De-escalation of systemic therapy when reaching **pCR** after neoadjuvant chemo?

- **Pembrolizumab** after surgery in <u>early triple negative breast cancer</u>

- **Trastuzumab** (+ Pertuzumab) after surgery in <u>early HER2+ breast cancer</u>

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pCR = pathological complete respons

Disclosure

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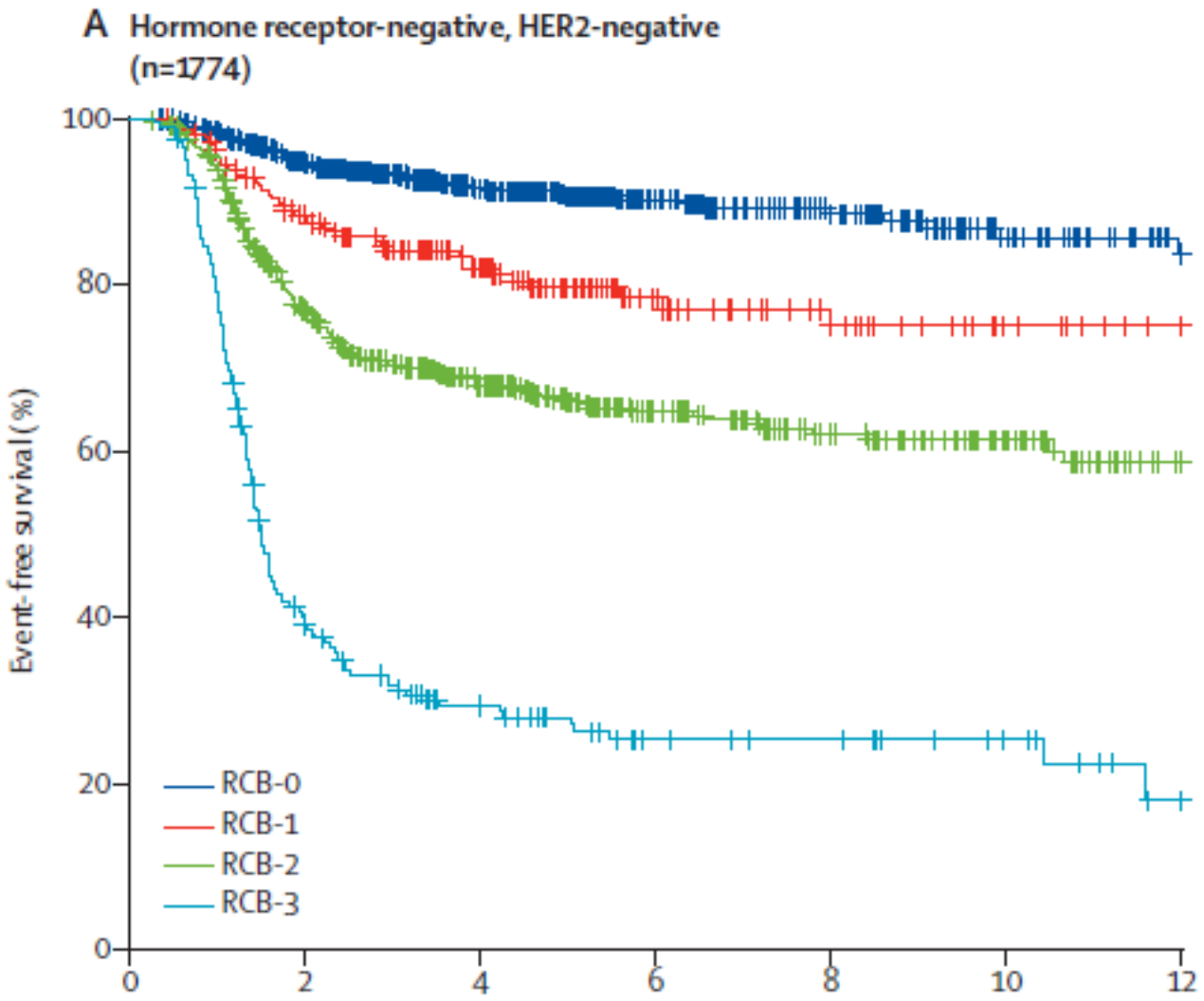
- I received travel support from Gilead, Daiichi Sankyo, Pfizer.

