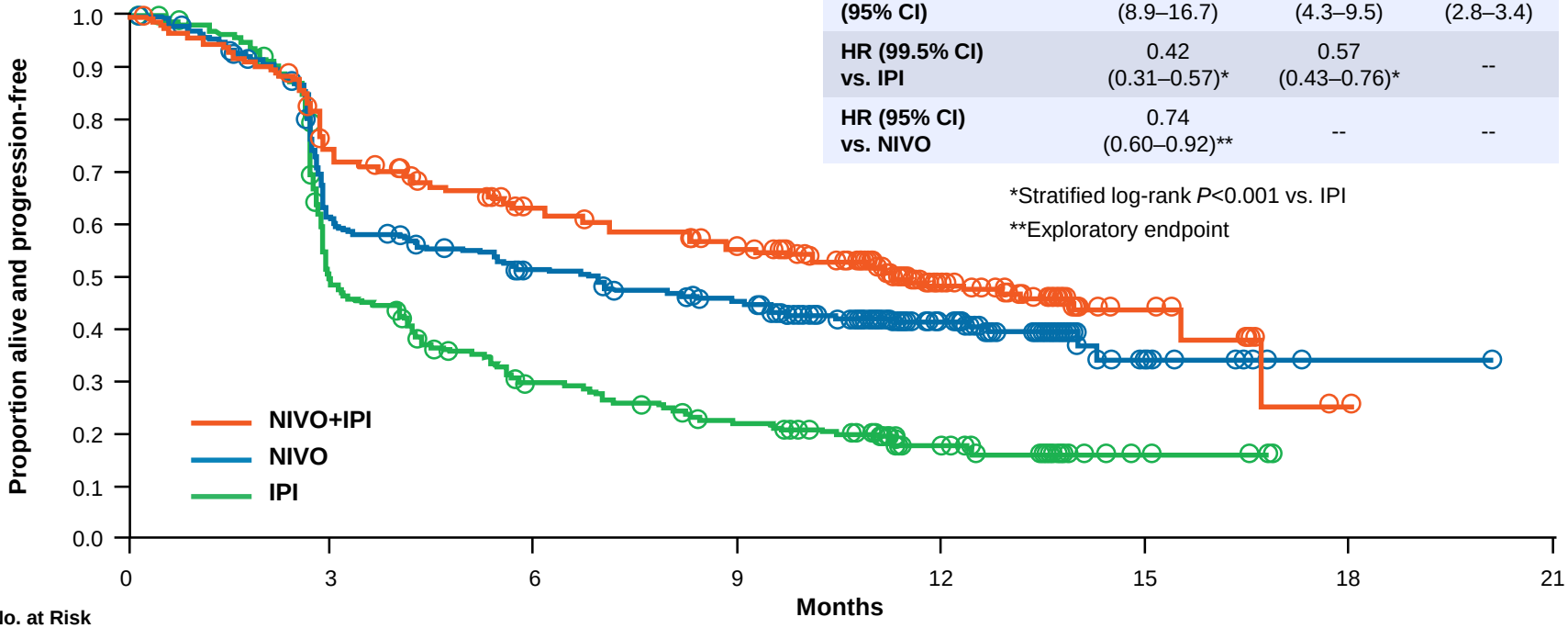
1. Atkinson V et al. Presented at SMR 2015. 2. Robert C, et al. *N Engl J Med.* 2015;372:320-323.

CheckMate 067: Progression-Free Survival (ITT Population) [1,2]

	NIVO+IPI (n=314)	NIVO (n=316)	IPI (n=315)
Median PFS, months (95% CI)	11.5 (8.9–16.7)	6.9 (4.3–9.5)	2.9 (2.8–3.4)
HR (99.5% CI) vs. IPI	0.42 (0.31–0.57)*	0.57 (0.43–0.76)*	--
HR (95% CI) vs. NIVO	0.74 (0.60–0.92)**	--	--

*Stratified log-rank *P*<0.001 vs. IPI

**Exploratory endpoint



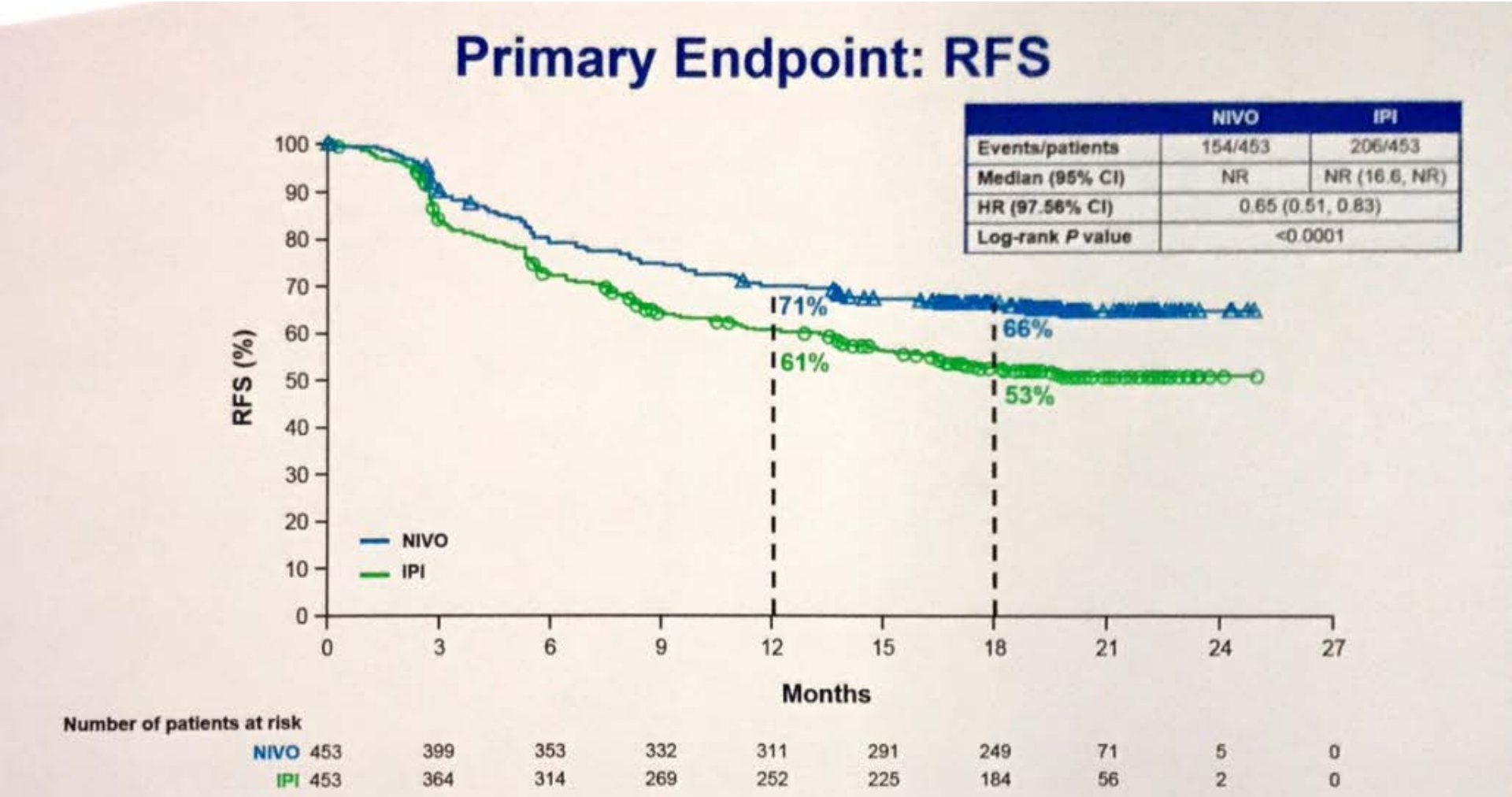
No. at Risk								
NIVO+IPI	314	219	173	151	65	11	1	0
NIVO	316	177	147	124	50	9	1	0
IPI	315	137	77	54	24	4	0	0

