Immunterapi til behandling af brystkræft

DBCGs repræsentantskabsmøde 16. januar 2023

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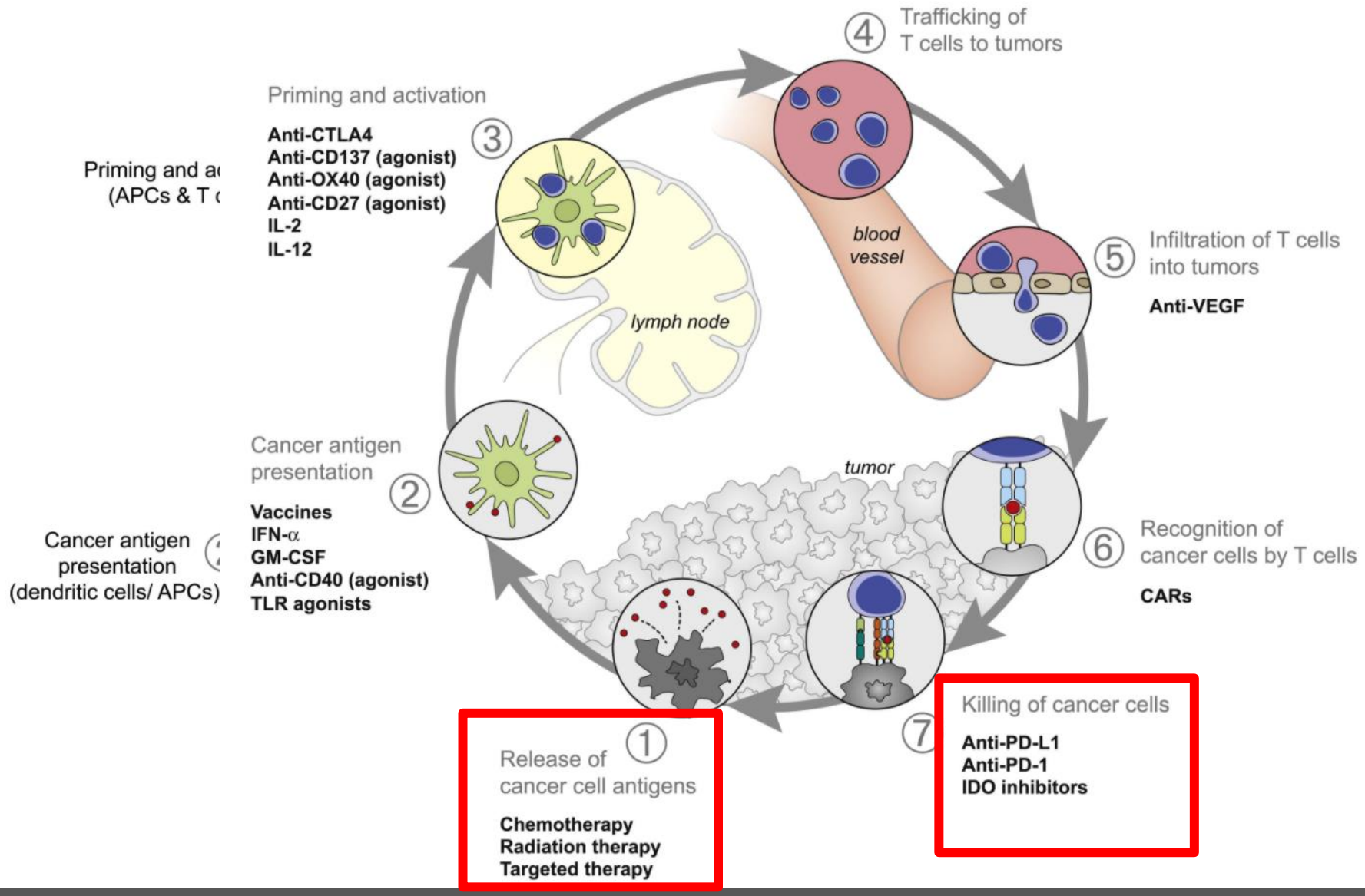
Agenda

- Introduktion
- Immunterapi til behandling af mTNBC
  - ALICE studiet
- Immunterapi til behandling af eTNBC
- Opsummerering og ”next wave” immunterapi til brystkræft

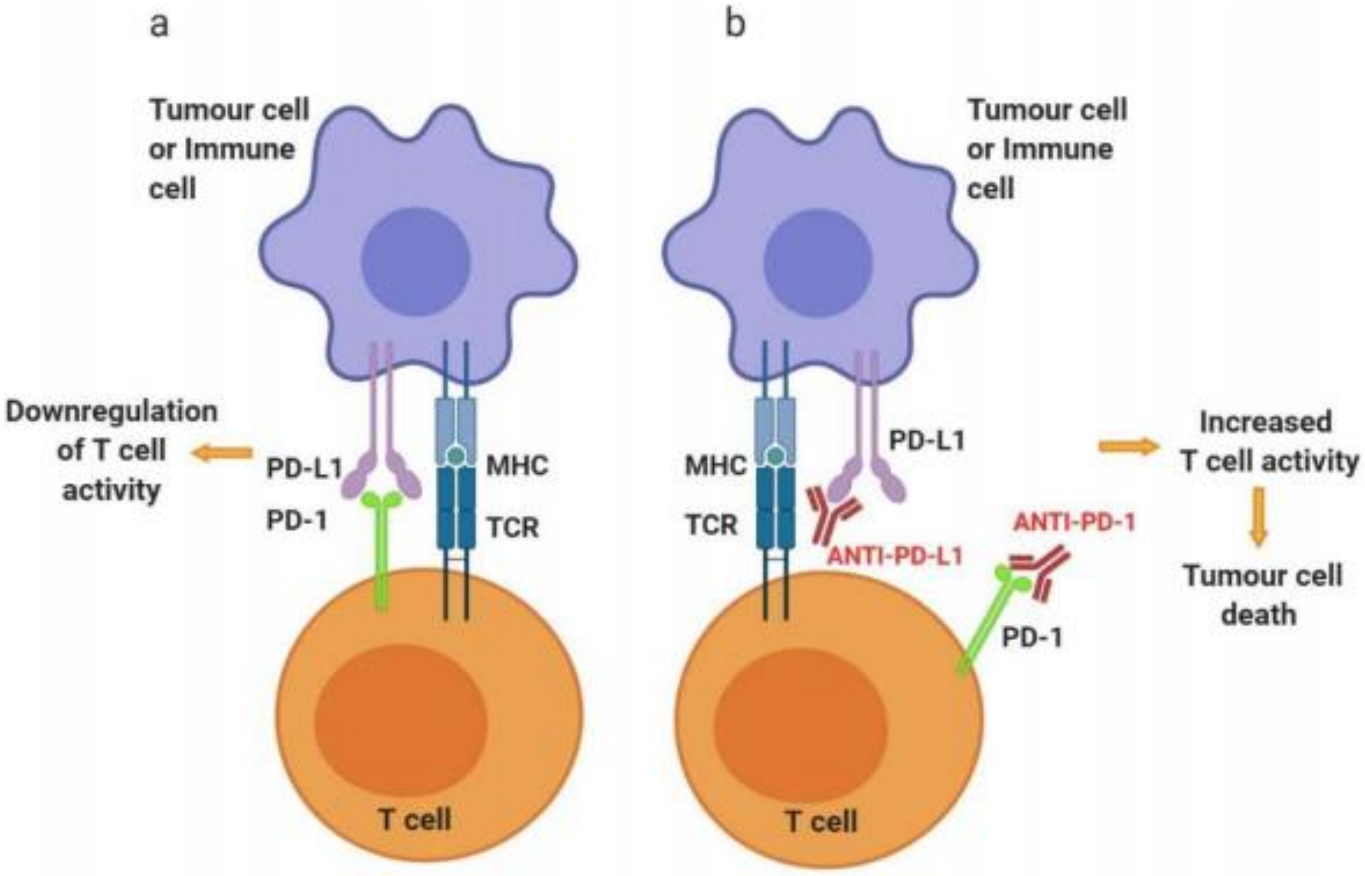
Cancer Immunity Cycle



Chen, Immunity 2013

PDL1/PD1

Programmed Death-Ligand 1

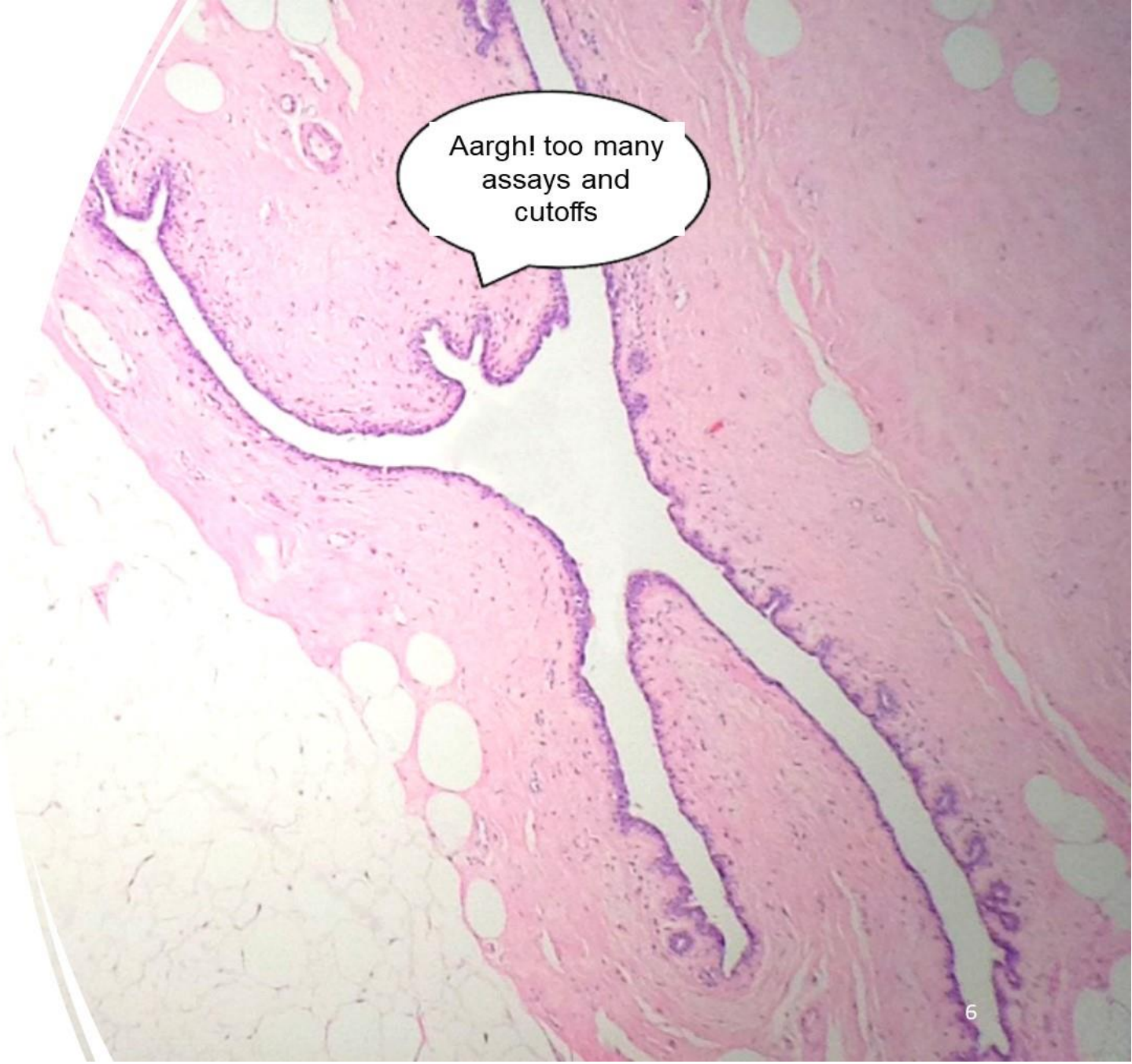


Alard, Cancers 2020

- **Anti PD1 antistoffer**
  - Pembrolizumab
  - Nivolumab
  - Cemiplimab
- **Anti-PDL1 antistoffer**
  - Atezolizumab
  - Durvalumab
  - Avelumab

PD-L1 protein expression by IHC

Beware high rates of discordance!