Importance of pCR (pathological complete respons) in TNBC



RCB 0 = pCR, no residual tumor

RCB 1 = good response but not complete

RCB 2 = moderate response

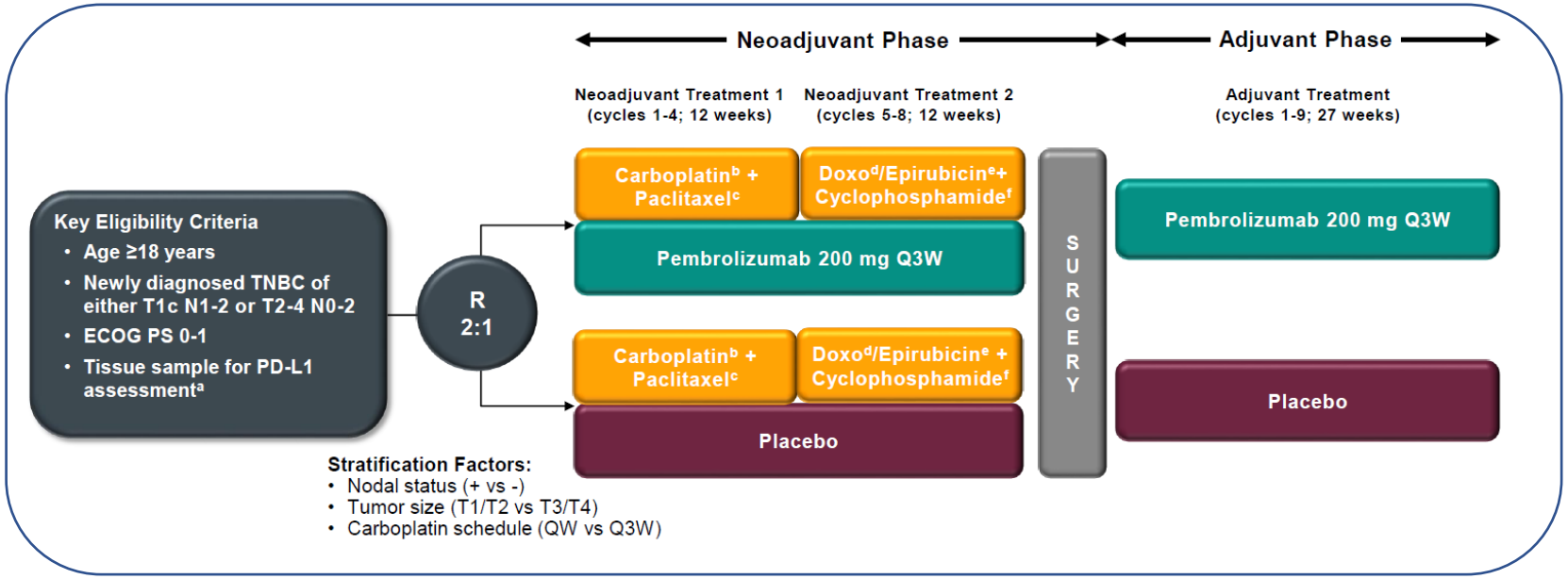
RCB 3 = no clear signs of response

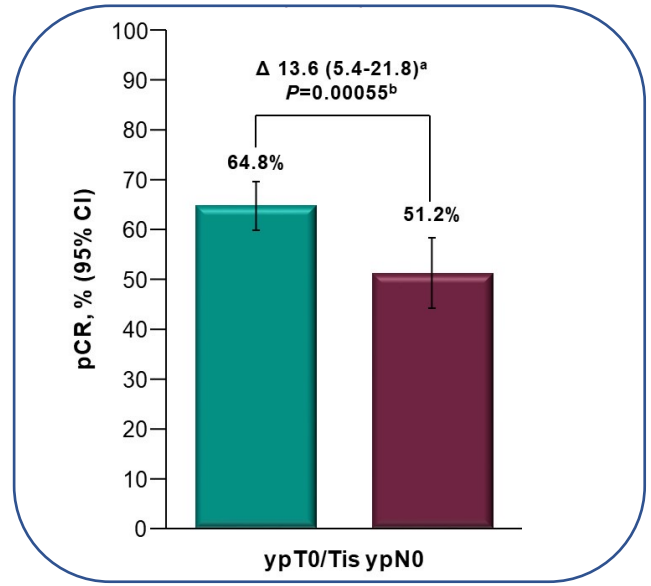
Yau et al. Lancet Oncol 2014