1. Larkin J, et al. *N Engl J Med.* 2015;373:23-34. 2. Wolchok JD, et al. Presented at ASCO 2015 abstract LBA1.

ESMO 2017

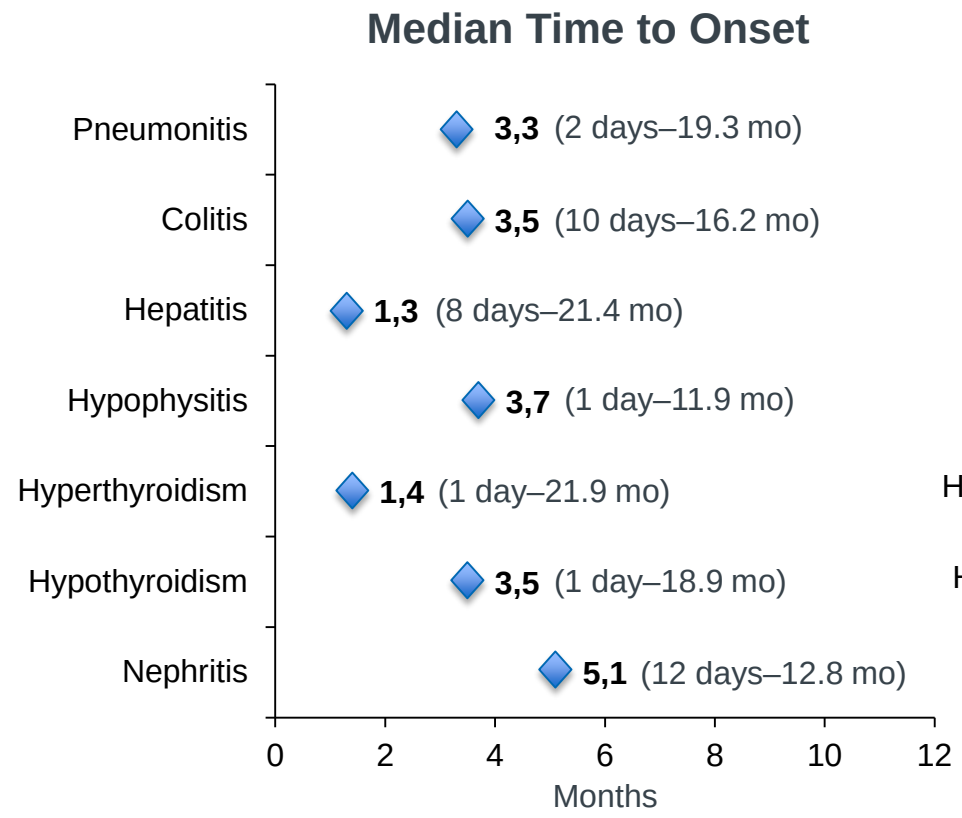
Chekmate 238

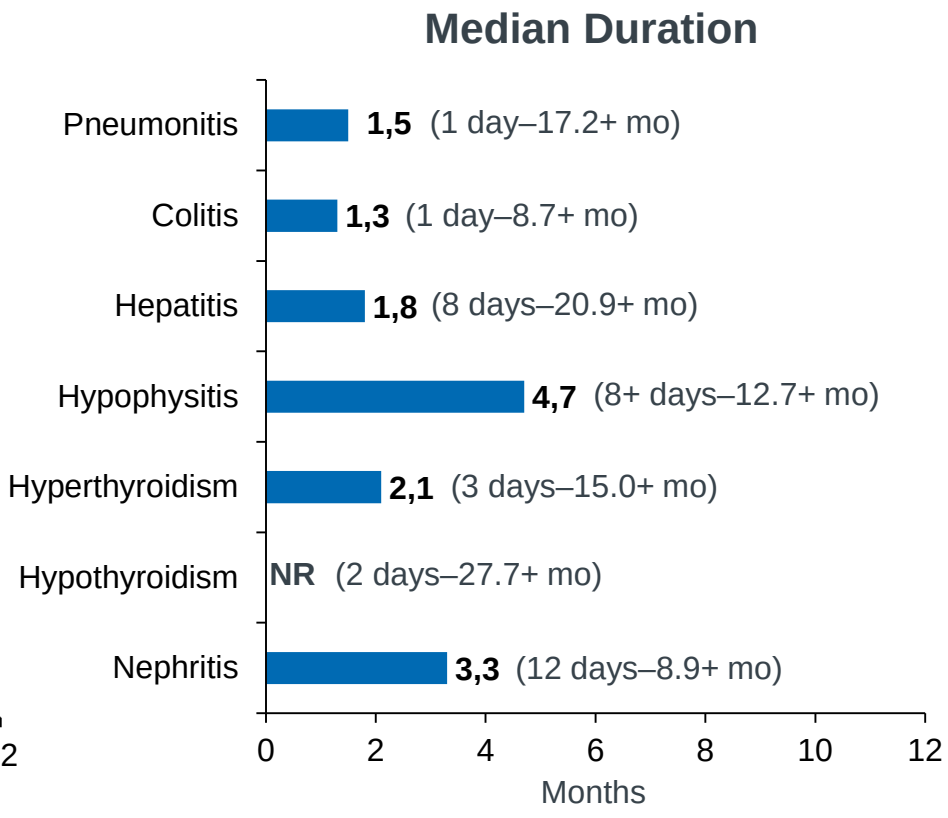
Melanoma: adjuvant opdivo vs ipilumumab



KEYTRUDA™ (pembrolizumab): Immune-mediated Adverse Reactions Median Time to Onset and Median Duration[1]

- Median time to onset and median duration of immune-mediated adverse reactions are presented based on 2799 patients with NSCLC and melanoma treated with KEYTRUDA





mo = months; NR = not reached; NSCLC = non–small cell lung cancer.

1. [Insert local label.]