Predictive PD-L1 testing for anti-PD1/PD-L1 inhibitors in cancer

FDA Approved Companion Diagnostic Indications for the Agilent/DAKO PD-L1 IHC 22C3 pharmDx Assay

Tumor Type	PD-L1 Cutoff Expression Level*	Therapy
Cervical Cancer	CPS ≥ 1	Pembrolizumab
Esophageal Squamous Cell Carcinoma	CPS ≥ 10	Pembrolizumab
Gastric or GEJxn Adenocarcinoma	CPS ≥ 1	Pembrolizumab
Head and Neck Squamous Cell Carcinoma	CPS ≥ 1	Pembrolizumab
Non Small Cell Lung Cancer	TPS ≥ 1%	Pembrolizumab
Non Small Cell Lung Cancer	TPS ≥ 50%	Cemiplimab-rwlc
Urothelial Carcinoma	CPS ≥ 10	Pembrolizumab
Triple Negative Breast Cancer	CPS ≥ 10	Pembrolizumab

*For Details on Immunohistochemical Test Scoring Methodology see Anti PD-L1 Immuno Therapy

FDA Approved Companion Diagnostic Indications for Ventana/Roche Diagnostics PD-L1 SP142 Assay

Tumor Type	PD-L1 Cutoff Expression Level*	Therapy
Non Small Cell Lung Cancer	≥ 50% TC or ≥ 10% IC	Atezolizumab
Triple Negative Breast Cancer **	≥ 1% IC	Atezolizumab
Urothelial Carcinoma	≥ 5% IC	Atezolizumab

*For Details on Immunohistochemical Test Scoring Methodology see Anti PD-L1 Immuno Therapy
** The indication for atezolizumab (Tecentriq) in combination with nab-paclitaxel (Abraxane) chemotherapy as treatment for patients with triple-negative breast cancer (TNBC) whose tumors express PD-L1 has been withdrawn by Roche

FDA Approved Companion Diagnostic Indications for Agilent/DAKO PD-L1 IHC 28-8 pharmDX Assay

Tumor Type	PD-L1 Cutoff Expression Level *	Therapy
Non Small Cell Lung Cancer	PD-L1 >=1% TC	Nivolumab

*For Details on Immunohistochemical Test Scoring Methodology see Anti PD-L1 Immuno Therapy

FDA Approved Companion Diagnostic Indications for Ventana/Roche Diagnostics PD-L1 SP263 Assay

Tumor Type	PD-L1 Cutoff Expression Level *	Therapy
Non-Small Cell Lung Cancer	PD-L1 >=1% TC	Atezolizumab

*For Details on Immunohistochemical Test Scoring Methodology see Anti PD-L1 Immuno Therapy

	Drug target	Clone	Epitope	Platform	Detection system
Nivolumab	PD1	28-8	Extracellular	Dako Link 48	Envision Flex
Pembrolizumab	PD1	22C3 SP263	Extracellular Cytoplasmic	Dako Link 48 Ventana	Envision Flex
Atezolizumab	PDL1	SP142	Cytoplasmic	Ventana	Optiview and amplification
Durvalumab	PDL1	SP263	Cytoplasmic	Ventana	Optiview
Avelumab	PDL1	73-10	Cytoplasmic	Dako Link 48	Envision Flex

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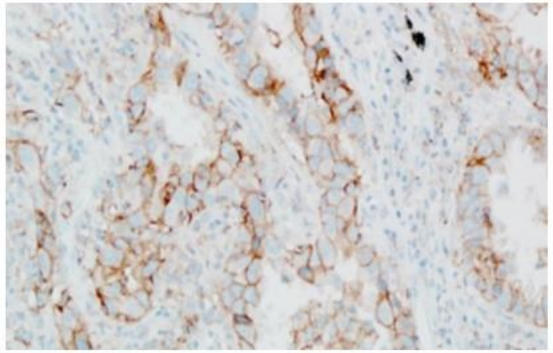
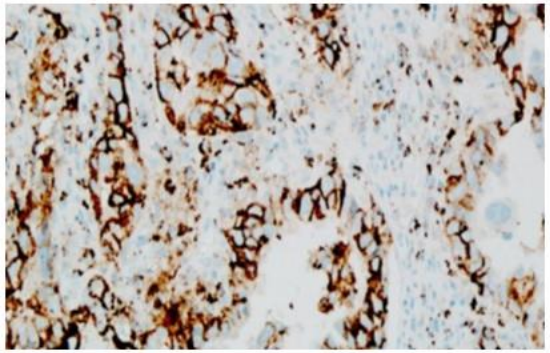
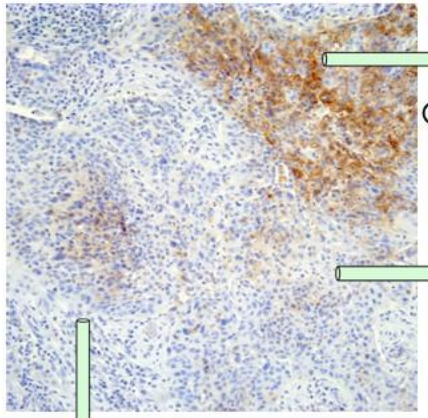
Reasons underlying different PD-L1 test results: tumour heterogeneity/treatment and anatomic site

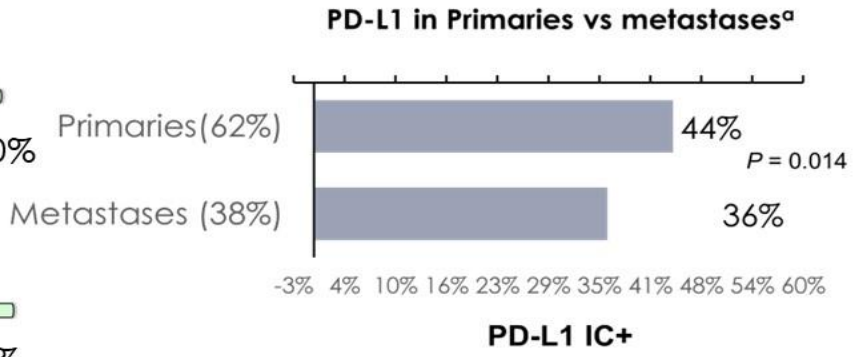


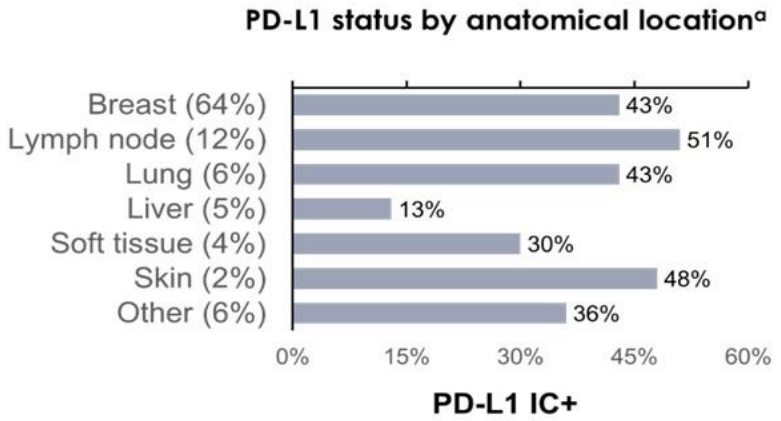
anti-PD-L1 (22C3)
IHC CPS



anti-PD-L1 (SP142)
IHC







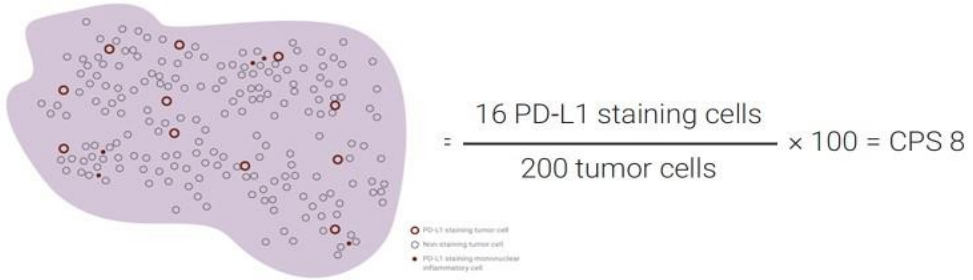
Sherene Loi, ASCO 2022

Reasons underlying different PD-L1 test results: different scoring systems

Pembrolizumab

Combined positive score (CPS)

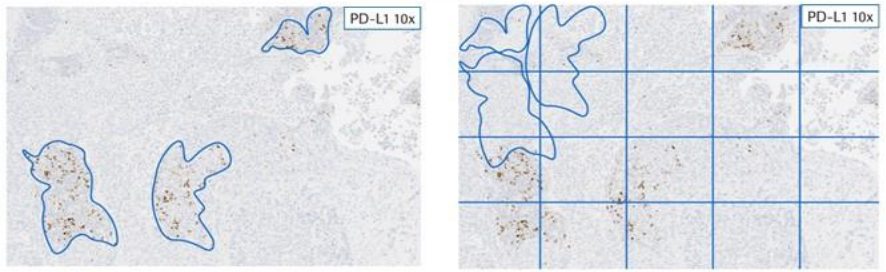
$$\text{CPS} = \frac{\text{+ve cells (tumour +ICs)}}{\text{+ve tumour cells}} \times 100$$



Atezolizumab

Immune cell score (IC)

$$\text{IC} = \frac{\text{area of +ve ICs}}{\text{tumour area}} \times 100$$



Durvalumab

IC +ve

IC +ve = % +ve ICs/Total IC

SP263

In: lymphocytes, macrophages, dendritic cells, histiocytes, plasma cells, and neutrophils

Out: none mentioned in Interpretation guide

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Monoterapi med CPIs, ikke-randomiserede studier

Trial	Key inclusion	Treatment	Subgroups	Sample size	ORR (%)	DCR (%)	Median DOR (months)	Median PFS (months)	Median OS (months)
NCT01772004[a] JAVELIN Solid Tumor	Any line	Avelumab		58	5.2	31	NR	5.9	9.2
NCT01375842	Any line	Atezolizumab		115	10	13	21.0	1.4	8.9
			PD-L1 IC ≥ 1%	91	12	15	21.0	1.4	10.1
			PD-L1 IC < 1 %	21	0	5	N/A	1.4	6.0
NCT01848834 KEYNOTE-012	Any line PD-L1 IC/TC ≥ 1%	Pembrolizumab		32	18.5	25.9	NR	1.9	11.2
NCT02447003 KEYNOTE-086 Cohort A	≥ 2nd line	Pembrolizumab		170	5.3	7.6	NR	2.0	9.0
			PD-L1 CPS ≥ 1	105	5.7	9.5	NR	2.0	8.8
			PD-L1 CPS < 1	64	4.7	4.7	4.4	1.9	9.7
NCT02447003 KEYNOTE-086 Cohort B	1st line PD-L1 CPS ≥ 1	Pembrolizumab		84	21.4	23.8	10.4	2.1	18.0

Howard, Breast Cancer Res Treat 2022

1st line CPI + chemo, TNBC mBC

IMpassion130 study design

Key IMpassion130 eligibility criteria[a]:

- Metastatic or inoperable locally advanced TNBC
  - Histologically documented[b]
- No prior therapy for advanced TNBC
  - Prior chemo in the curative setting, including taxanes, allowed if TFI ≥ 12 mo
- ECOG PS 0-1

Stratification factors:

- Prior taxane use (yes vs no)
- Liver metastases (yes vs no)
- PD-L1 status on IC (positive [≥ 1%] vs negative [< 1%])[c]

R 1:1

Atezo + nab-P arm:

Atezolizumab 840 mg IV
- On days 1 and 15 of 28-day cycle

+ *nab*-paclitaxel 100 mg/m^2 IV
- On days 1, 8 and 15 of 28-day cycle

Double blind; no crossover permitted

Plac + nab-P arm:

Placebo IV
- On days 1 and 15 of 28-day cycle

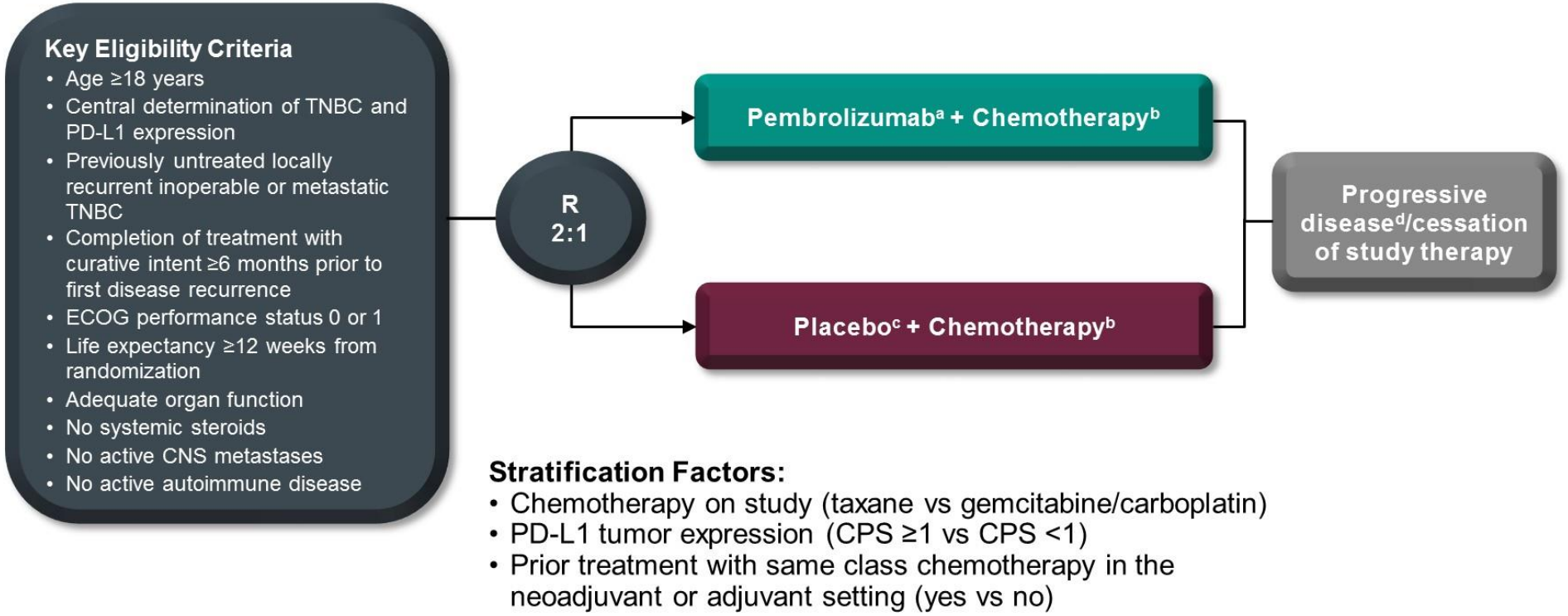
+ *nab*-paclitaxel 100 mg/m^2 IV
- On days 1, 8 and 15 of 28-day cycle