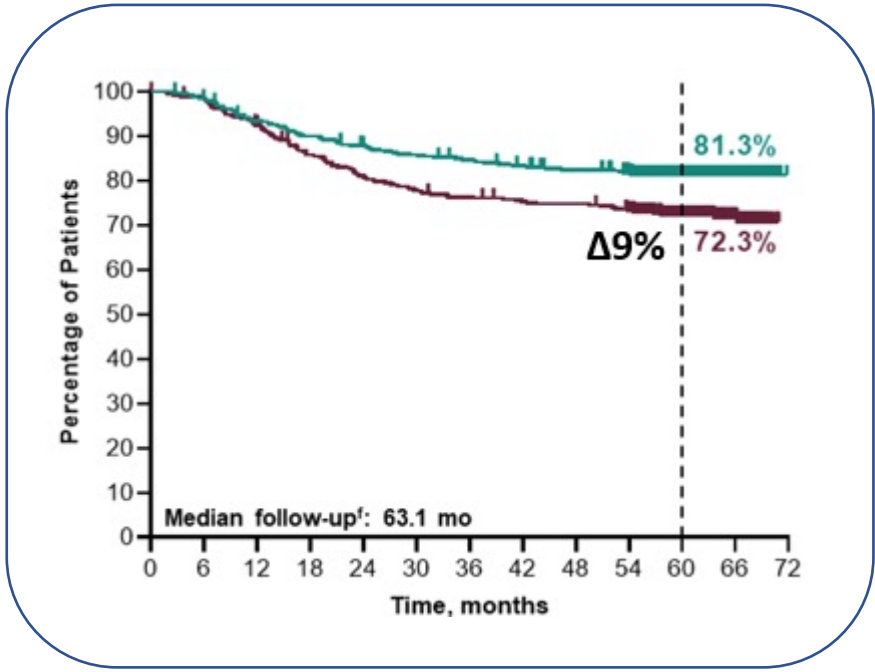
Pembrolizumab in early TNBC

New standard of care stage II/II TNBC: **Keynote 522 study**

4 chemo's plus pembro (20-24 weeks neoadjuvant)
followed by 27 weeks pembro adjuvant





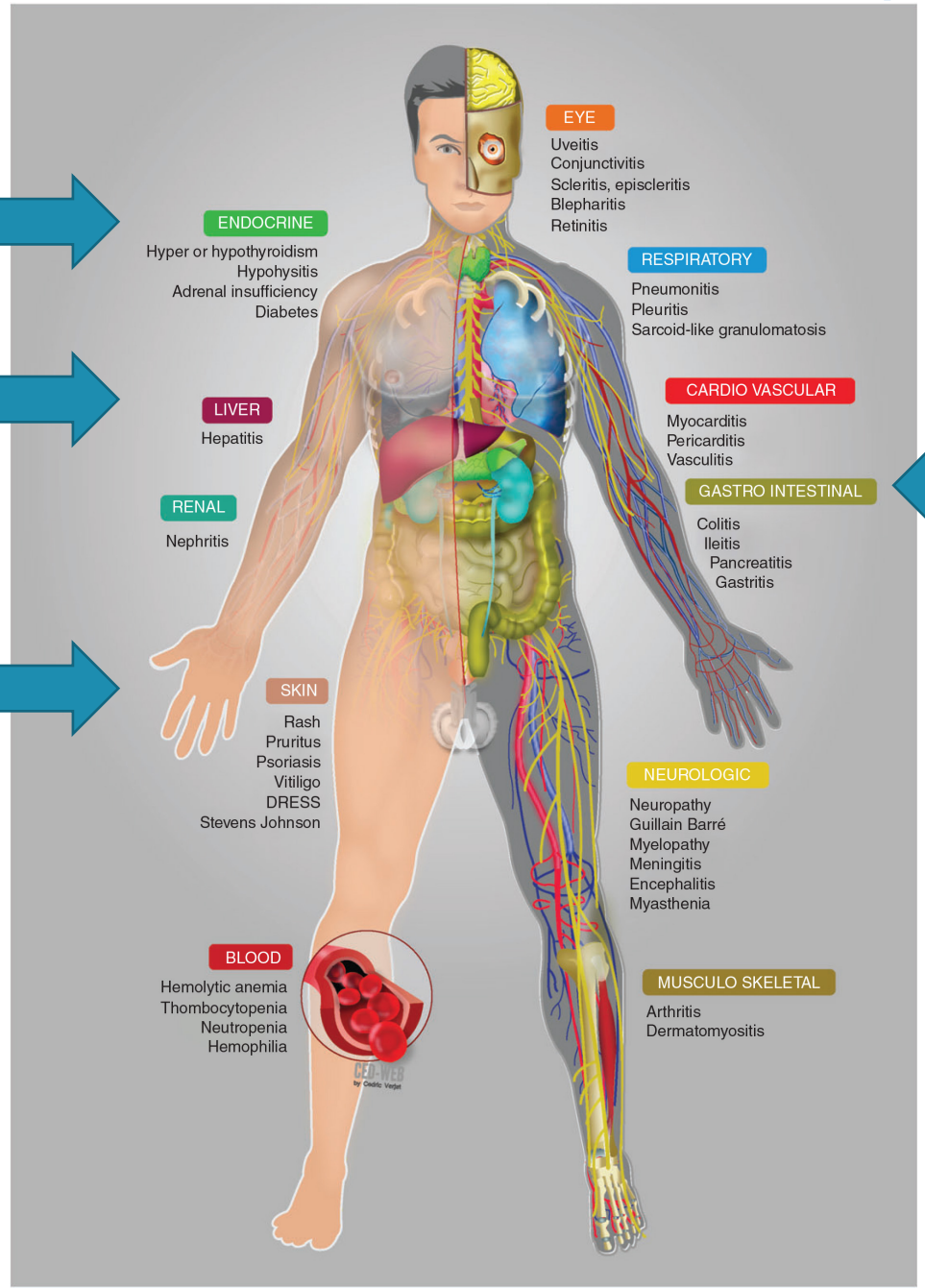


Important step forward for TNBC patients, however:

1) No evidence that adjuvant pembro contributes
2) This pivotal trial did not use the optimal treatment backbone:
   - i) no dose dense AC (OS-benefit 12%),
   - ii) no adjuvant capecitabine if non-pCR (OS-benefit 8.5%)
   - iii) no adjuvant olaparib if BRCA+ and non-pCR (OS-benefit 3.4%)

ESMO 2023 LBA18 Schmid P

Possible side effects of immune therapy



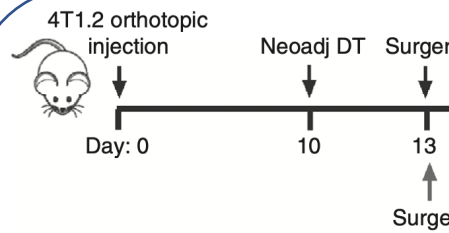
- **± 10% clinically relevant**
- **± 1% severe/life threatening**

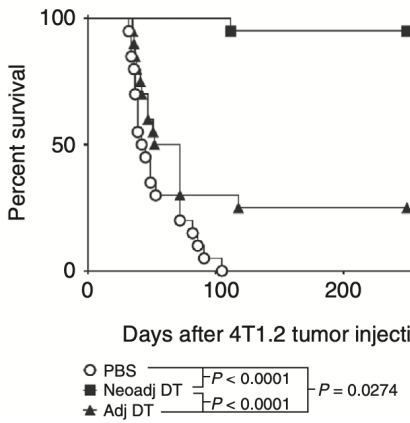
Champiat, Ann Oncol 2016

What is the contribution of the adjuvant pembrolizumab part??

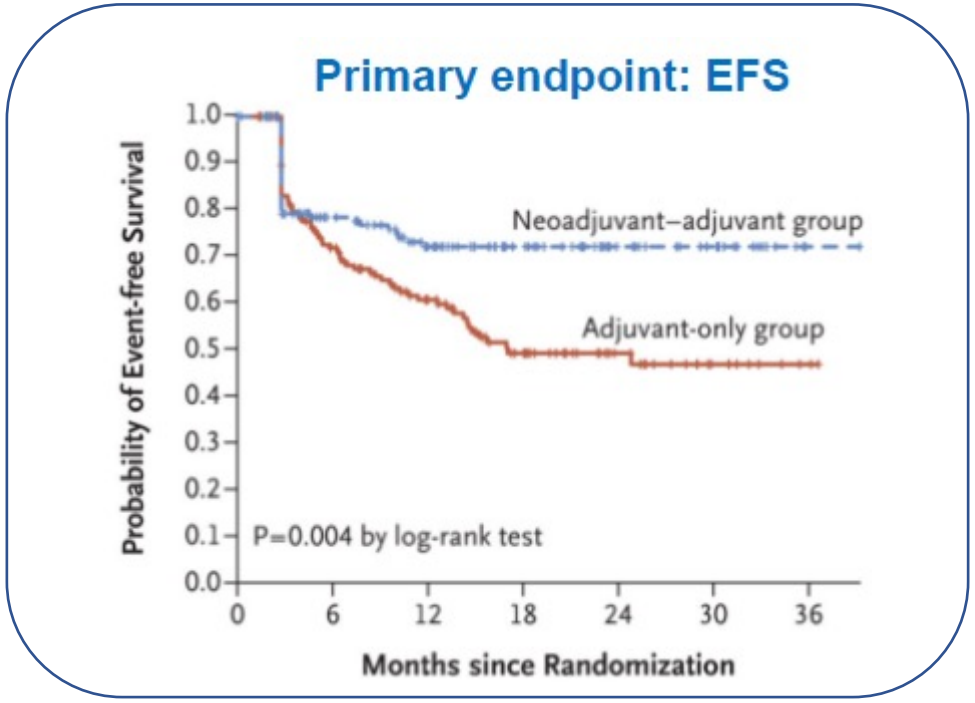
Neoadjuvant immunotherapy superior to adjuvant immunotherapy in melanoma

More expansion of tumor-specific T cells neoadjuvant vs adjuvant in mice





Better EFS (HR 0,59 p=0,0015) and OS (HR 0,63 p=0,09) neoadjuvant-> adjuvant vs only adjuvant Pembrolizumab in melanoma stage IIB-III (SWOG S1801)