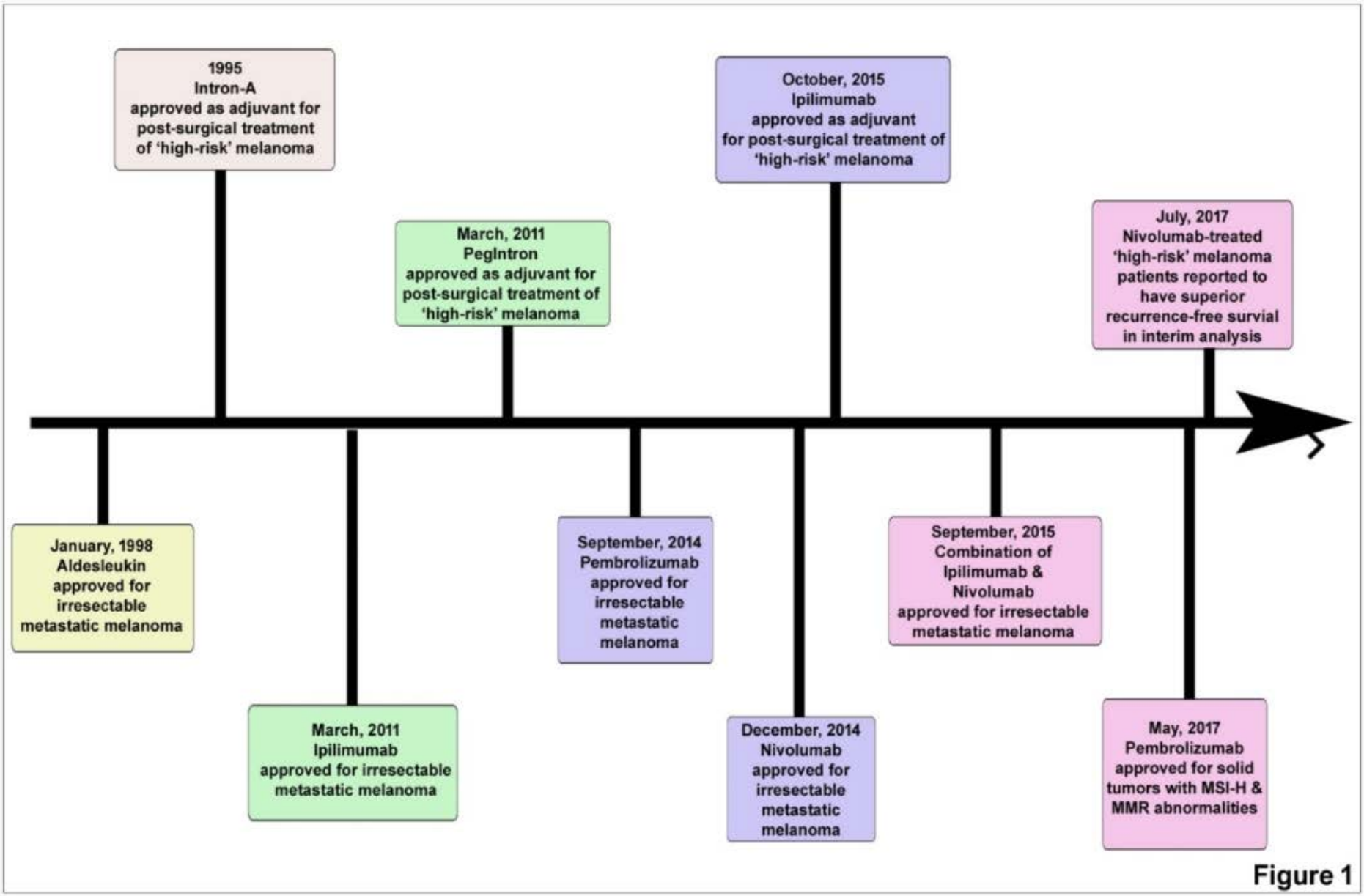
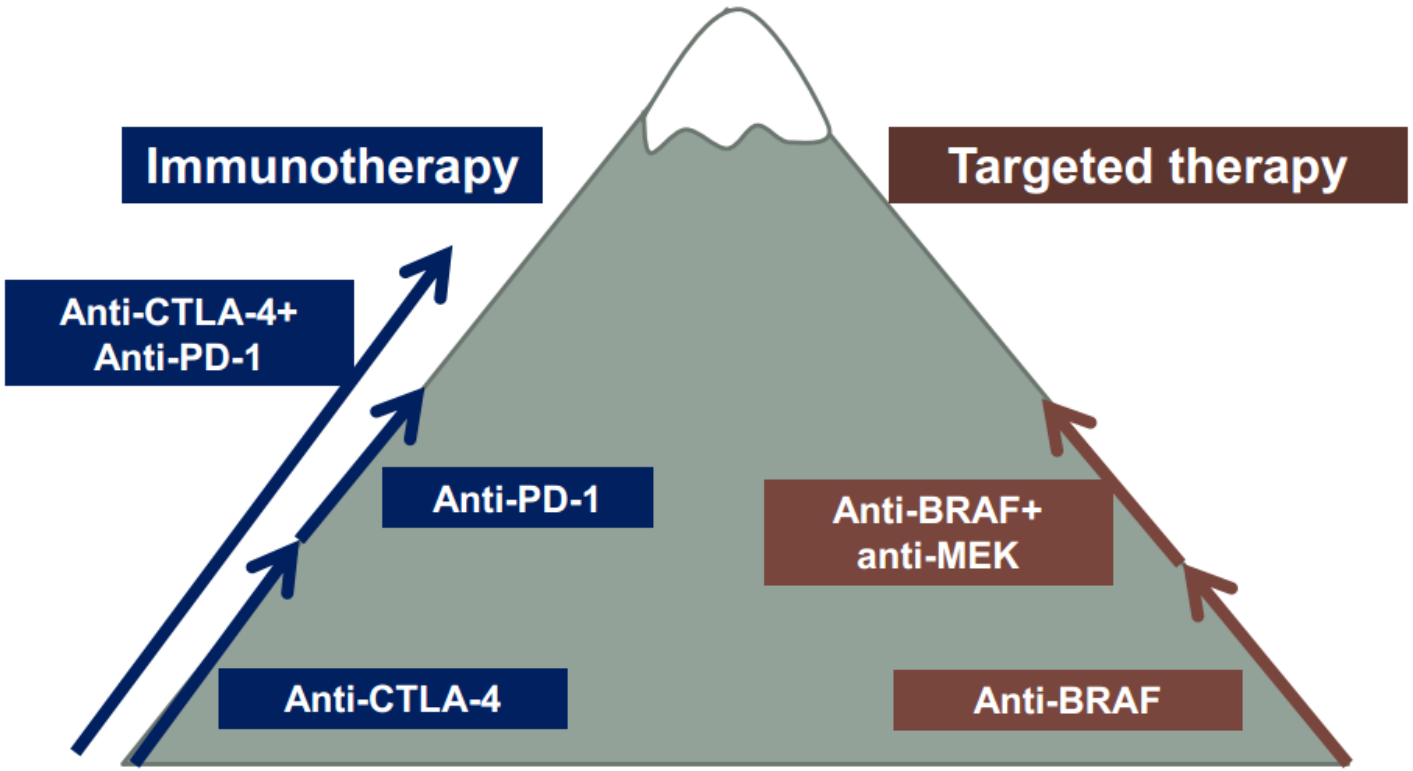


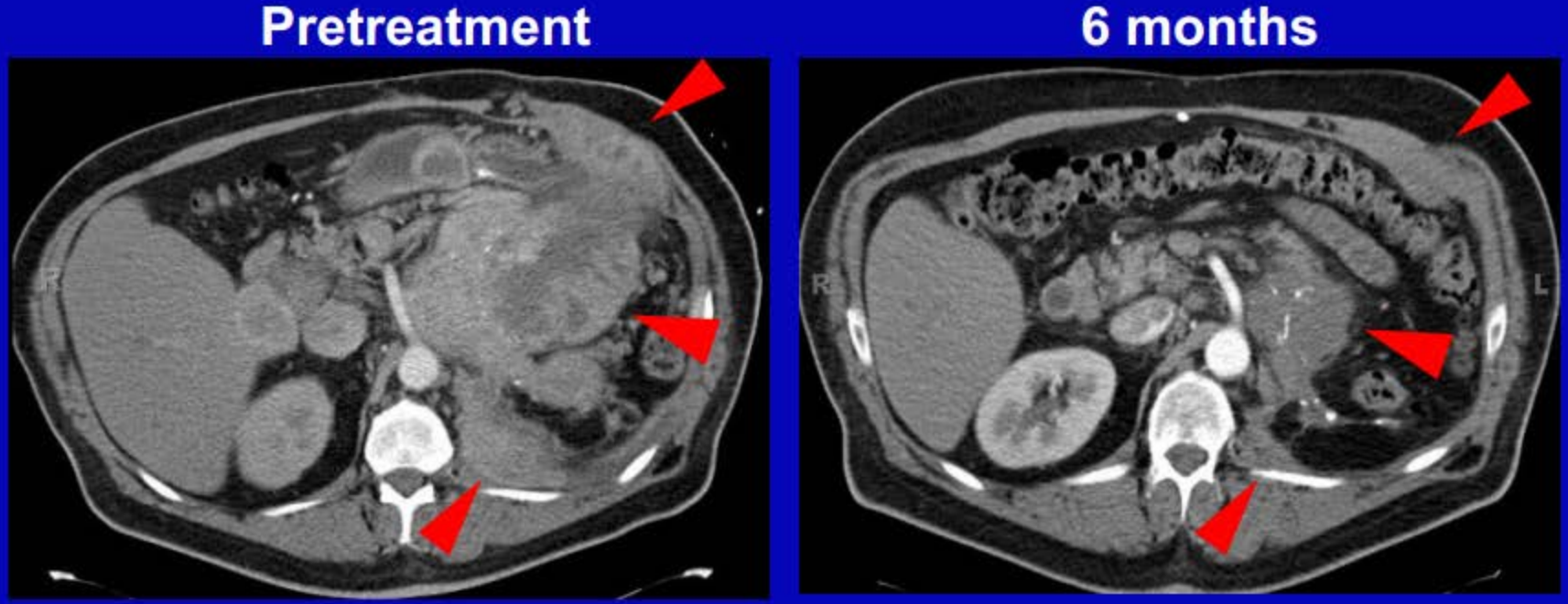
Figure 1.

Milestones in the clinical development of immunotherapy of melanoma

Melanoma


Immunotherapy
Targeted therapy
Anti-CTLA-4+
Anti-PD-1
Anti-PD-1
Anti-BRAF+
anti-MEK
Anti-CTLA-4
Anti-BRAF

Partial regression of metastatic kidney cancer in response to anti-PD-1

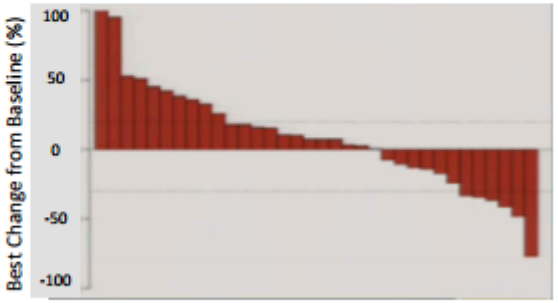


- 57-year-old patient developed progressive disease after receiving sunitinib, temsirolimus, sorafenib, and pazopanib
- Currently in cycle 12 anti-PD-1 therapy (~23 months) with ongoing PR

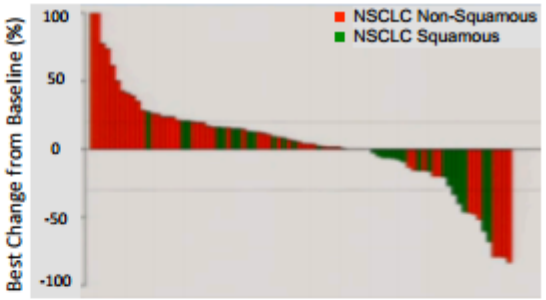
Clinical Activity of Anti-PD-L1 antibody MEDI4736