RECIST v1.1
PD or toxicity

Schmid, NJEM 2018

1st line CPI + chemo, TNBC mBC

KEYNOTE-355 Study Design (NCT02819518)



Stratification Factors:
- Chemotherapy on study (taxane vs gemcitabine/carboplatin)
- PD-L1 tumor expression (CPS ≥1 vs CPS <1)
- Prior treatment with same class chemotherapy in the neoadjuvant or adjuvant setting (yes vs no)

Cortes, Lancet 2020

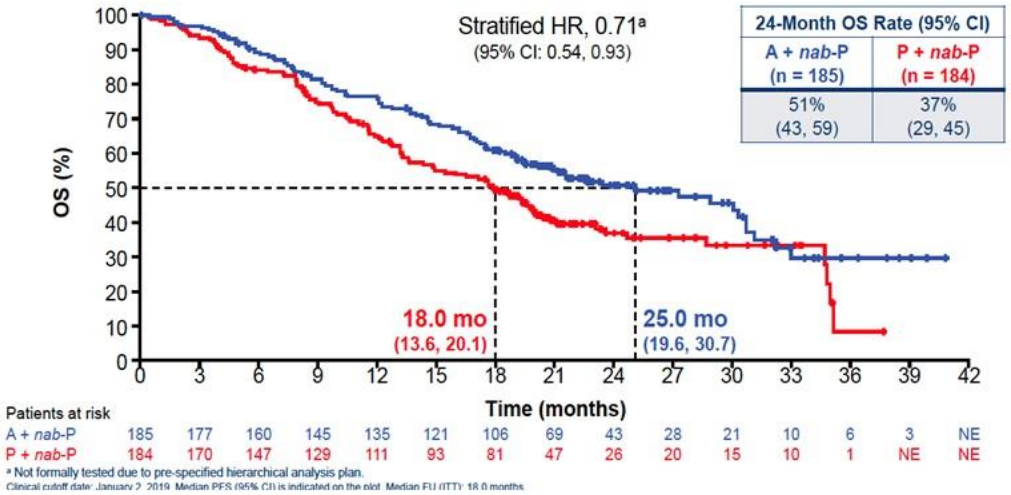
[a]Pembrolizumab 200 mg intravenous (IV) every 3 weeks (Q3W)
[b]Chemotherapy dosing regimens are as follows:
Nab-paclitaxel 100 mg/m^2 IV on days 1, 8, and 15 every 28 days
Paclitaxel 90 mg/m^2 IV on days 1, 8, and 15 every 28 days
Gemcitabine 1000 mg/m^2/carboplatin AUC 2 on days 1 and 8 every 21 days

[c]Normal saline
[d]Treatment may be continued until confirmation of progressive disease
CNS=central nervous system; ECOG=Eastern Cooperative Oncology Group; PD-L1=programmed death ligand 1; R=randomized; TNBC=triple-negative breast cancer

Pivotal phase III studies in advanced TNBC

IMpassion130

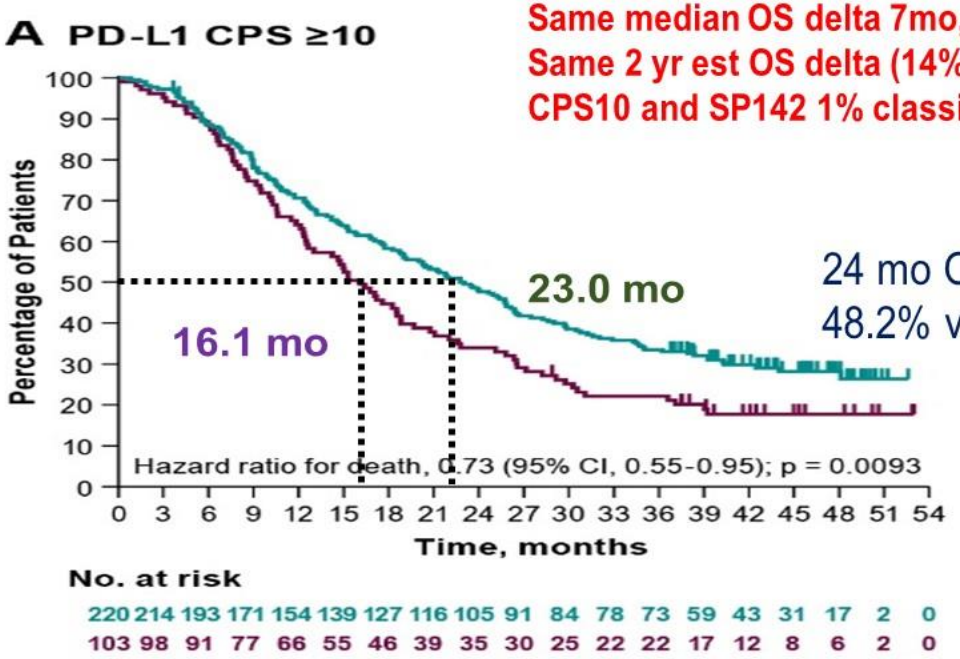
OS in PD-L1+ Population



PD-L1 positive using SP142 or 1% or more
IMpassion131- negative trial with paclitaxel

KEYNOTE-355

Note similar HRs, despite 6 mo vs 12 mo DFI different ChT
Same median OS delta 7mo,
Same 2 yr est OS delta (14%)
CPS10 and SP142 1% classify similar %



Schmid et al NEJM 2018
Cortes et al NEJM in press

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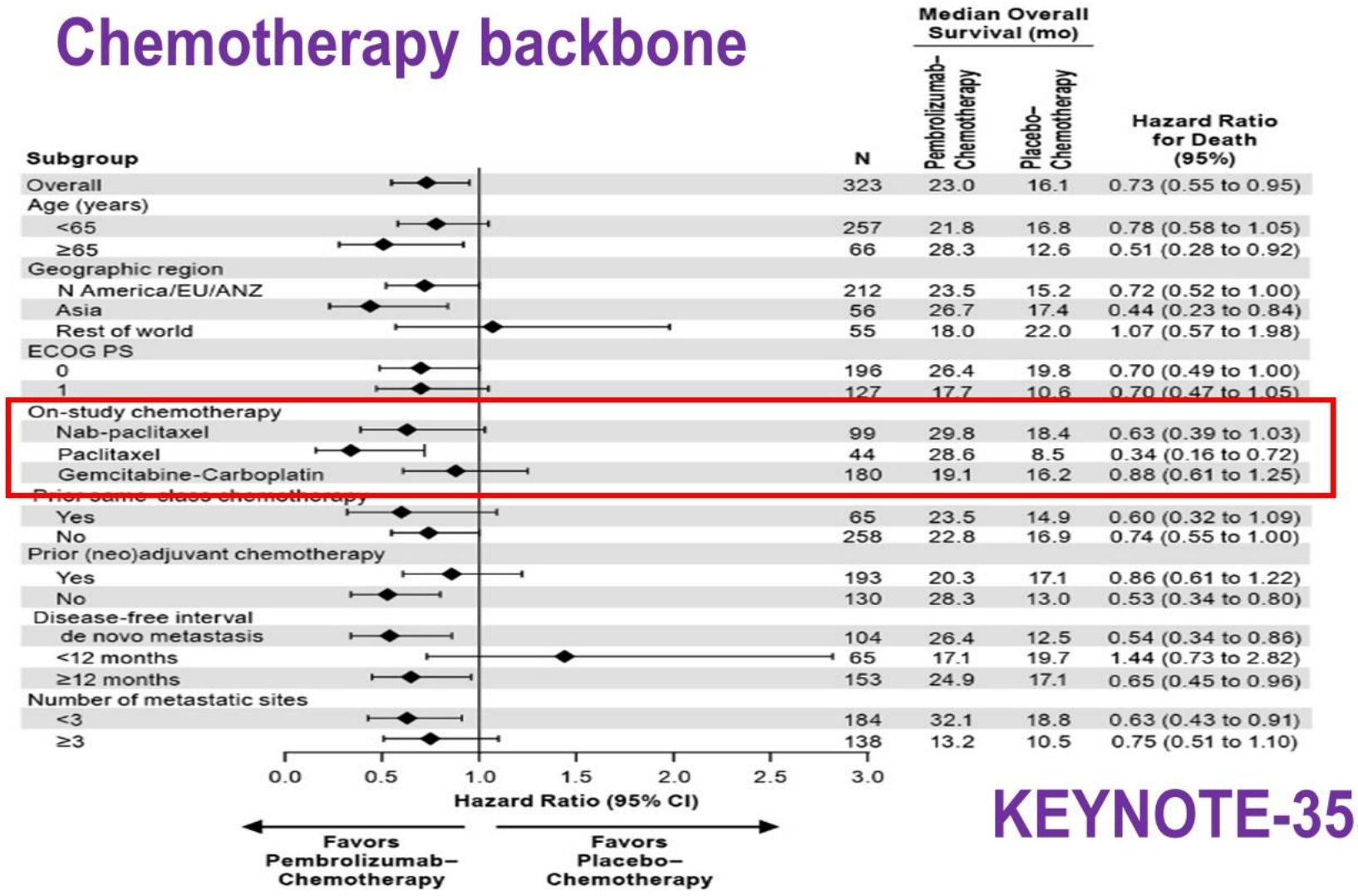
Chemotherapy backbone



KEYNOTE-355 CPS>=10

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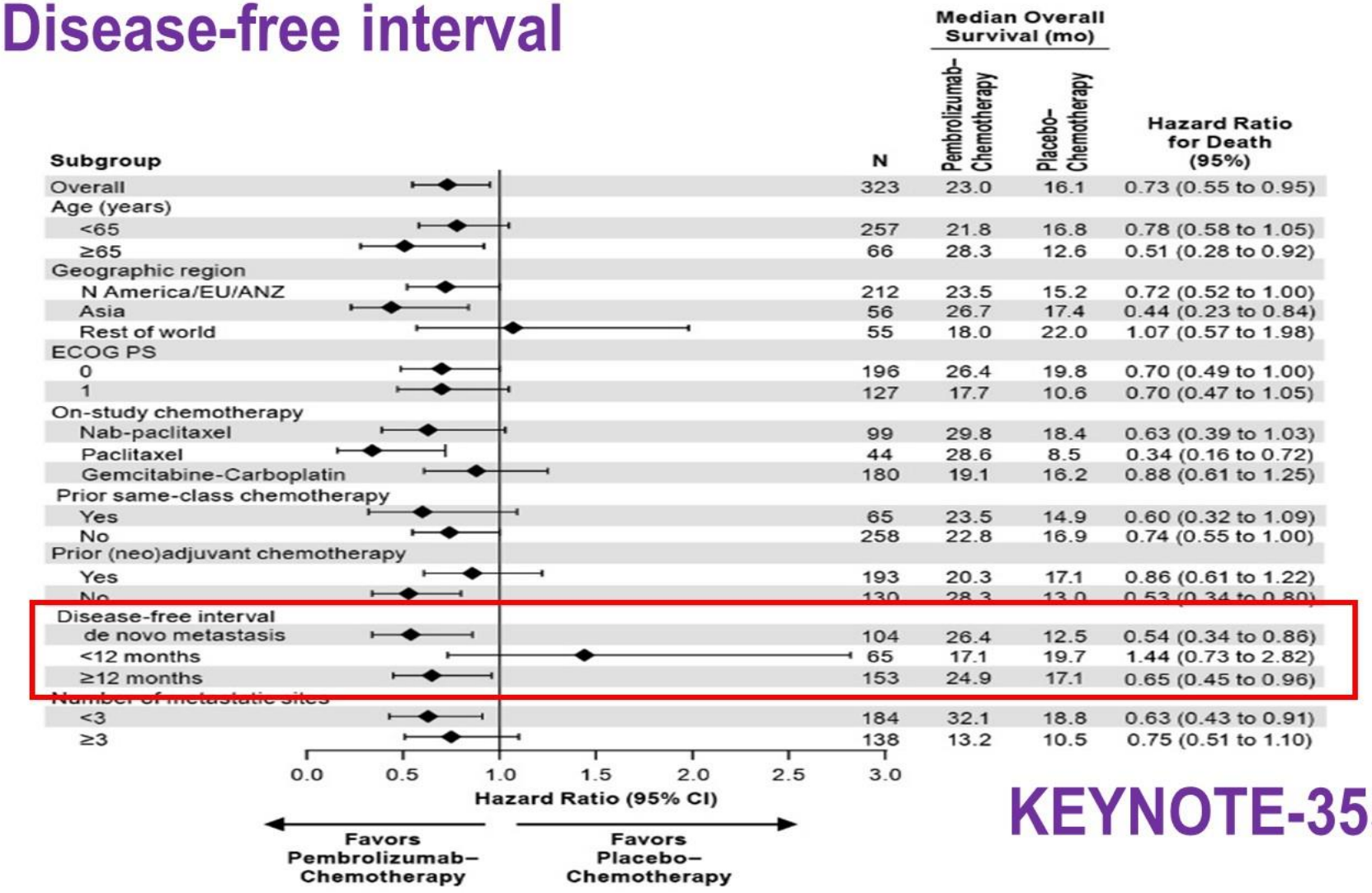
Disease-free interval