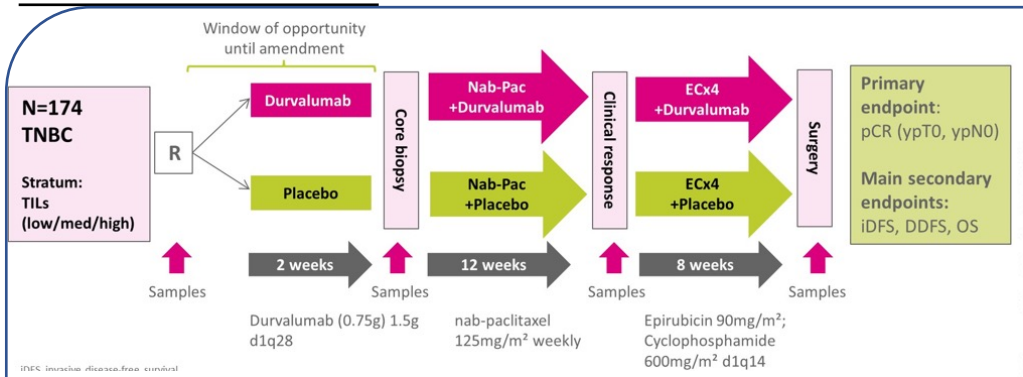


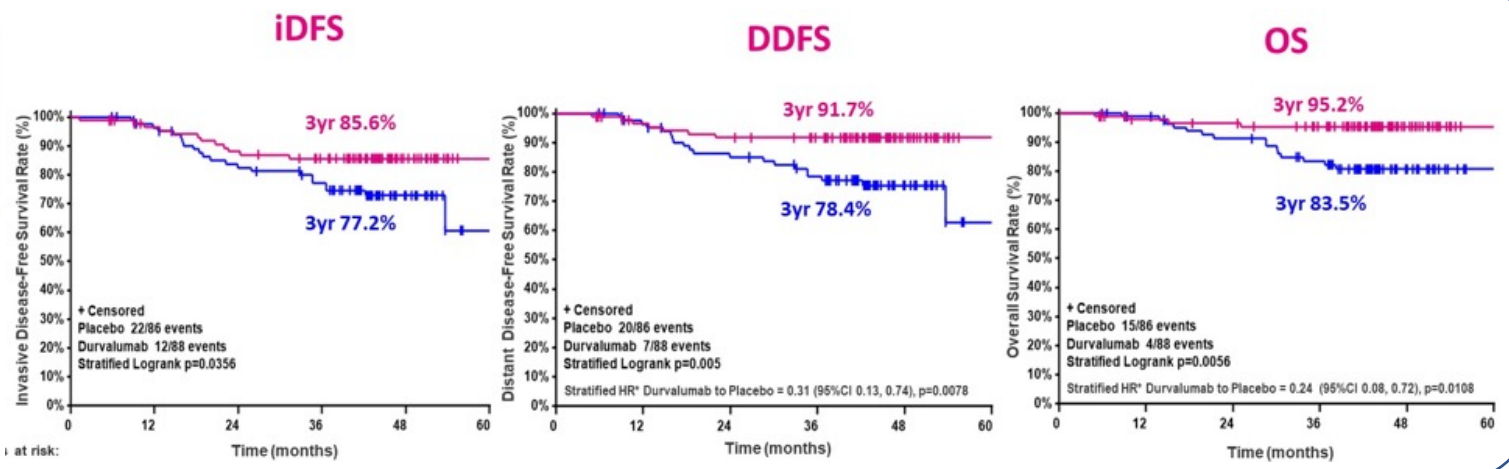
Immune therapy seems much more active when **tumor is in place** (neoadjuvant setting) compared to adjuvant setting where at most very low tumor load remains present

Liu et al. Cancer Discovery 2016 ; Patel et al. NEJM 2023

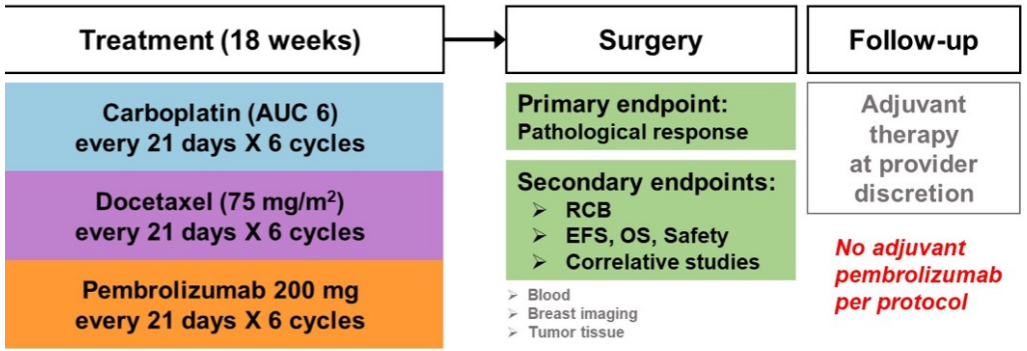
TNBC neoadjuvant immunotherapy studies show excellent outcome without adjuvant immunotherapy