Waterfall plots

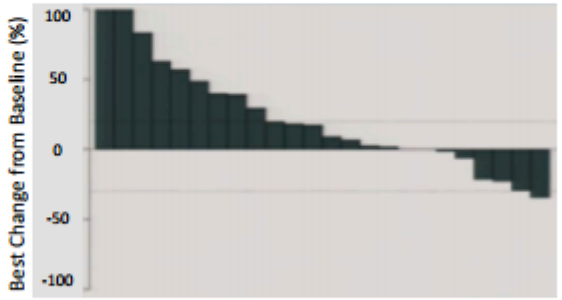
Squamous Cell Carcinoma of Head & Neck



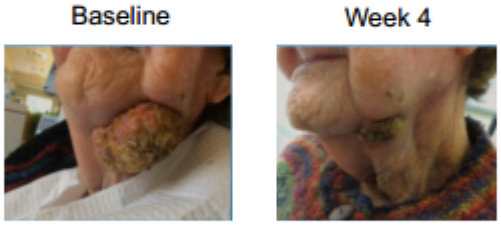
Non-Small Cell Lung Cancer



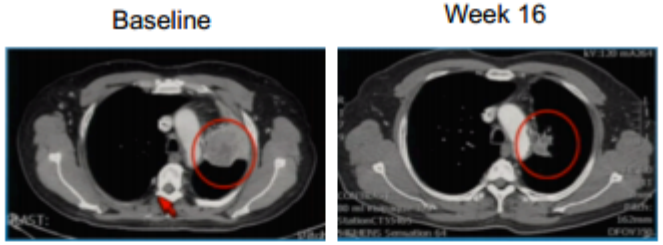
Pancreatic Cancer



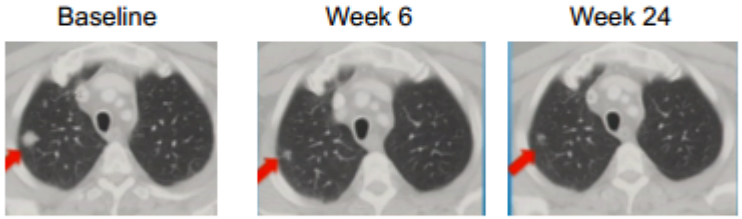
Clinical Examples



96 year old female

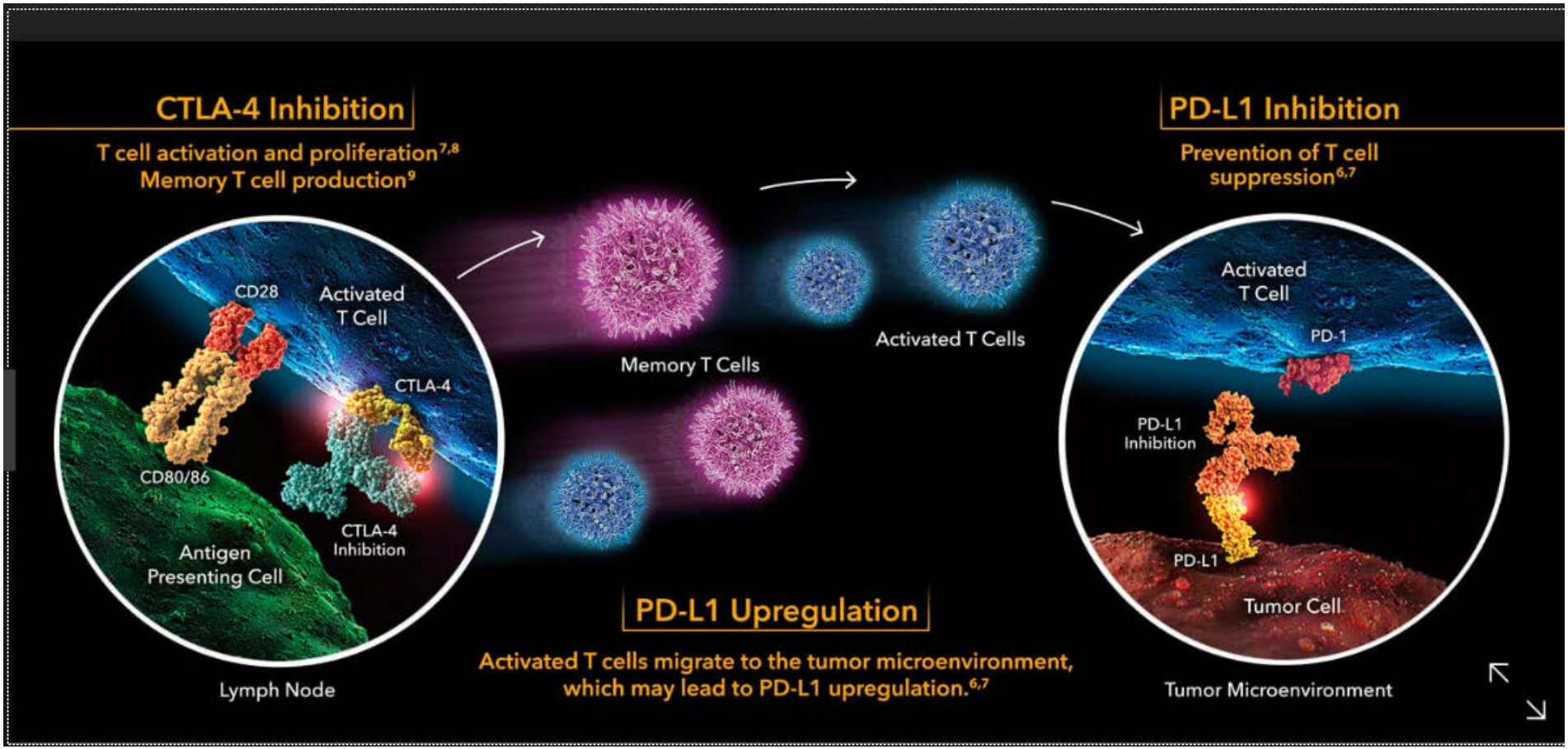