KEYNOTE-355 CPS>=10

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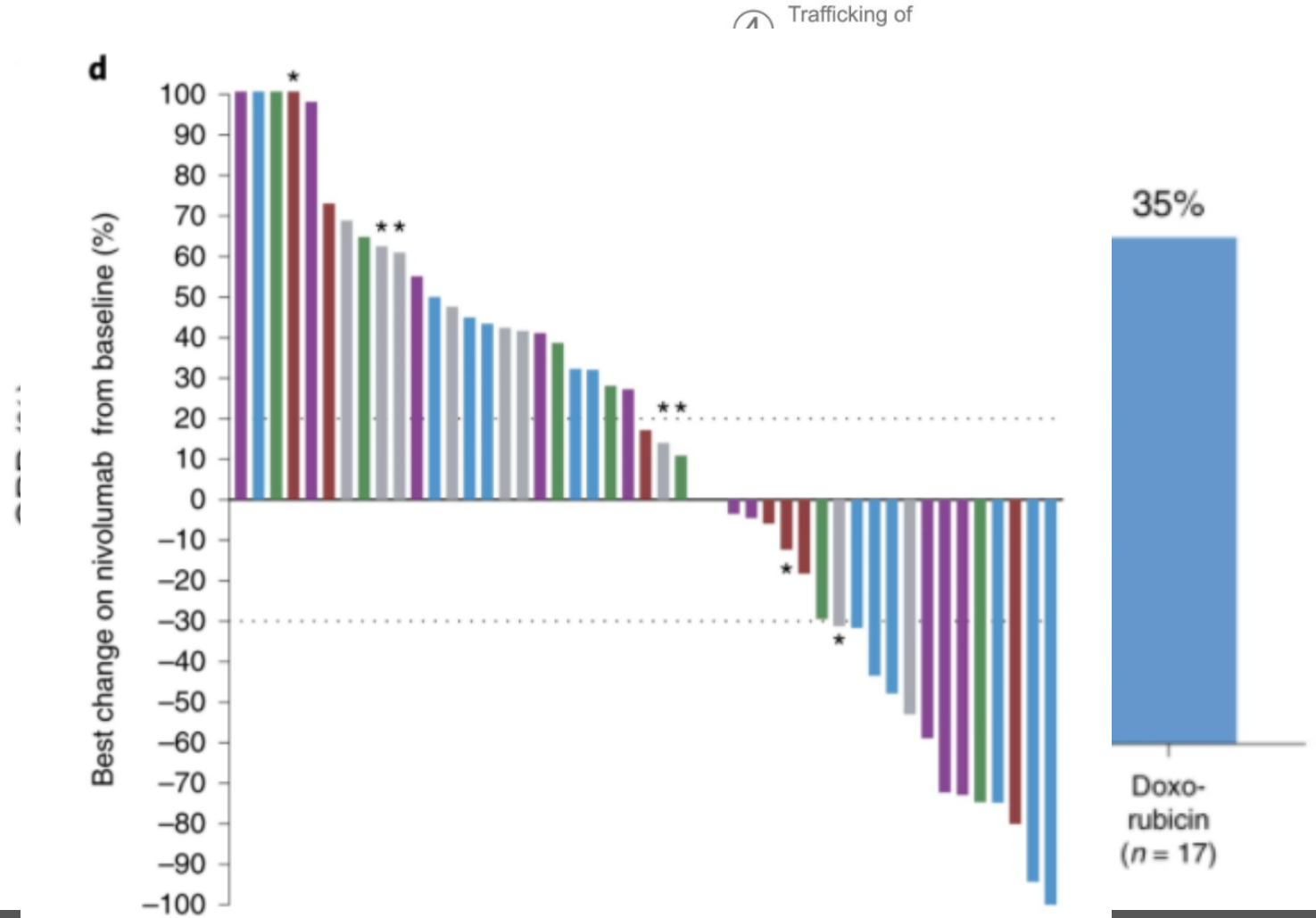
Immunogen celledød – betydning af (kemo)partner til CPI

Tonic trial



Voorwerk, Nature Med 2019

nature medicine

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Article | Open Access | Published: 08 December 2022

Atezolizumab plus anthracycline-based chemotherapy in metastatic triple-negative breast cancer: the randomized, double-blind phase 2b ALICE trial

Andreas Hagen Røssevold, Nikolai Kragøe Andresen, Christina Annette Bjerre, Bjørnar Gilje, Erik Hugger Jakobsen, Sunil Xavier Raj, Ragnhild Sørum Falk, Hege Giercksky Russnes, Thea Jahr, Randi Ruud Mathiesen, Jon Lømo, Øystein Garred, Sudhir Kumar Chauhan, Ragnhild Reehorst Lereim, Claire Dunn, Bjørn Naume & Jon Amund Kyte ✉

Nature Medicine (2022) | Cite this article

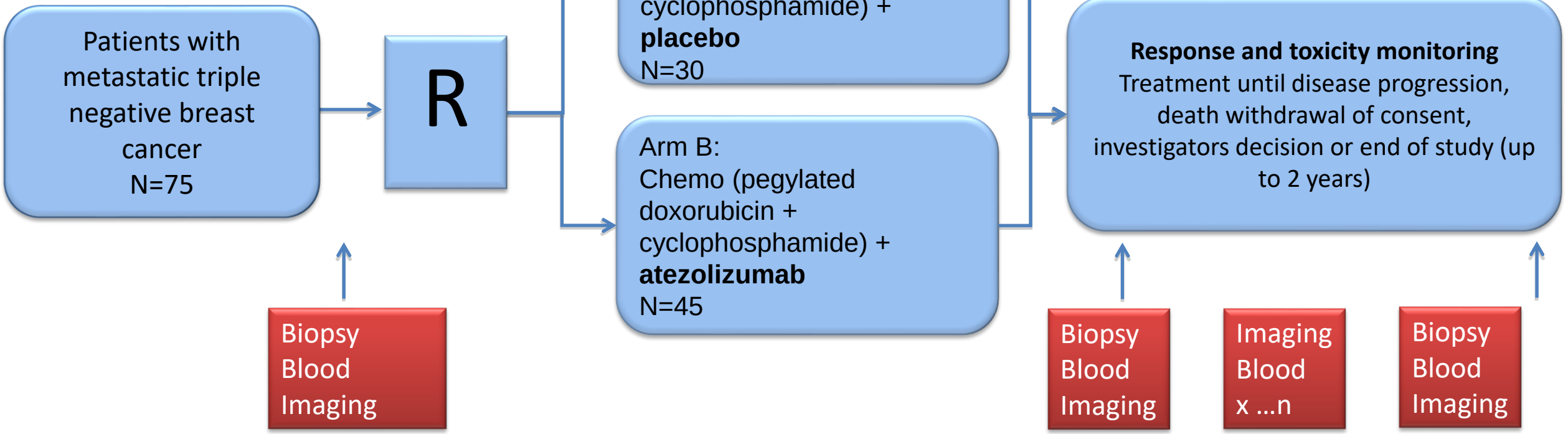
ALICE: Study overview

- Minimum 12 months between treatment with antracyclines or cyclophosphamide and disease relapse
- A maximum of one previous line with chemotherapy in the metastatic setting

- Target 25 DK pts/ 20 pts randomized
- Randomisering aug 2017-dec 2021

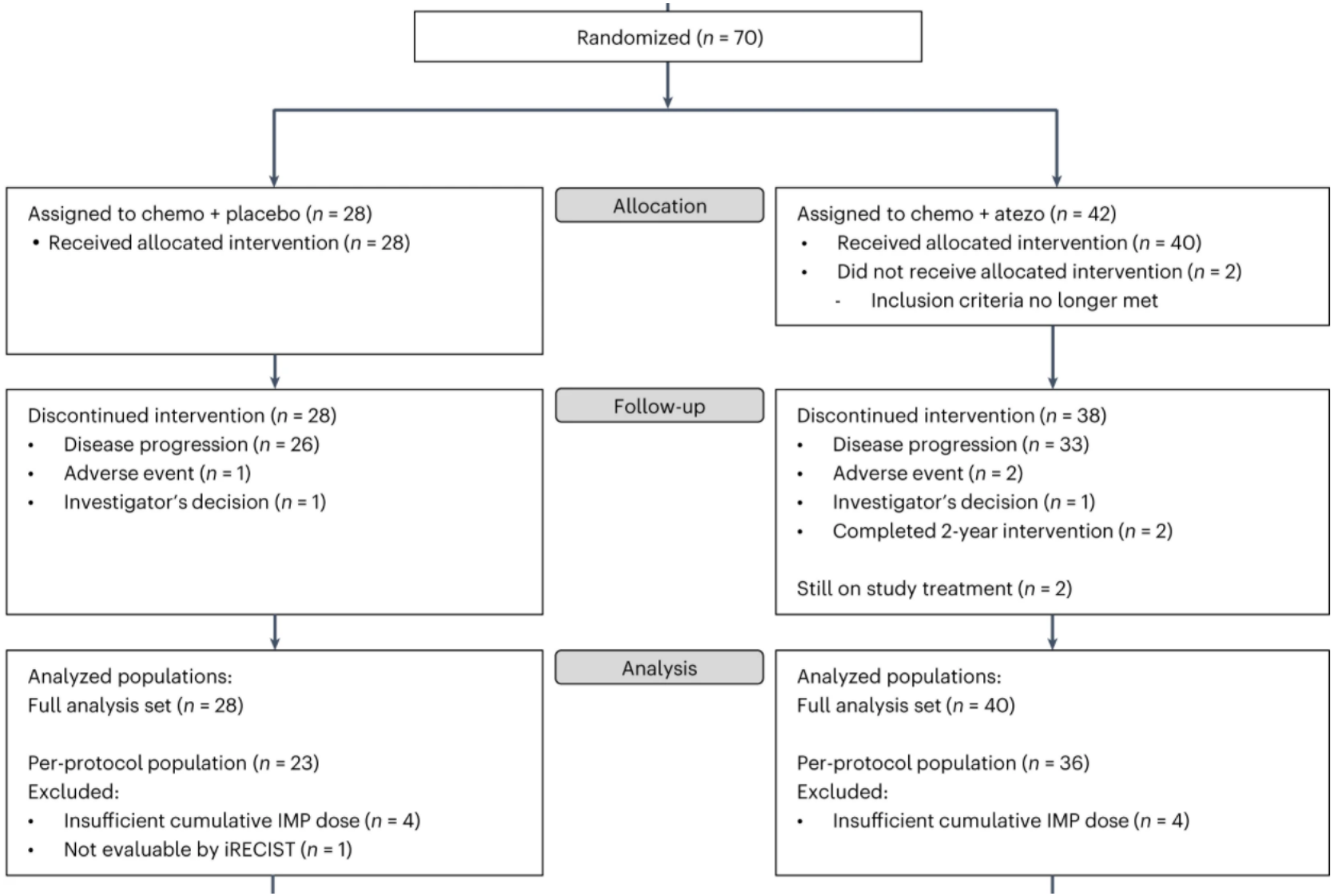
”Metronomic” chemo +/- anti-PD-L1

Translational research

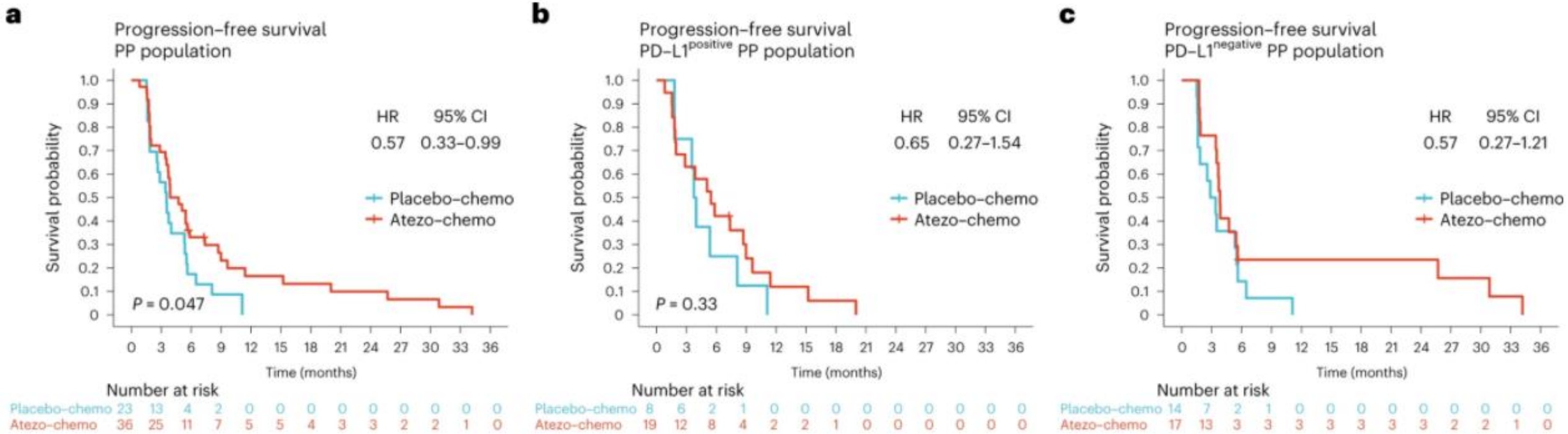


Study treatment

- Atezolizumab (or placebo) intravenously 840mg every 2nd week until disease progression or for a maximum of 24 months
- Pegylated liposomal doxorubicin (PLD; Caelyx) 20mg/m^2 i.v. every 2nd week.
- Cyclophosphamide (Sendoxan) tablets 50 mg per day, daily as continuous treatment for the first 2 weeks in each 4 week period
- No upper limit for the the number of cycles of pegylated liposomal doxorubicin/cyclophosphamide.