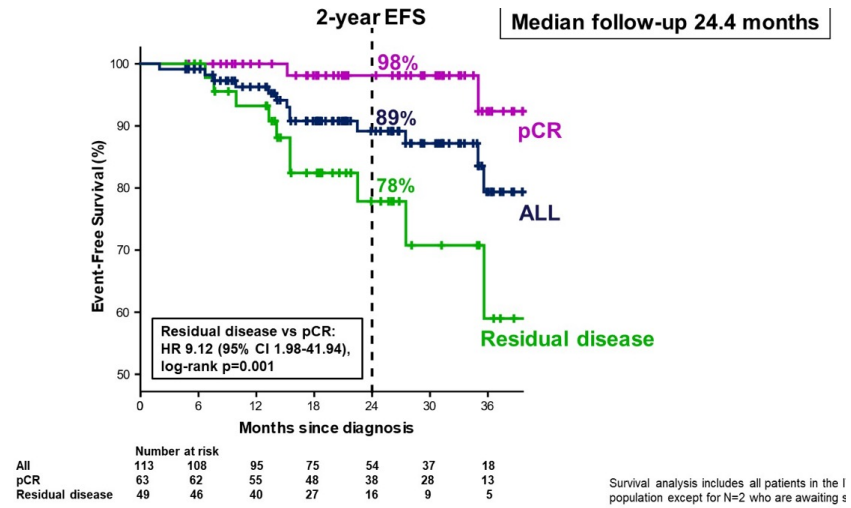
GEPARNUEVO





NEOPACT

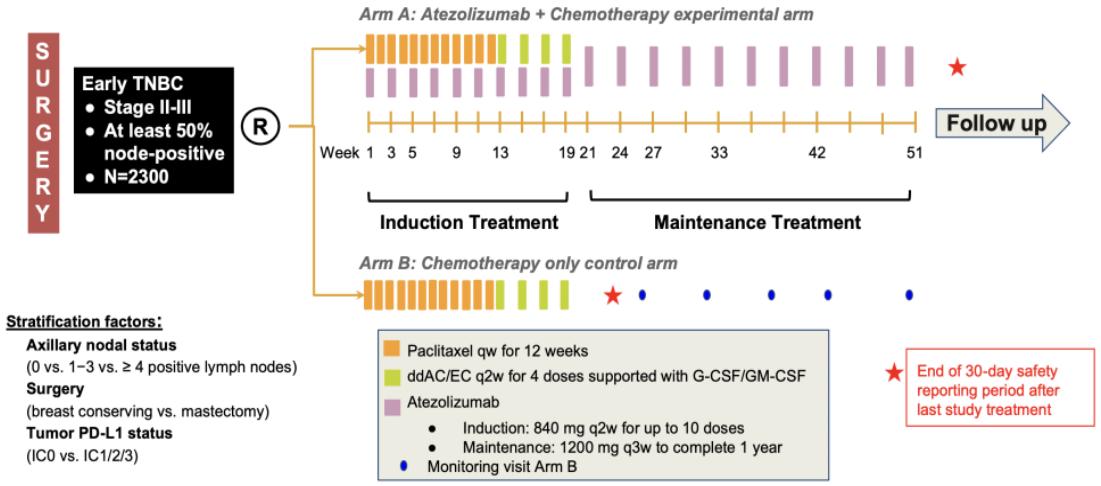


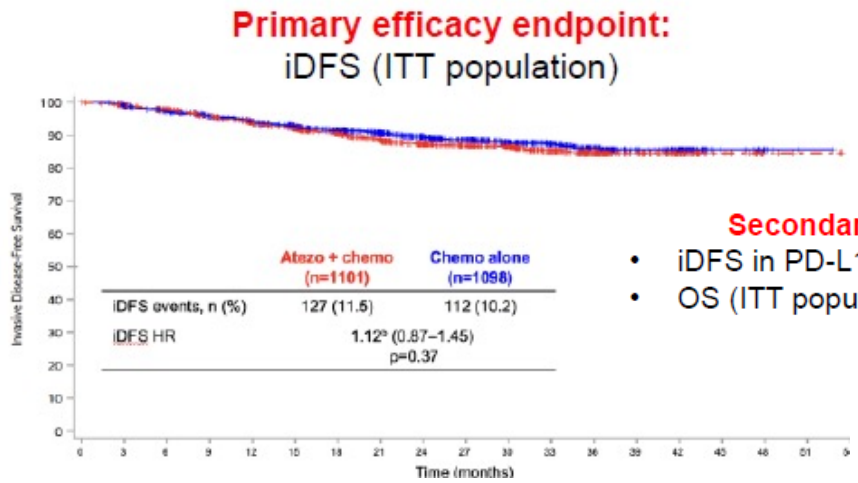


Loibl et al. Ann Oncol 2022
Sharma et al. ASCO 2022

Only adjuvant Atezolizumab in early TNBC gives NO benefit

ALEXANDRA (Impassion 030)





Reasons for lack of benefit of adjuvant atezolizumab?

- lack of primary tumor?
- Is PD-L1 inhibition inferior to PD-1 inhibition?
- other reason?

Ignatiadis et al. SABCS 2023

Cost implications of pembrolizumab adjuvant

In Belgium

- 1500 TNBC/y
- 900 stage II-III
- 720 eligible for neoadj chemo + pembro
- 460 achieve pCR
- 260 achieve non-pCR

Cost of **adjuvant pembrolizumab** part

(assuming 61.500 euro per patient)

- 460 achieve pCR:

  28.290.000 euro/y

- 260 achieve non-pCR:

  15.990.000 euro/y

PS: calculation estimates are rough estimates by myself; true costs depend on many factors that are difficult to evaluate

What is the contribution of **adjuvant pembrolizumab**???