64 year old male



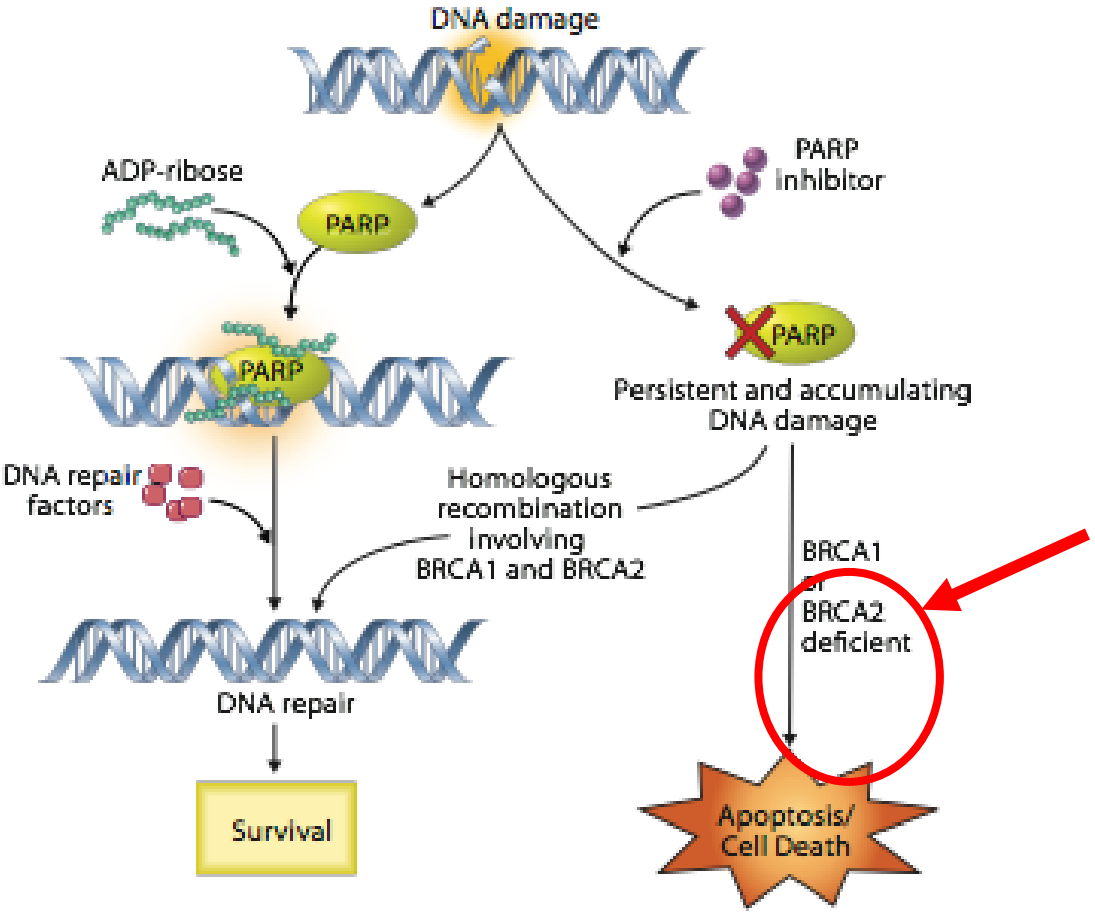
59 year old male

N. Seigel, ASCO 2014

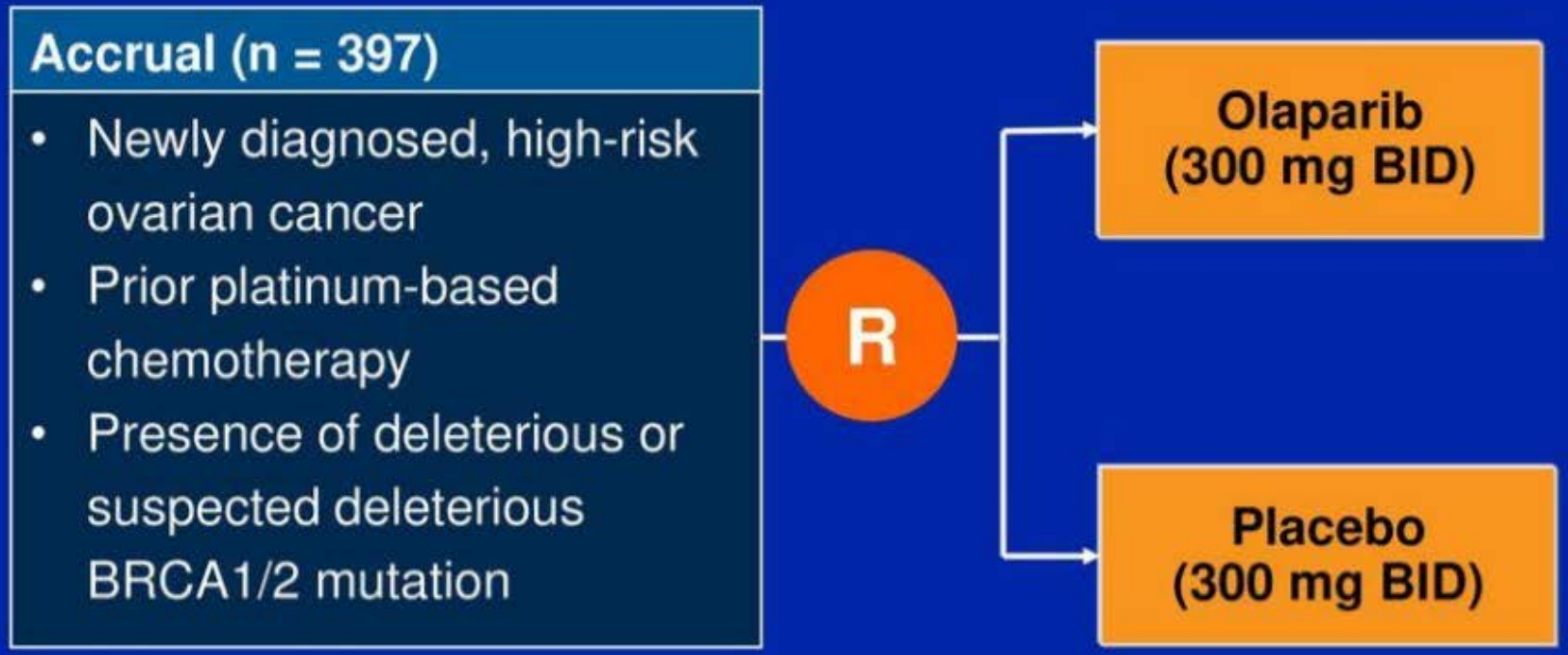


PARP inhibitoren

Role of the PARP in the DNA reparation: actief bij BRCA mutatie

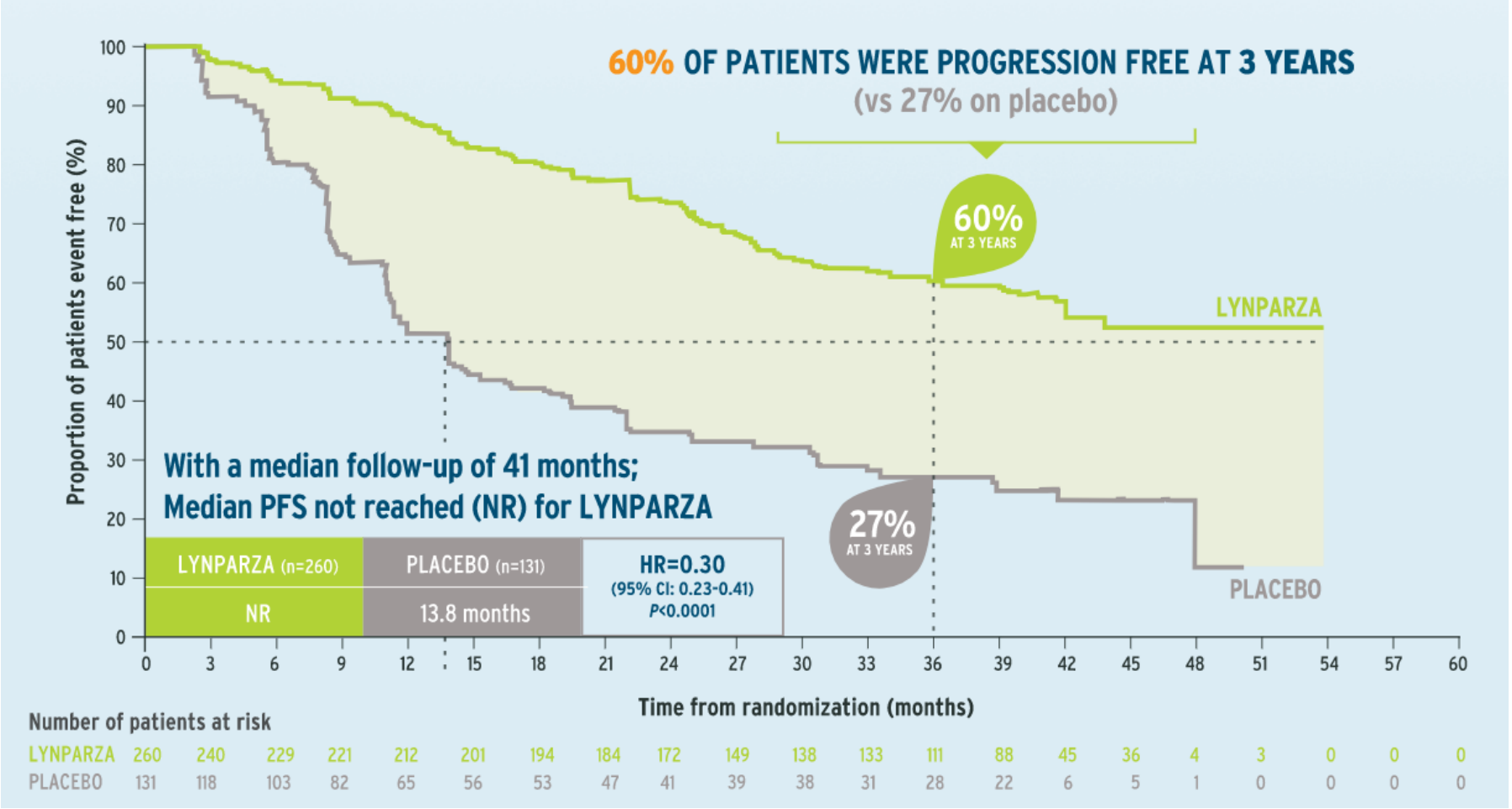


SOLO-1: A Phase III Trial of Olaparib Monotherapy for BRCA-Mutated Ovarian Cancer