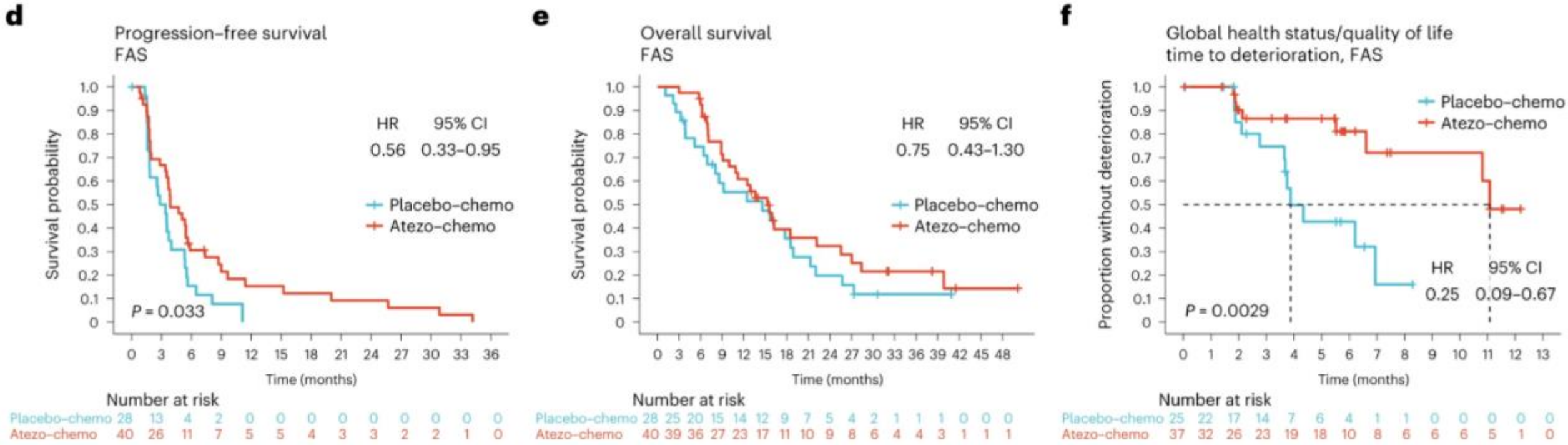

Randomized (n = 70)
Assigned to chemo + placebo (n = 28)
• Received allocated intervention (n = 28)
Allocation
Assigned to chemo + atezo (n = 42)
• Received allocated intervention (n = 40)
• Did not receive allocated intervention (n = 2)
- Inclusion criteria no longer met
Discontinued intervention (n = 28)
• Disease progression (n = 26)
• Adverse event (n = 1)
• Investigator's decision (n = 1)
Follow-up
Discontinued intervention (n = 38)
• Disease progression (n = 33)
• Adverse event (n = 2)
• Investigator's decision (n = 1)
• Completed 2-year intervention (n = 2)
Still on study treatment (n = 2)
Analyzed populations:
Full analysis set (n = 28)
Per-protocol population (n = 23)
Excluded:
• Insufficient cumulative IMP dose (n = 4)
• Not evaluable by iRECIST (n = 1)
Analysis
Analyzed populations:
Full analysis set (n = 40)
Per-protocol population (n = 36)
Excluded:
• Insufficient cumulative IMP dose (n = 4)

	FAS			PP population		
	Placebo-chemo (*n* = 28)	Atezo-chemo (*n* = 40)	*P* value	Placebo-chemo (*n* = 23)	Atezo-chemo (*n* = 36)	*P* value
Line of chemotherapy			0.81			0.37
1st	16 (57.1%)	24 (60.0%)		12 (52.2%)	23 (63.9%)	
2nd	12 (42.9%)	16 (40.0%)		11 (47.8%)	13 (36.1%)	
Previous anthracycline treatment			0.90			0.71
Yes	20 (71.4%)	28 (70.0%)		17 (73.9%)	25 (69.4%)	
No	8 (28.6%)	12 (30.0%)		6 (26.1%)	11 (30.6%)	
PD-L1 status			0.22			0.22
Negative	17 (60.7%)	19 (47.5%)		14 (60.9%)	17 (47.2%)	
Positive	10 (35.7%)	21 (52.5%)		8 (34.8%)	19 (52.8%)	
Missing	1 (3.6%)	0 (0%)		1 (4.3%)	0 (0%)	
Intrinsic breast cancer subtype			0.44			0.48
Luminal A	2 (7.1%)	0 (0%)		2 (8.7%)	0 (0%)	
Luminal B	1 (3.6%)	1 (2.5%)		1 (4.3%)	1 (2.8%)	
HER2-enriched	2 (7.1%)	4 (10.0%)		2 (8.7%)	4 (11.1%)	
Basal	12 (42.9%)	22 (55.0%)		11 (47.8%)	20 (55.6%)	
Missing	11 (39.3%)	13 (32.5%)		7 (30.4%)	11 (30.6%)	
***BRCA* mutation status**			0.54			0.54
BRCA1 mutation	1 (3.6%)	2 (5.0%)		1 (4.3%)	2 (5.6%)	
Normal variant	12 (42.9%)	22 (55.0%)		11 (47.8%)	22 (61.1%)	
Missing	15 (53.6%)	16 (40.0%)		11 (47.8%)	12 (33.3%)	

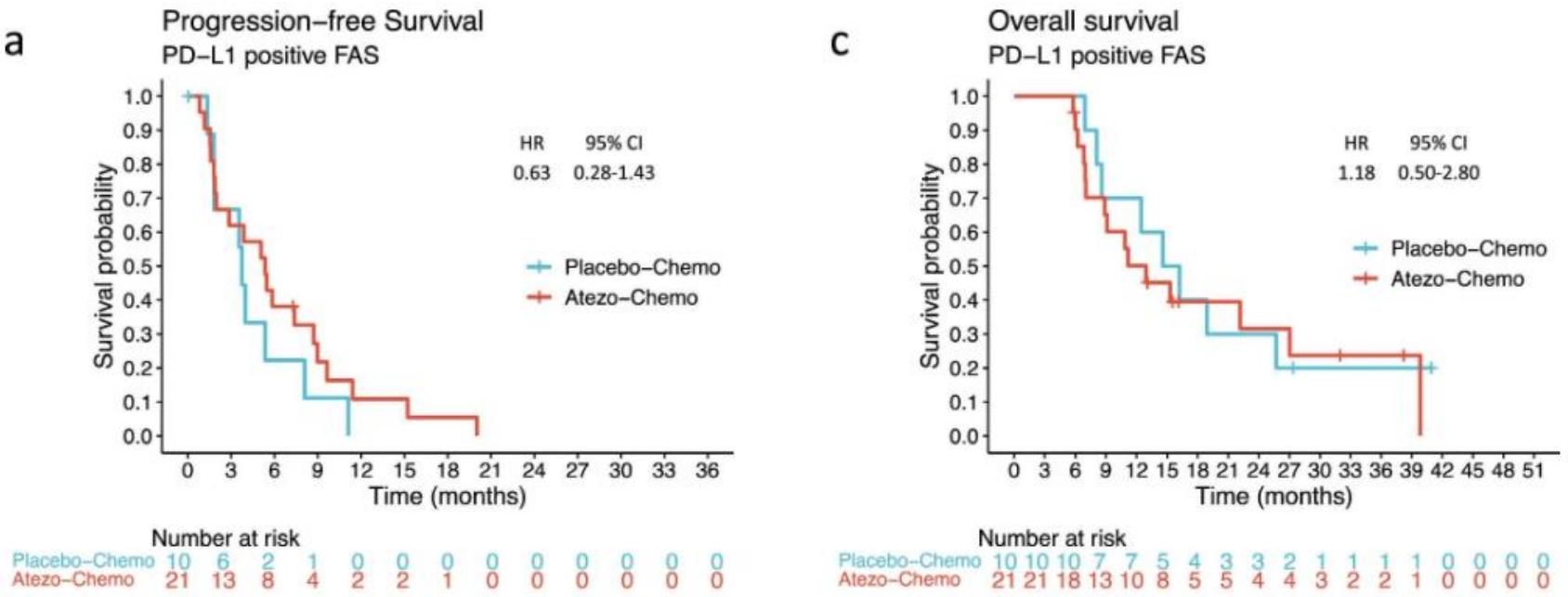


"PFS per protocol population (median 4.3 months versus 3.5 months; hazard ratio (HR) = 0.57; 95% confidence interval (CI) 0.33–0.99; log-rank *P* = 0.047
The progression-free proportion after 15 months was 14.7% (5/34; 95% CI 6.4–30.1%) in the atezo-chemo arm versus 0% in the placebo-chemo arm"

"Interestingly, the PFS advantage appears to apply even to the PD-L1negative population, and the three patients with >24-month PFS in the PD-L1negative group had all been randomized to the atezo-chemo arm."


d
Progression-free survival
FAS
Survival probability
HR 95% CI
0.56 0.33–0.95
Placebo–chemo
Atezo–chemo
P = 0.033
Time (months)
Number at risk
Placebo–chemo 28 13 4 2 0 0 0 0 0 0 0 0 0
Atezo–chemo 40 26 11 7 5 5 4 3 3 2 2 1 0
e
Overall survival
FAS
Survival probability
HR 95% CI
0.75 0.43–1.30
Placebo–chemo
Atezo–chemo
Time (months)
Number at risk
Placebo–chemo 28 25 20 15 14 12 9 7 5 4 2 1 1 1 0 0 0
Atezo–chemo 40 39 36 27 23 17 11 10 9 8 6 4 4 3 1 1 1
f
Global health status/quality of life
time to deterioration, FAS
Proportion without deterioration
Placebo–chemo
Atezo–chemo
HR 95% CI
0.25 0.09–0.67
P = 0.0029
Time (months)
Number at risk
Placebo–chemo 25 22 17 14 7 6 4 1 1 0 0 0 0 0
Atezo–chemo 37 32 26 23 19 18 10 8 6 6 6 5 1 0

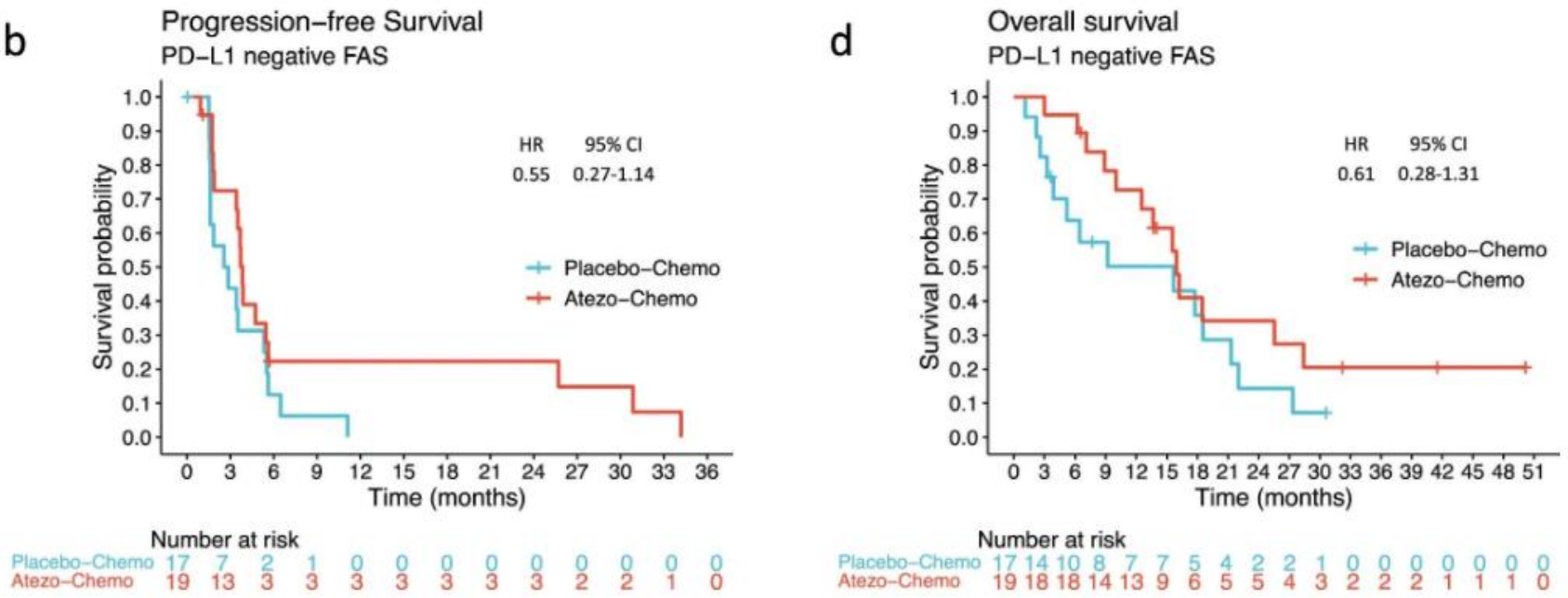
a


Progression–free Survival
PD–L1 positive FAS
Survival probability
HR 95% CI
0.63 0.28-1.43
Placebo–Chemo
Atezo–Chemo
Time (months)
Number at risk
Placebo–Chemo 10 6 2 1 0 0 0 0 0 0 0 0 0
Atezo–Chemo 21 13 8 4 2 2 1 0 0 0 0 0 0