Patients with <u>pCR</u> after neoadjuvant chemo+pembro:

* excellent outcome: does adjuvant pembrolizumab provide benefit? Benefit of the doubt or doubt of the benefit?
  - Should adjuvant pembrolizumab be **considered as a standard?**
  - Should adjuvant pembrolizumab be stopped after surgery as a standard?
  - Should adjuvant pembrolizumab be administered taking side effects and patient wishes into account?
* US-collaborative groups: **non-inferiority study** adjuvant pembro vs no adjuvant pembro, n=1295 (OptimICE-pCR, PI Tolaney)

Patients with <u>non-pCR</u> after neoadjuvant chemo+pembro:

* higher risk of relapse, but no evidence that adjuvant pembro would make the difference.
  - Should adjuvant pembrolizumab be **considered as a standard?**
  - Should adjuvant pembrolizumab be stopped after surgery as a standard?
  - Should adjuvant pembrolizumab be administered taking side effects and patient wishes into account?
* **escalation trials** ongoing SASKIA, TROPION-B03, ASCENT-05

WHY DO WE CARE?

- Adjuvant pembrolizumab is expensive (**61.500 euro per patient** for adjuvant part (at full price))
- Additional toxicity

HER2+ early breast cancer

- **Adjuvant** trastuzumab (added to chemo) has improved survival significantly (8-10% OS benefit)
- Pivotal trials (HERA, American trials) mostly used **1y** of adjuvant Trastuzumab
- HERA trial showed equivalence of 1y versus 2y of trastuzumab
- **Pertuzumab** added to trastuzumab adds 1-2% OS benefit, mainly in N+ disease

- Several **short duration** trials of adjuvant trastuzumab (next slide)
  - Minor benefit of 1y versus shorter duration mainly in ‘high risk’

Short duration trials of adjuvant trastuzumab

Authors/Study	Period	N	Study Design	Treatment	MF	Survival HR (95% CI)	Cardiac events (shorter vs 1y)
Conte et al. Short-HER	2007.12–2013.10	1253	multicenter, phase III RCT, non-inferiority (HR < 1.29)	D + H → FEC AC/EC → T/D + H 9w vs 1y	6 y	DFS:1.13 (0.89–1.42) OS: 1.07 (0.74–1.56)	8/626 vs 18/627
Earl et al. PERSEPHONE	2007.10–2015.7	4088	multicenter, phase III RCT, open-label non-inferiority (HR < 1.29)	Anthracycline/ Taxane +H (concurrent/sequential) 6 m vs 1y	64.8m	DFS: 1.07 (0.90–1.28) OS: 1.14 (0.92–1.42)	82/2043 vs 164/2045
Joensuu et al. SOLD	2008.1–2014.12	2174	multicenter, phase III RCT, open-label superiority → non-inferiority (HR < 1.3)	D + H → FEC ± H 9w vs 1y	62.4m	DFS: 1.39 (1.08–1.79) OS: 1.36 (0.92–2.01)	22/1085 vs 42/1089
Mavroudis et al. HORG	2004.6–2012.5	481	multicenter, phase III RCT, non-inferiority (HR < 1.53)	FEC → D + H 6 m vs 1y	51m	DFS: 1.57 (0.86–2.10) OS: 1.45 (0.57–3.67)	–
Pivot et al. PHARE	2006.5–2010.7	3380	multicenter, phase III RCT, open-label non-inferiority (HR < 1.15)	Anthracycline/ Taxane +H (concurrent/sequential) 6 m vs 1y	7.5y	DFS: 1.08 (0.93–1.25) OS: 1.13 (0.92–1.39)	67/1690 vs 111/1690
Schneider et al. E2198	1999.8–2000.10	120*	phase II RCT	T + H → AC ± H 12w vs 1y	77m	DFS: 0.85 (0.41–1.77) OS: 1.21 (0.46–3.13)	–

Meta-analysis (n= 11.496 pts)

DFS HR 1,13 (1,03-1,25)

OS HR 1,16 (1,01-1,32)

DFS ER+ HR 1,10 (0,97-1,25)

DFS ER- HR 1,23 (1,07-1,41)

DFS N- HR 1,11 (0,93-1,32)

DFS N+ HR 1,18 (1,01-1,38)

Cardiac events: HR 0,52 (0,43-0,62)