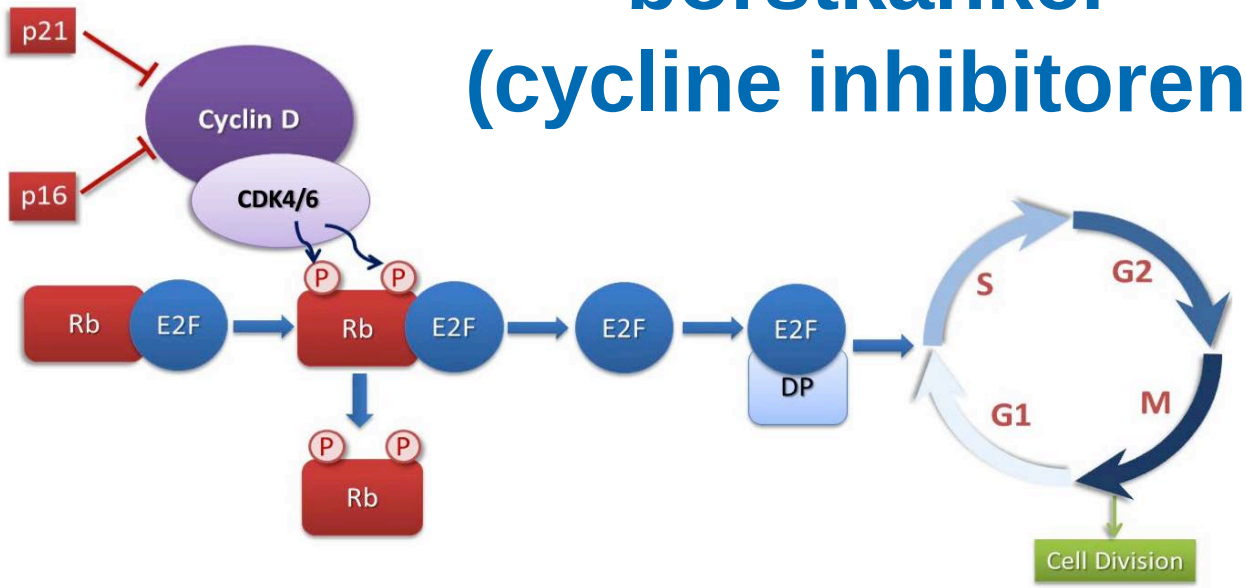
Primary endpoint: PFS

SOLO-1 (adjuvant ovariumca, BRCA+)



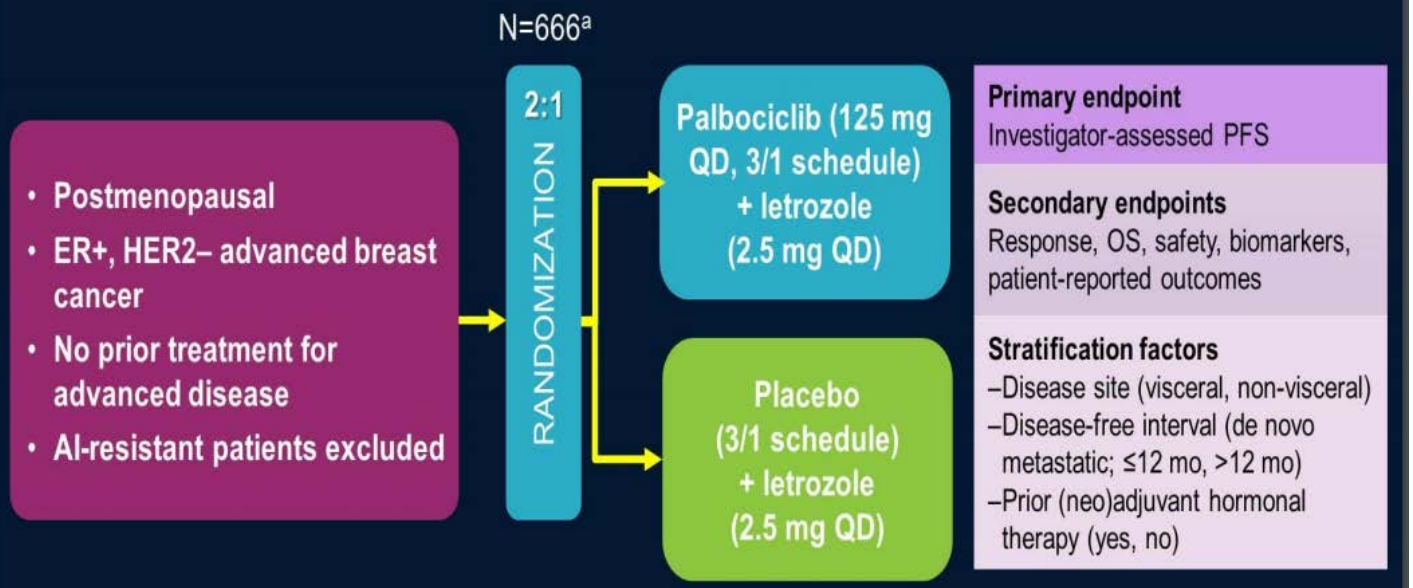
azWest
Zorg op mensenmaat

CDK 4/6 inhibitoren bij borstkanker (cycline inhibitoren)



- Cyclin D1 is expressed at a high level, in many ER positive breast cancers
- Amplification of CDK4 and cyclin D1 reported in 15-25% breast cancer
- Cyclin D1 overexpression occur in over half of all breast cancers
- Amplification of both cyclin D1 and CDK4 is especially high in luminal B (58% and 25%) and HER2 positive subtypes (29% and 14%)
- Endocrine resistance is associated with persistent cyclin D1 expression

PALOMA-2: Study Design (1008)[1]



- Statistical analysis designed to detect an increase in PFS with a true HR of 0.69 (representing a 31% improvement) with 347 events - 90% power with 1-sided α=0.025

  Assumptions: Median PFS of placebo plus letrozole = 9 mos vs. palbociclib plus letrozole = 13 mos
- Blinded independent central review of efficacy endpoints performed as supportive analysis

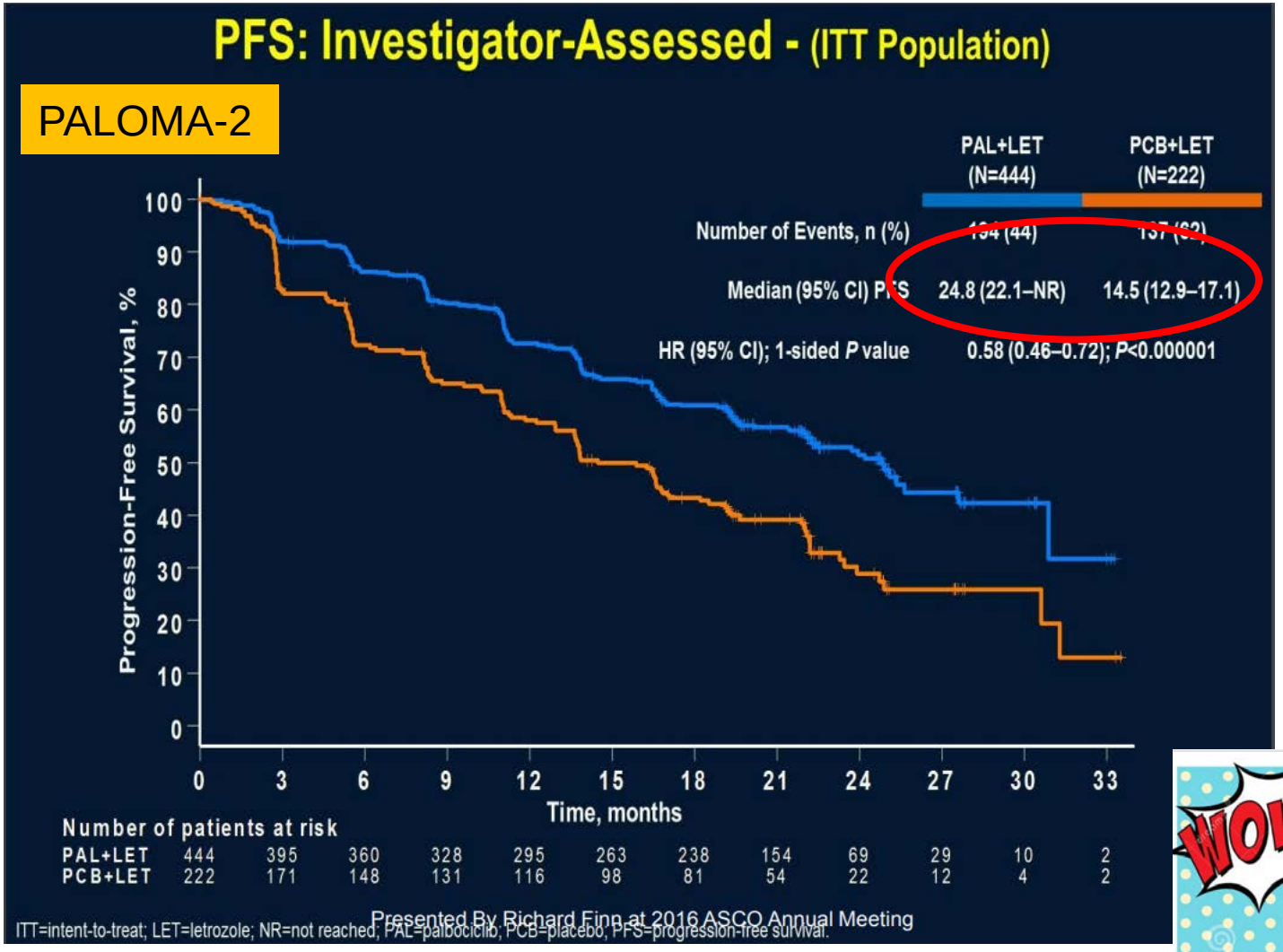
[a]Actual. AI=aromatase inhibitor; HER2=human epidermal growth factor receptor 2; OS=overall survival; PFS=progression-free survival; QD=once daily.