c

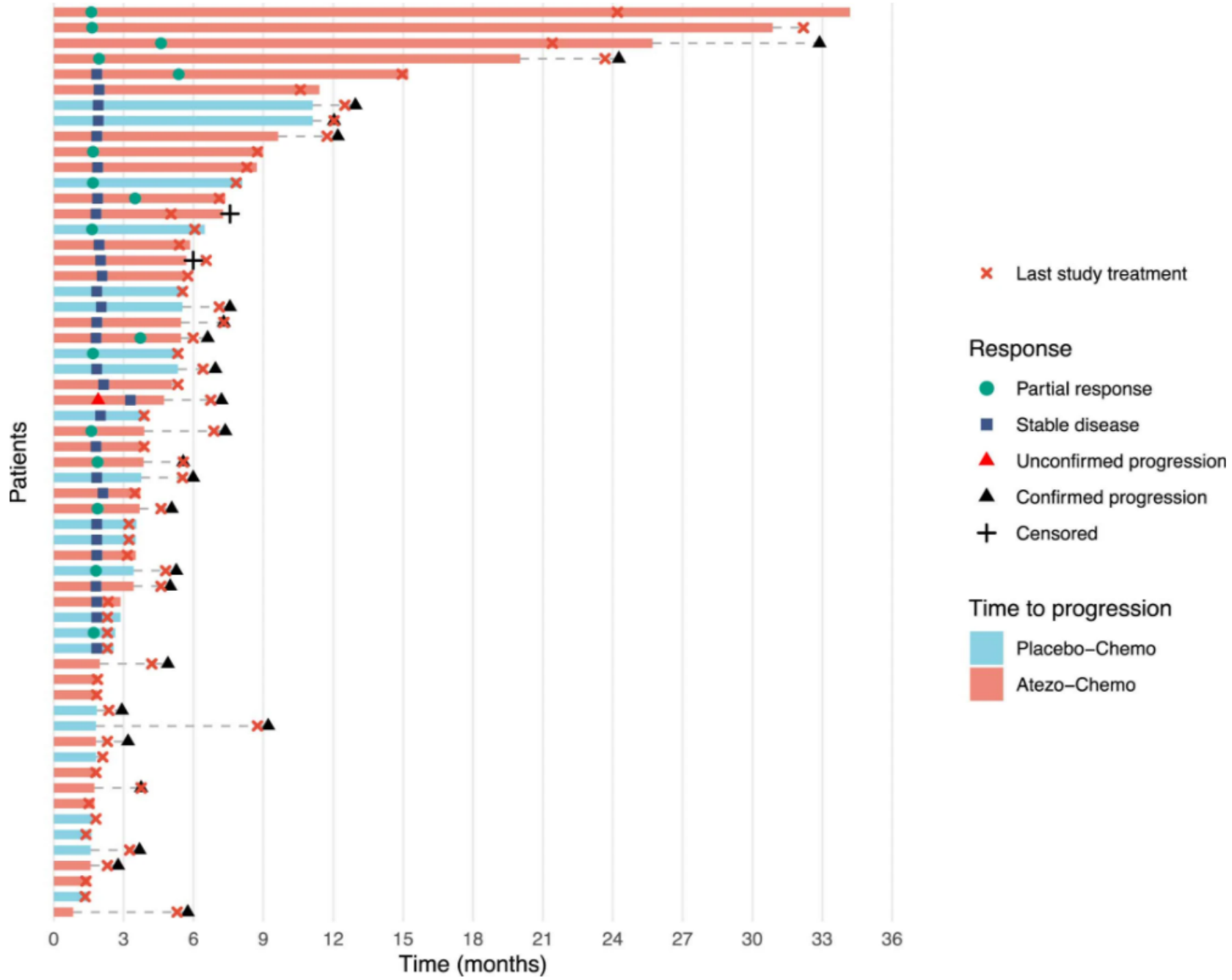
Overall survival
PD–L1 positive FAS
Survival probability
HR 95% CI
1.18 0.50-2.80
Placebo–Chemo
Atezo–Chemo
Time (months)
Number at risk
Placebo–Chemo 10 10 10 7 7 5 4 3 3 2 1 1 1 1 0 0 0 0
Atezo–Chemo 21 21 18 13 10 8 5 5 4 4 3 2 2 1 0 0 0 0

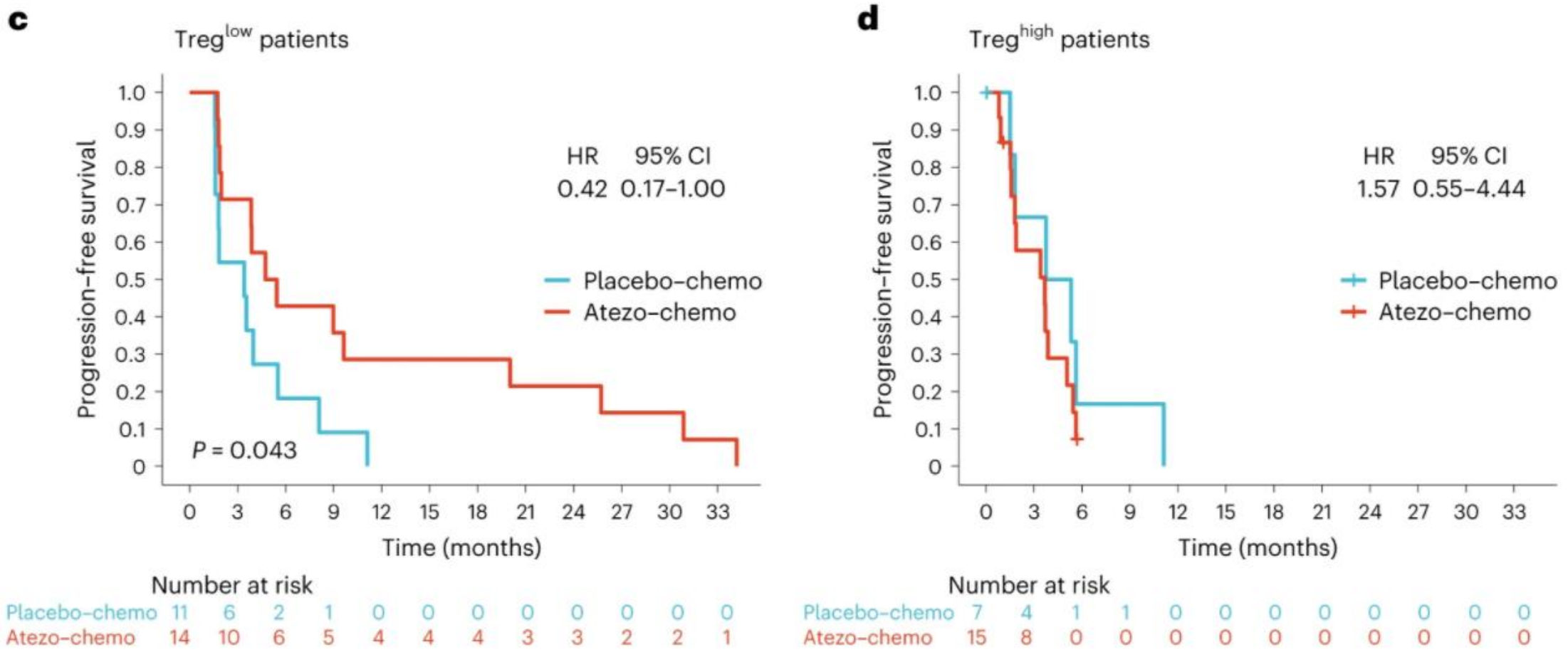
b


Progression–free Survival
PD–L1 negative FAS
Survival probability
HR 95% CI
0.55 0.27-1.14
Placebo–Chemo
Atezo–Chemo
Time (months)
Number at risk
Placebo–Chemo 17 7 2 1 0 0 0 0 0 0 0 0 0
Atezo–Chemo 19 13 3 3 3 3 3 3 3 2 2 1 0

d

Overall survival
PD–L1 negative FAS
Survival probability
HR 95% CI
0.61 0.28-1.31
Placebo–Chemo
Atezo–Chemo
Time (months)
Number at risk
Placebo–Chemo 17 14 10 8 7 7 5 4 2 2 1 0 0 0 0 0 0 0
Atezo–Chemo 19 18 18 14 13 9 6 5 5 4 3 2 2 2 1 1 1 0


Patients
0
3
6
9
12
15
18
21
24
27
30
33
36
Time (months)
Last study treatment
Response
Partial response
Stable disease
Unconfirmed progression
Confirmed progression
Censored
Time to progression
Placebo–Chemo
Atezo–Chemo


c
Treg^low patients
Progression-free survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
HR 95% CI
0.42 0.17–1.00
Placebo–chemo
Atezo–chemo
P = 0.043
0 3 6 9 12 15 18 21 24 27 30 33
Time (months)
Number at risk
Placebo–chemo 11 6 2 1 0 0 0 0 0 0 0 0
Atezo–chemo 14 10 6 5 4 4 4 3 3 2 2 1
d
Treg^high patients
Progression-free survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
HR 95% CI
1.57 0.55–4.44
Placebo–chemo
Atezo–chemo
0 3 6 9 12 15 18 21 24 27 30 33
Time (months)
Number at risk
Placebo–chemo 7 4 1 1 0 0 0 0 0 0 0 0
Atezo–chemo 15 8 0 0 0 0 0 0 0 0 0 0

Små tal - men

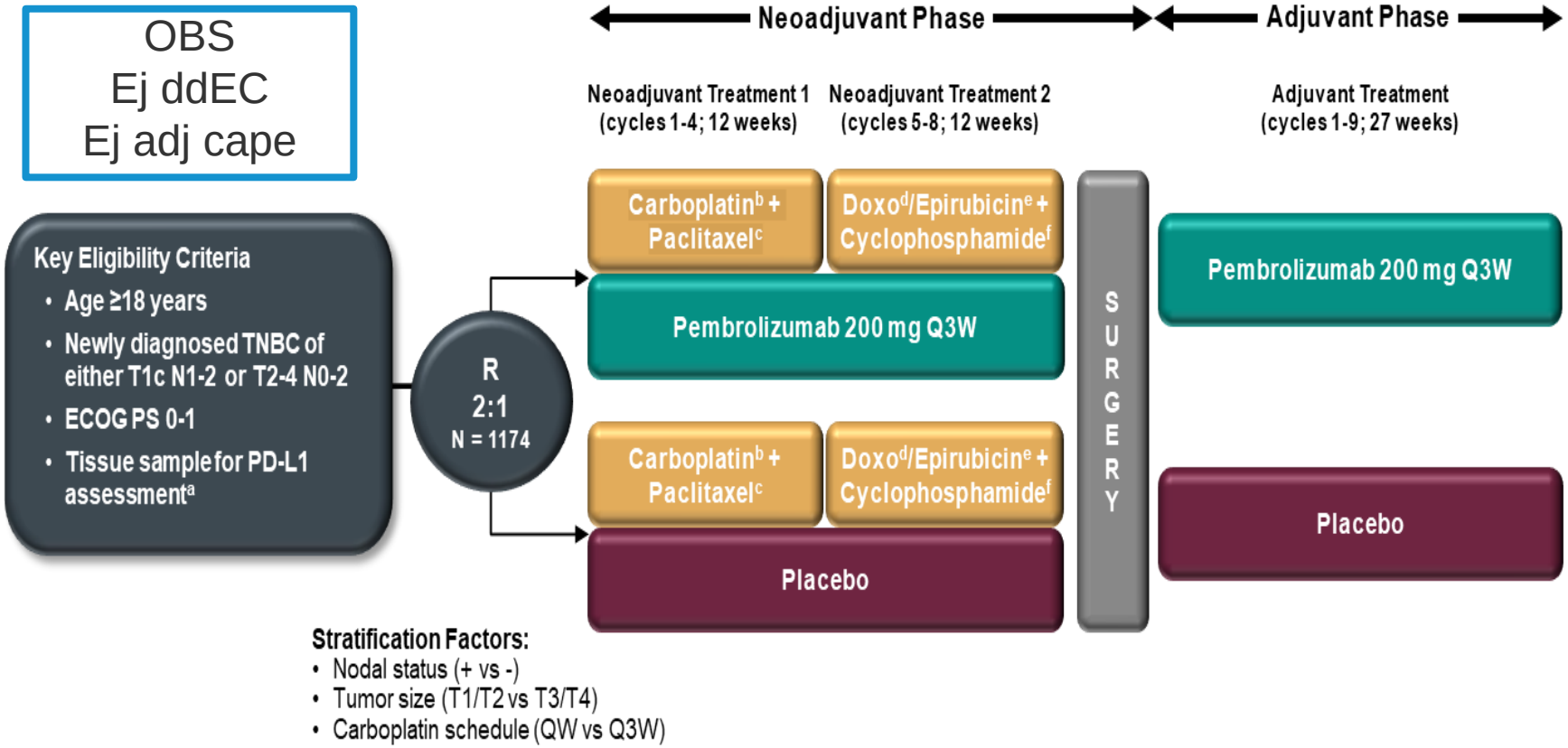
- Første data på antracyclin+CPI i mTNBC, ej standard regime
- Lille gruppe af long term responders
- Effekt hos PDL1neg pt?
- Translationelle del – prædiktive markører, ”making cold tumors hot”