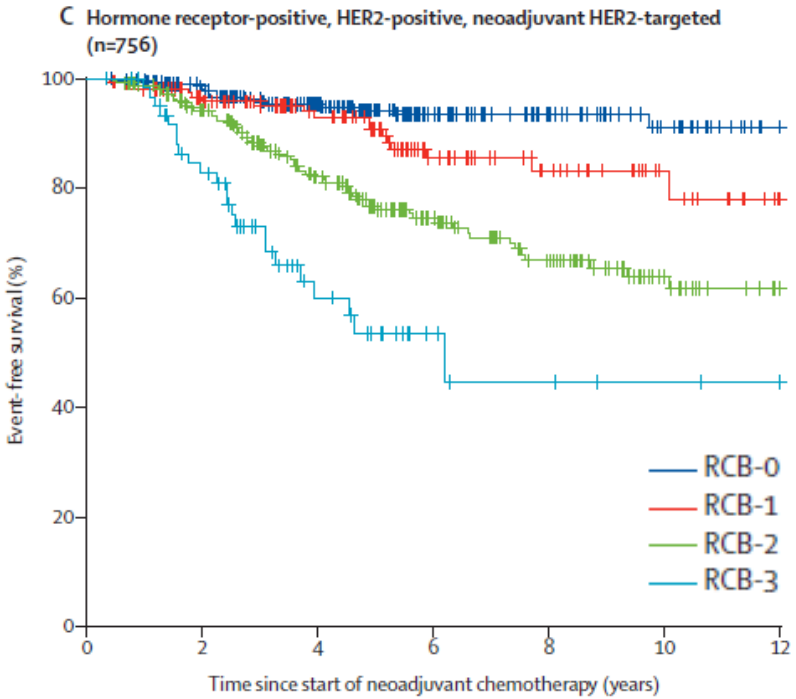
Cancer Treat Rev 2019 Lujia

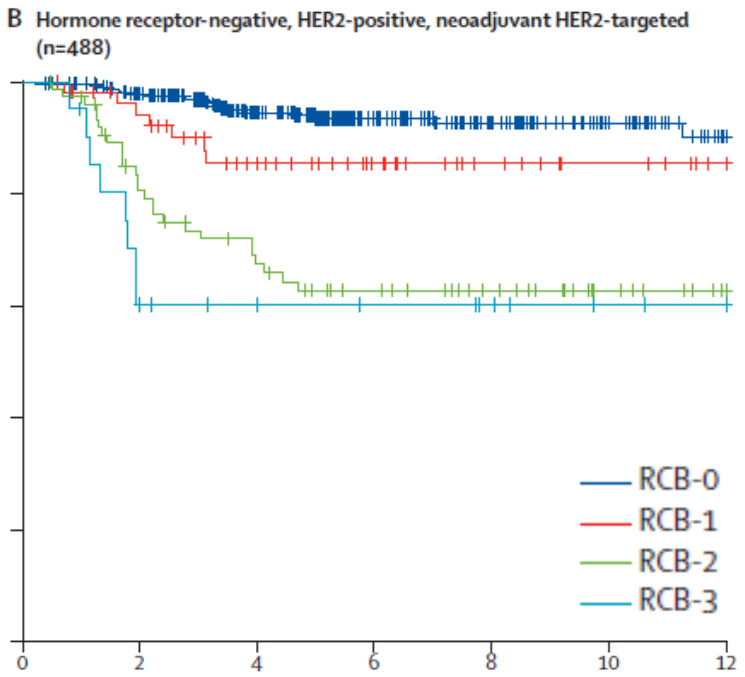
HER2+ early breast cancer

Shift towards neoadjuvant chemo + antiHER2 !

- If **non-pCR**, adjuvant **T-DM1** improves DFS and OS compared to trastuzumab continuation
- If **pCR**, excellent prognosis

  NO data if 'adjuvant' antiHER2 therapy improves outcome





Cost implications of trastuzumab/pertuzumab adjuvant

In Belgium

- 1200 HER2+ /y
- 750 stage II-III
- 600 eligible for neoadj chemo + trastuzumab +/- pertuzumab
- 370 achieve pCR (220 with P, 150 without P)

Cost of 12 x **adjuvant trastuzumab** (+ **pertuzumab** if N+)

trastuzumab: 1.009 euro/600 mg sc

pertuzumab: 2.015 euro/420 mg iv

- 370 achieve pCR:

  +/- 15.600.000 euro/y

PS: calculation estimates are rough estimates by myself; true costs depend on many factors that are difficult to evaluate

What is the contribution of **adjuvant trastuzumab (+/- pertuzumab)** ???

Patients with <u>pCR</u> after neoadjuvant chemo + trastuzumab (+pertuzumab):

* excellent outcome: does adjuvant trastuzumab (+pertuzumab) provide additional benefit?
  - Should adjuvant trastuzumab (+pertuzumab) be considered as a standard??
    Difference with pembrolizumab: adjuvant only antiHER2trials also showed benefit!
  - If yes, is 1 year the standard or is **shorter duration** (e.g. 6 months) acceptable??
  - If yes, is **pertuzumab** needed in N+ who achieve pCR?
* No trials ongoing in this setting because of insufficient interest of industry and academia.

WHY DO WE CARE?

- Adjuvant trastuzumab (+pertuzumab) is expensive (**12-36.000 euro per patient** for adjuvant part)
- Additional toxicity (cardiac failure)

Challenges when prescribing expensive drugs as an oncologist

Follow clinical trial regimens and indications

Integrate knowledge from other settings

Financial responsability towards society

Integrate treatment risk

Integrate patients wishes