Presented By Richard F, MD at 2016 ASCO Annual Meeting

1.clinicaltrials.gov
NCT01740427

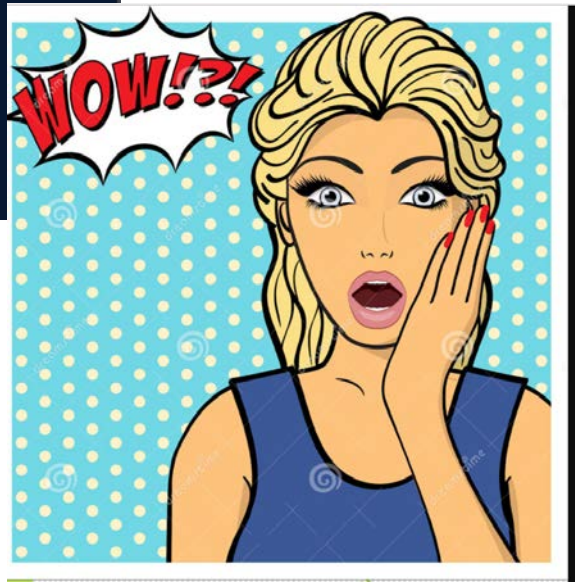
PFS: Investigator-Assessed - (ITT Population)

PALOMA-2

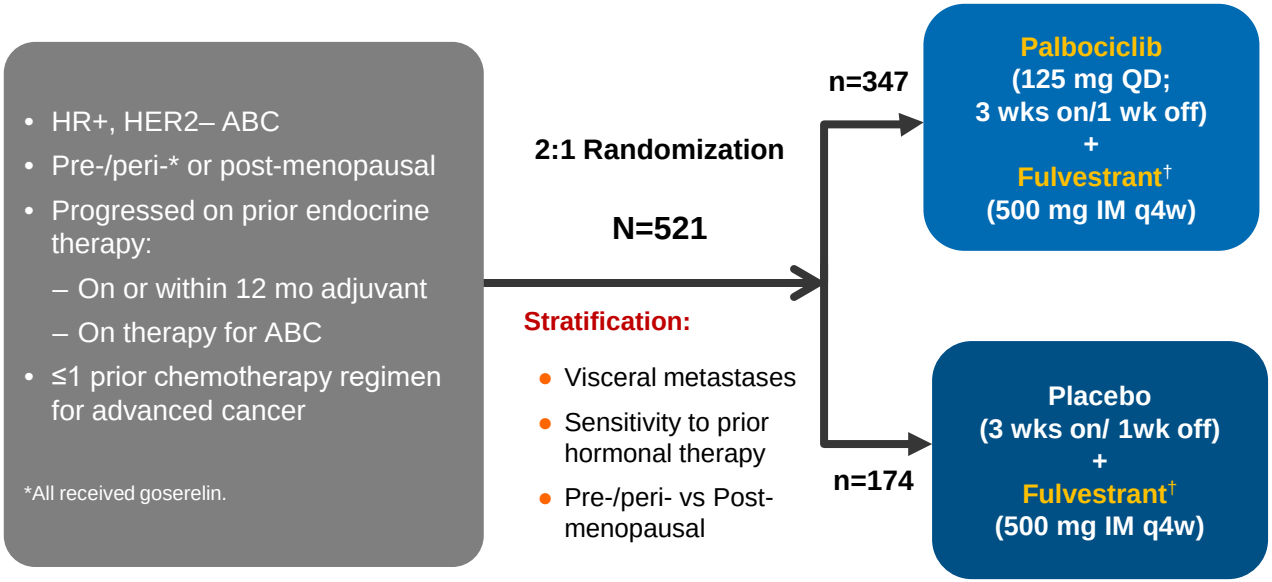


Presented By Richard Finn at 2016 ASCO Annual Meeting

ITT=intent-to-treat; LET=letrozole; NR=not reached; PAL=palbociclib; PCB=placebo; PFS=progression-free survival.



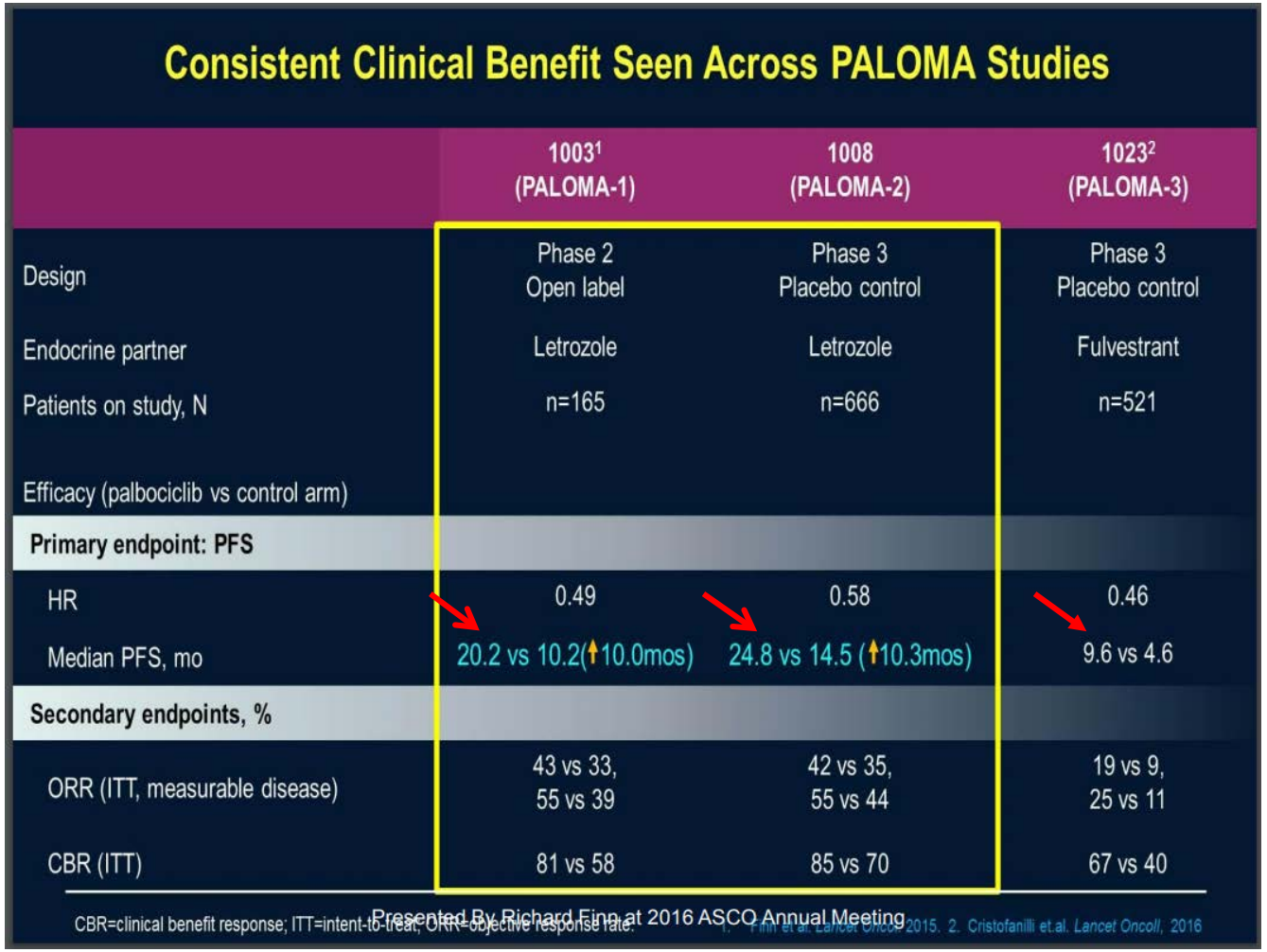
PALOMA-3: Study Design



- ***Post-menopausal patients must have progressed on prior aromatase inhibitor therapy.***

†administered on Days 1 and 15 of Cycle 1.