Agenda

- Introduktion
- Immunterapi til behandling af mTNBC
  - ALICE studiet
- **Immunterapi til behandling af eTNBC**
- Opsummerering og ”next wave” immunterapi til brystkræft

Keynote 522

OBS
Ej ddEC
Ej adj cape



Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post treatment included)

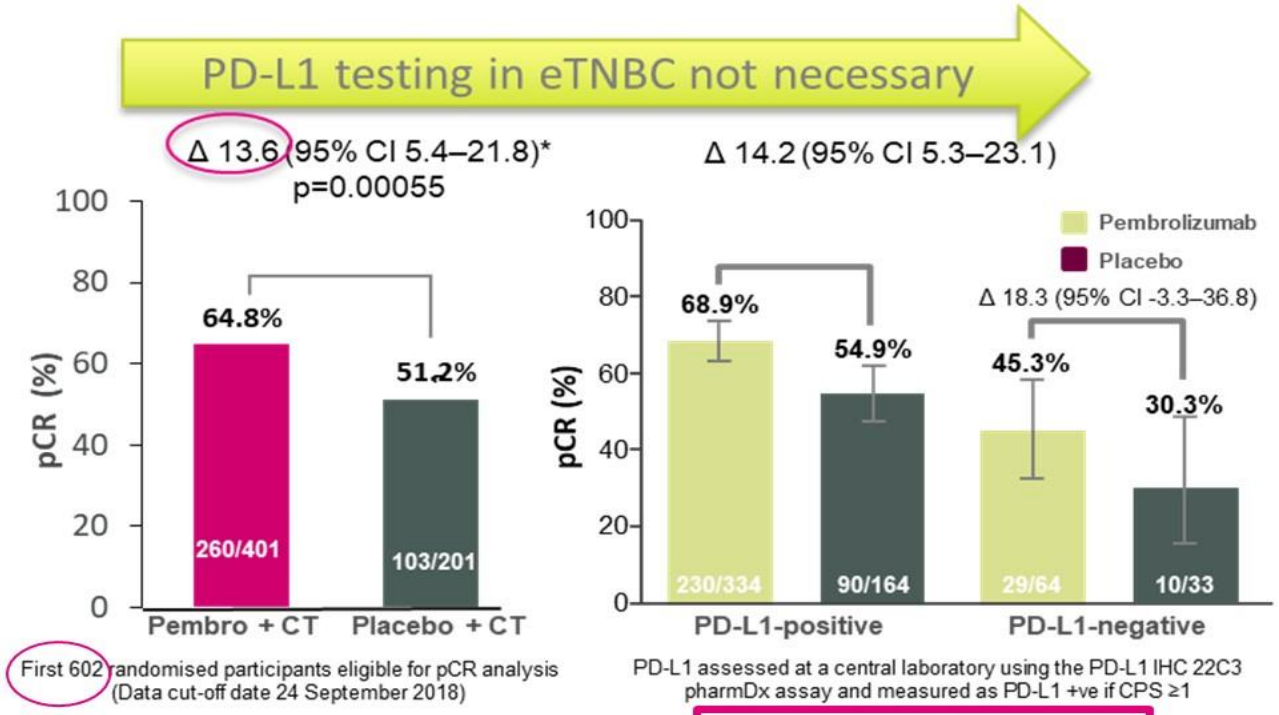
Adjuvant phase: starts from the first adjuvant treatment and includes radiation therapy as indicated (post treatment included)

Schmid ,NJEM 2020

KN 522 pCR results

KEYNOTE-522[1] (IA1)
Pembrolizumab + CT vs placebo + CT in early TNBC

PD-L1 testing in eTNBC not necessary

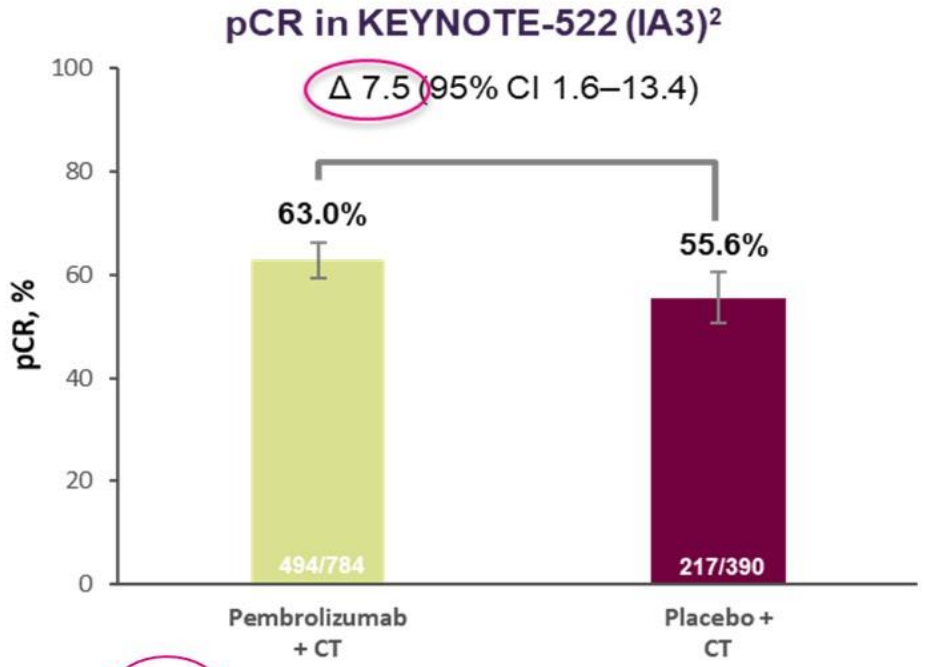


First 602 randomised participants eligible for pCR analysis (Data cut-off date 24 September 2018)

PD-L1 assessed at a central laboratory using the PD-L1 IHC 22C3 pharmDx assay and measured as PD-L1 +ve if CPS ≥1

83% PD-L1 +

KEYNOTE-522 (IA3)*[2]
Pembrolizumab + CT vs placebo + CT in early TNBC



All 1174 participants in ITT (Data cut-off date 23 March 2020,

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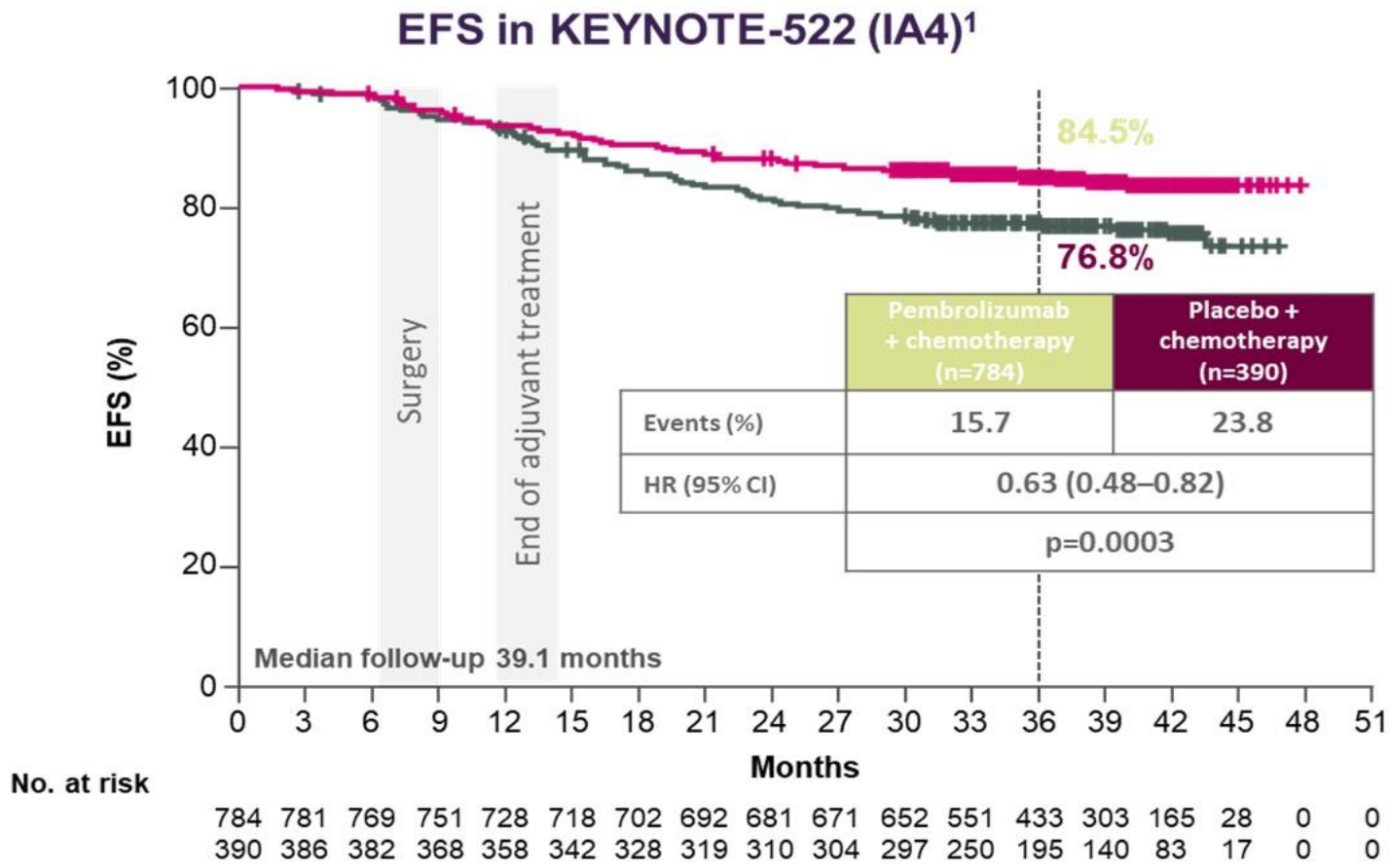
EFS KN 522

KEYNOTE-522[1] (IA4)
Pembrolizumab + CT vs placebo + CT in early TNBC

PD-L1$_{\text{-negative}}$ (HR 0.48, 95% CI 0.28–0.85)

PD-L1$_{\text{+ positive}}$ (HR 0.67, 95% CI 0.49–0.92)