Turner et al. New Engl J Med. 2015

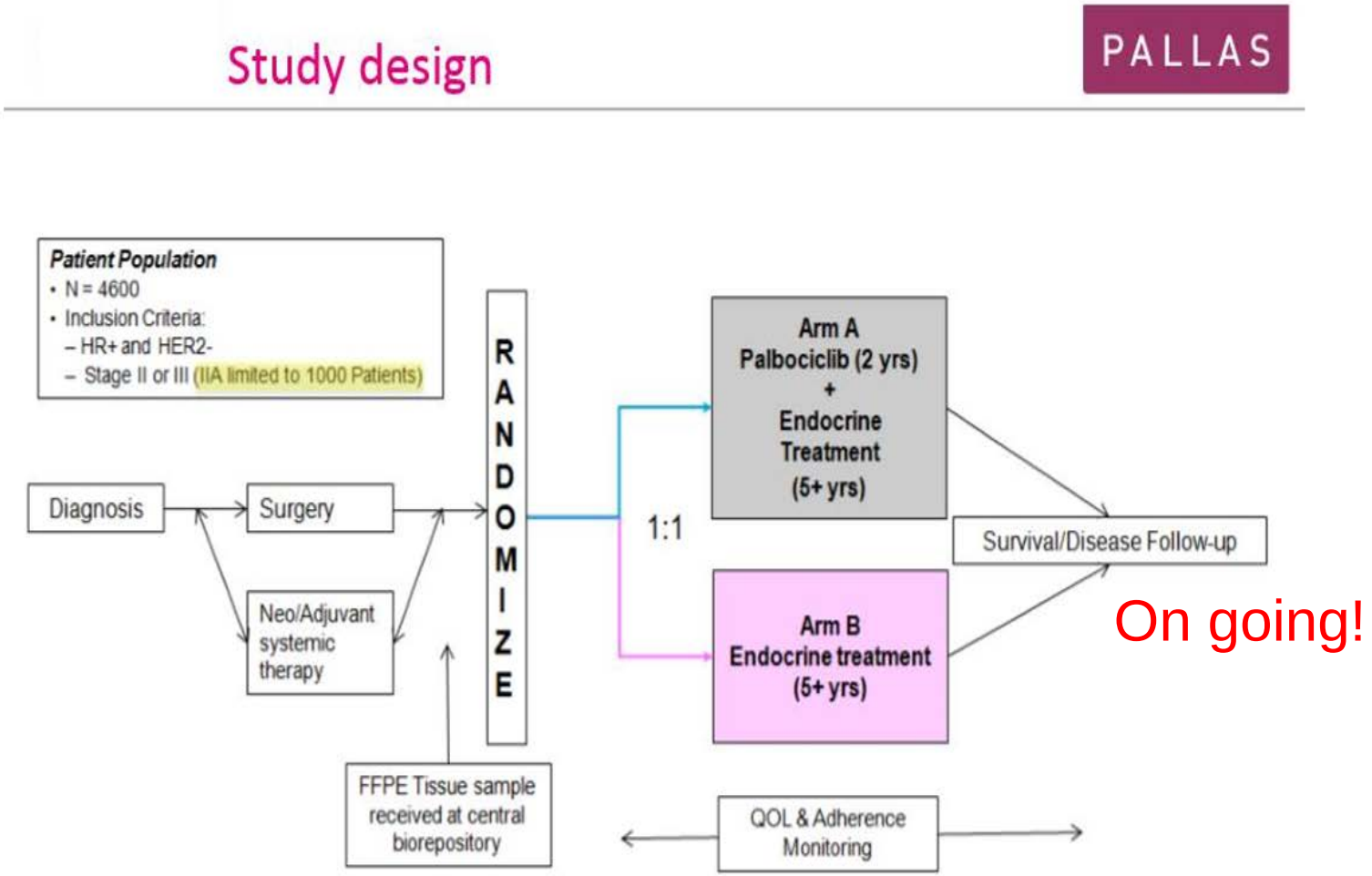


Presented By Richard Finn at 2016 ASCO Annual Meeting

Cycline -inhibotoren

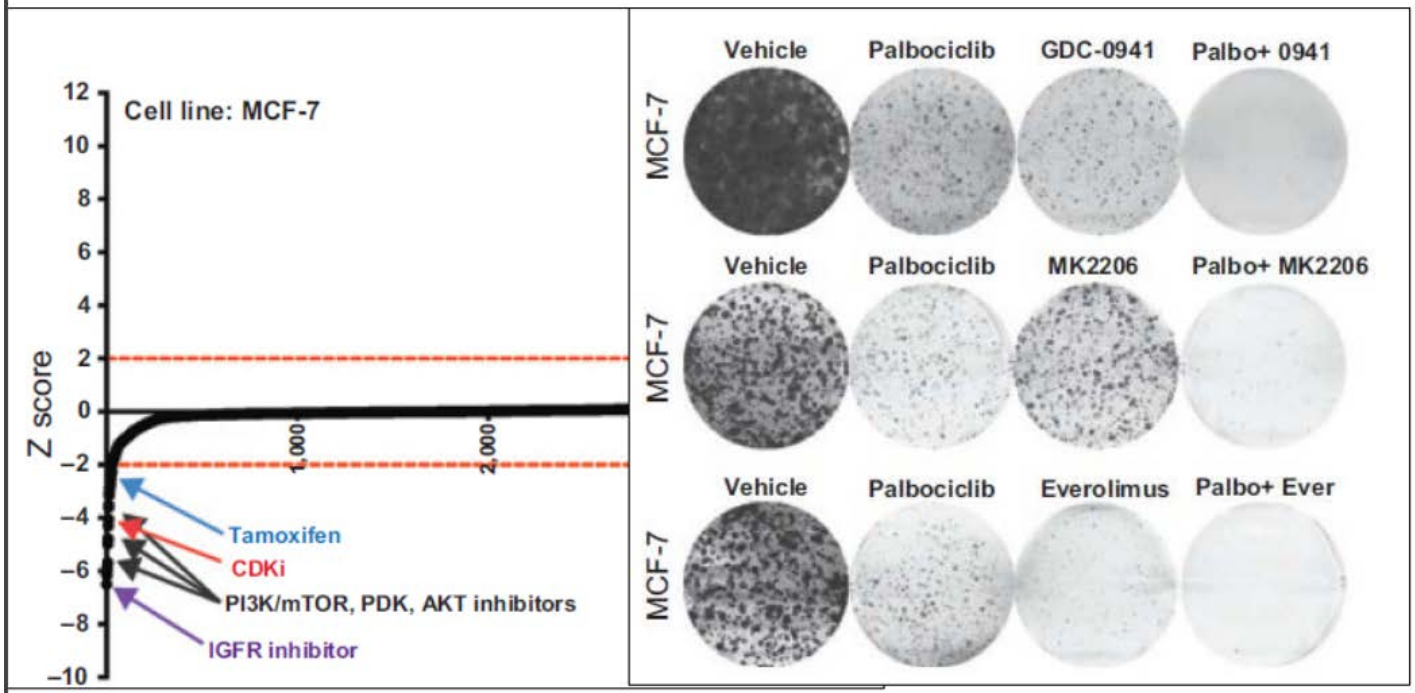
- Palbociclib = Ibrance
- Ribociclib = Kisqali
- Abemaciclib = Verzenios

Cycline inhibitoren:
ook *adjuvant* survival benefit??



On going!

Combined targeting of both CDK4/6 and PI3K can block early adaptation



Herrera-Abreu MT, et al. Cancer Res 2016;1-13

Algemene besluiten

Chemotherapie

- Blijft vaak basisbehandeling
- Celdodend maar niet selectief
- Nieuwe cytostatica: significante verbetering mbt toxiciteit en patiëntvriendelijker
- Bijwerkingen
- Immunoconjugaten (TDM-1)

Algemene besluiten

Targeted therapy

- Selectieve therapie gericht op tumor/cel specifieke kenmerken
- → selectie pten vs mutatie'prevalentie'
- Neveneffecten

- Kostprijs!!

IMMUNOTHERAPIE
Challenges

1. Selectie pten!
2. Uniformiseren PD1 expressie graad
3. Tumor selectie!
    1. Immuungevoelige (melanomen)
    2. “koude” tumoren, niet omringd door lymfocyten
    3. Eerst lymfocyten stimuleren/activeren
    4. Eerst ipilumumab, gevolgd door selectievere tumorgerichte anti-PD1

ONE ~~FITS~~ ALL → personalized