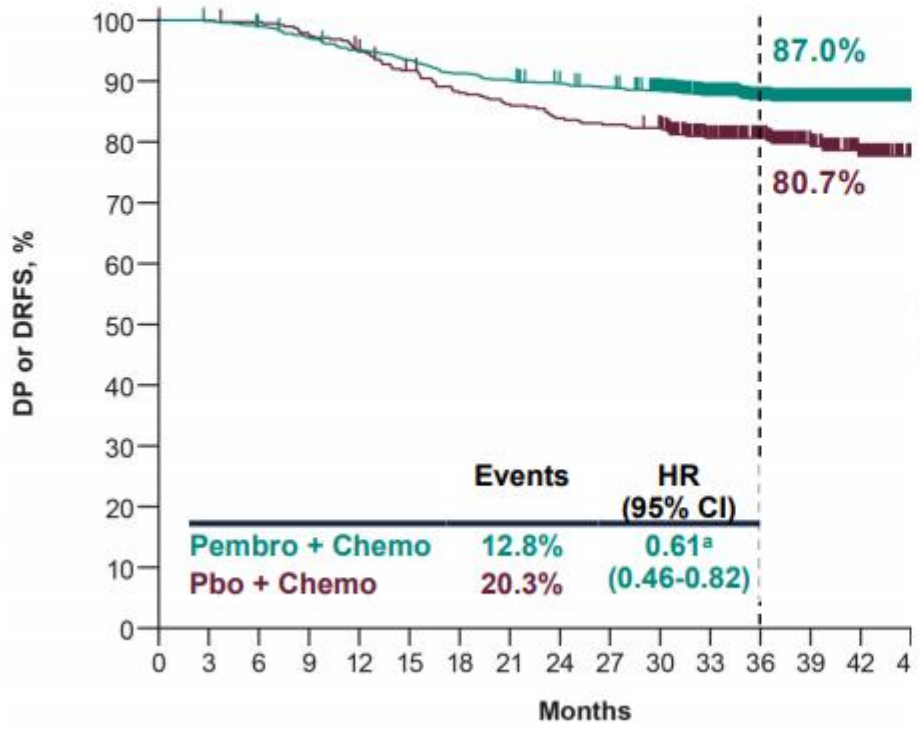
Schmid P et al. New Engl J Med 2022

KN522

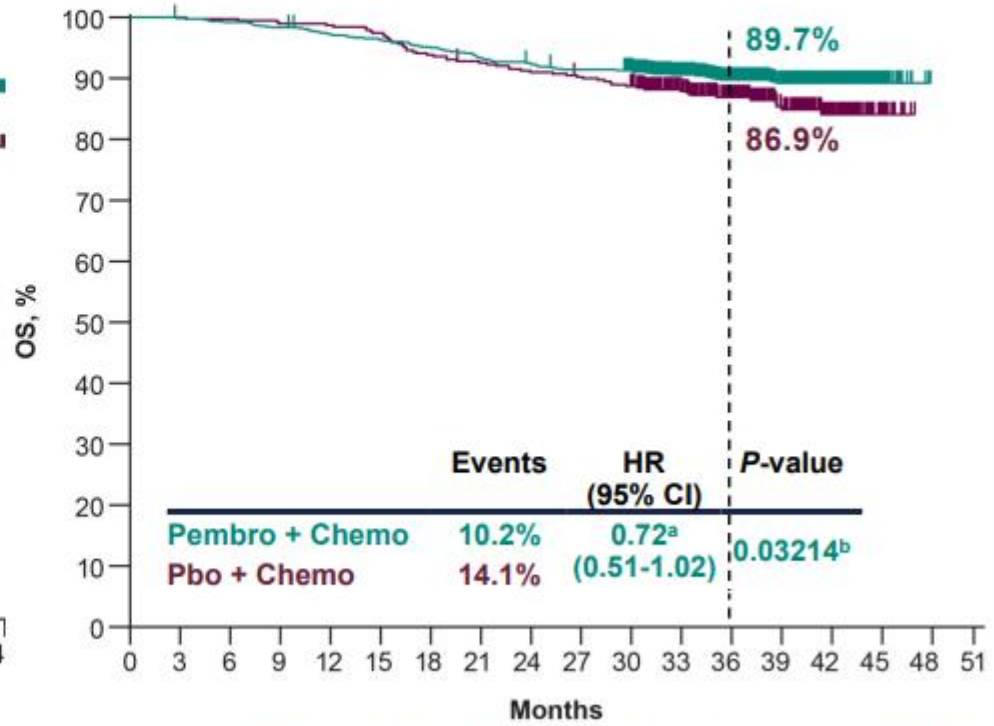
San Antonio Breast Cancer Symposium*, December 6-10, 2022

Neoadjuvant CIT in TNBC: Distant RFS and Overall Survival

Distant Recurrence-Free Survival

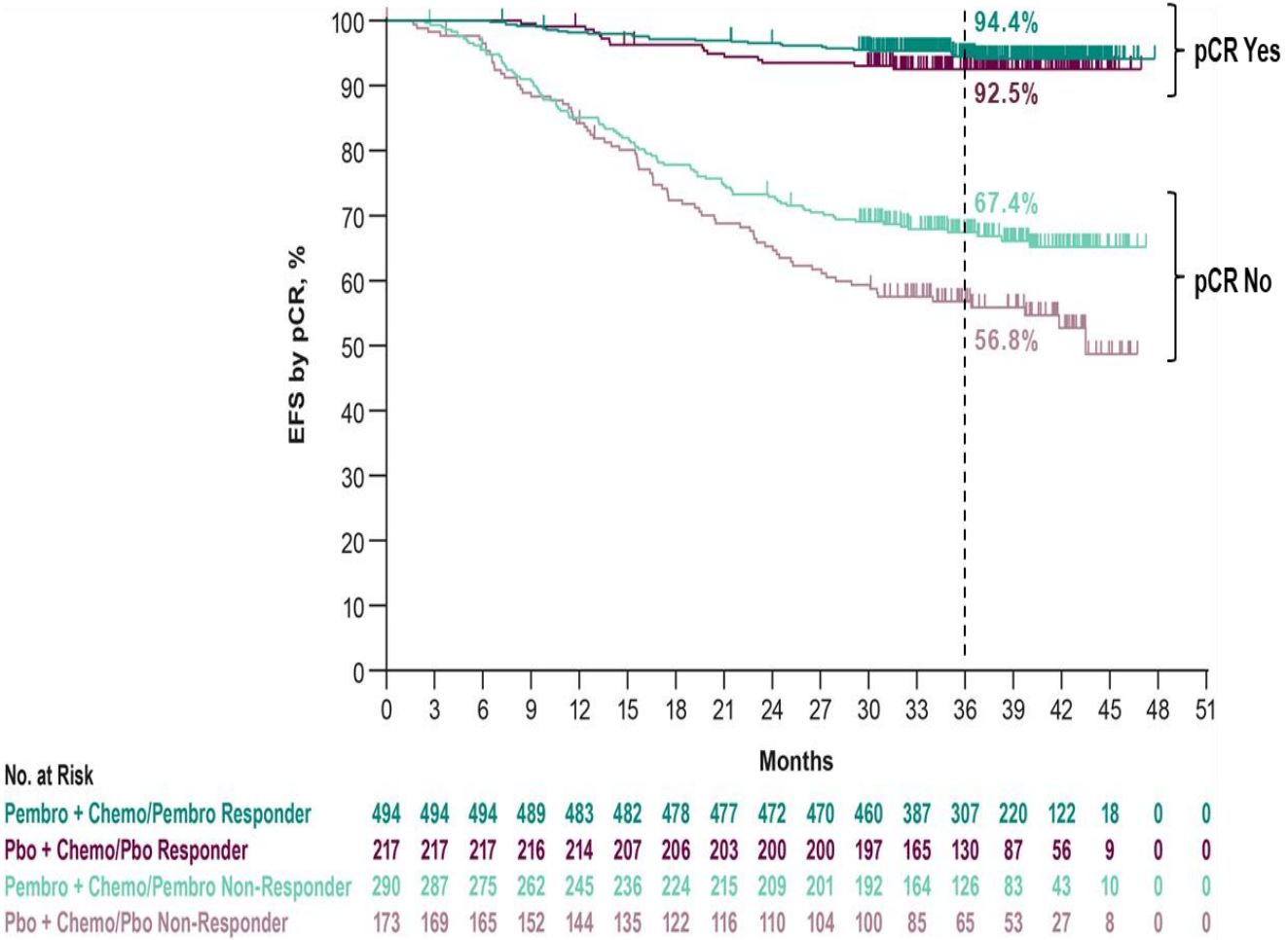


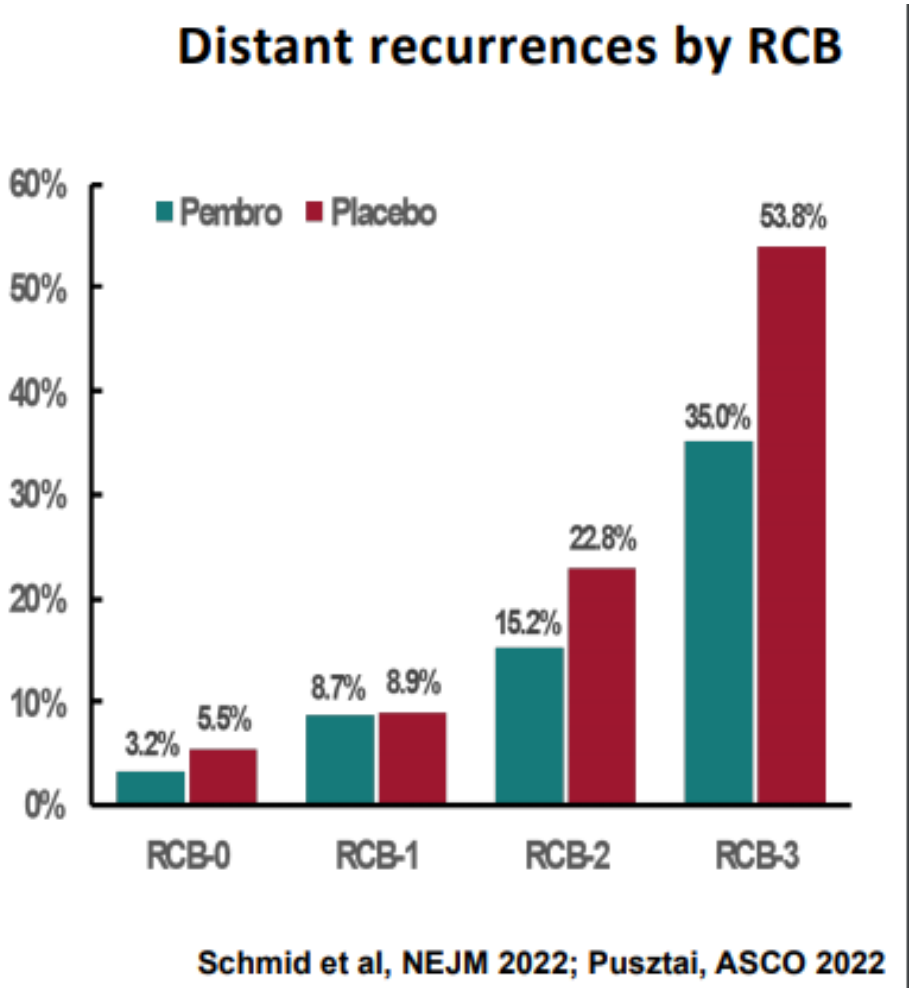
Overall Survival



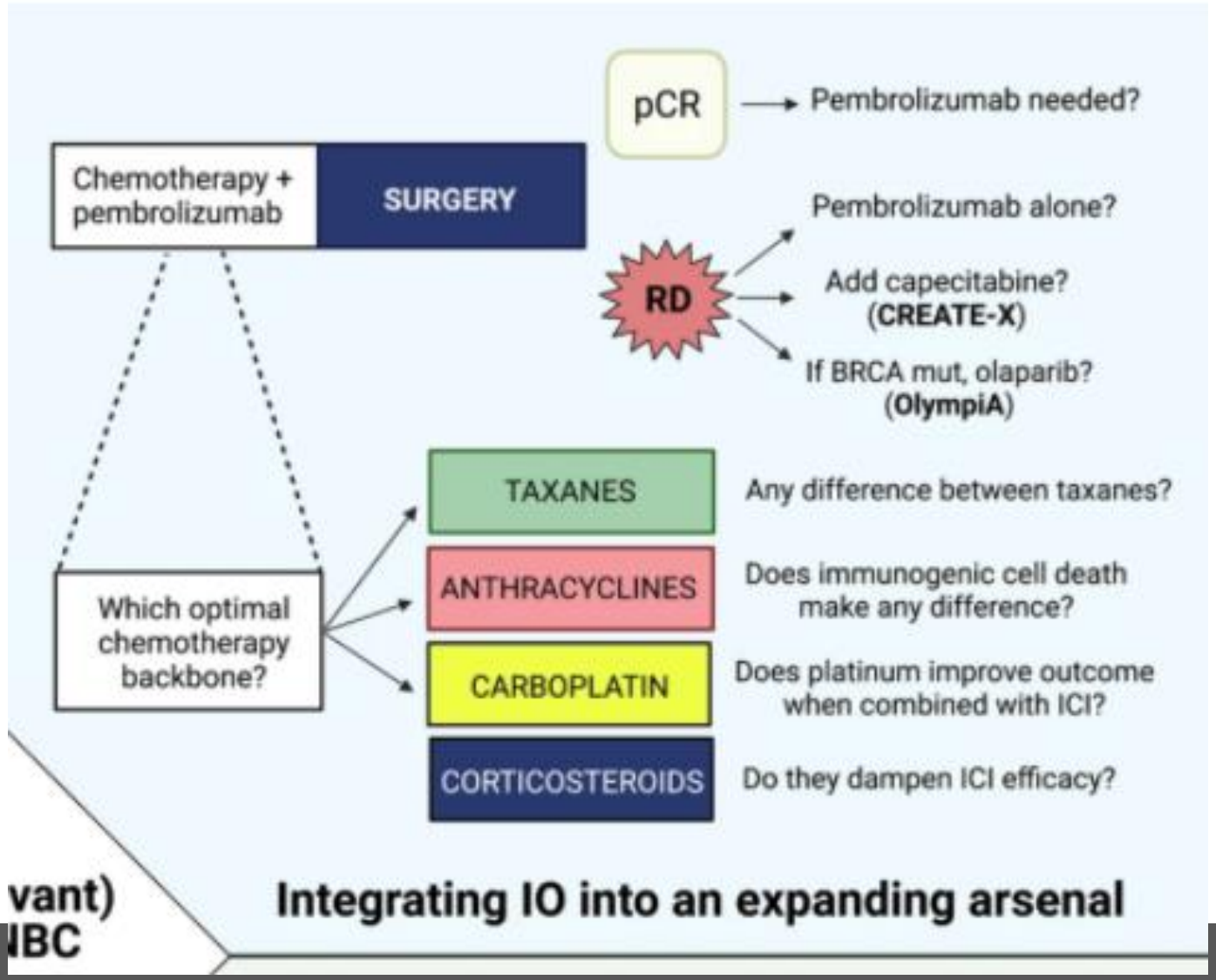
Schmid, et al NEJM 2020, Schmid et al, ESMO 2021, Schmid et al, NEJM 2022

KN522 EFS by pCR



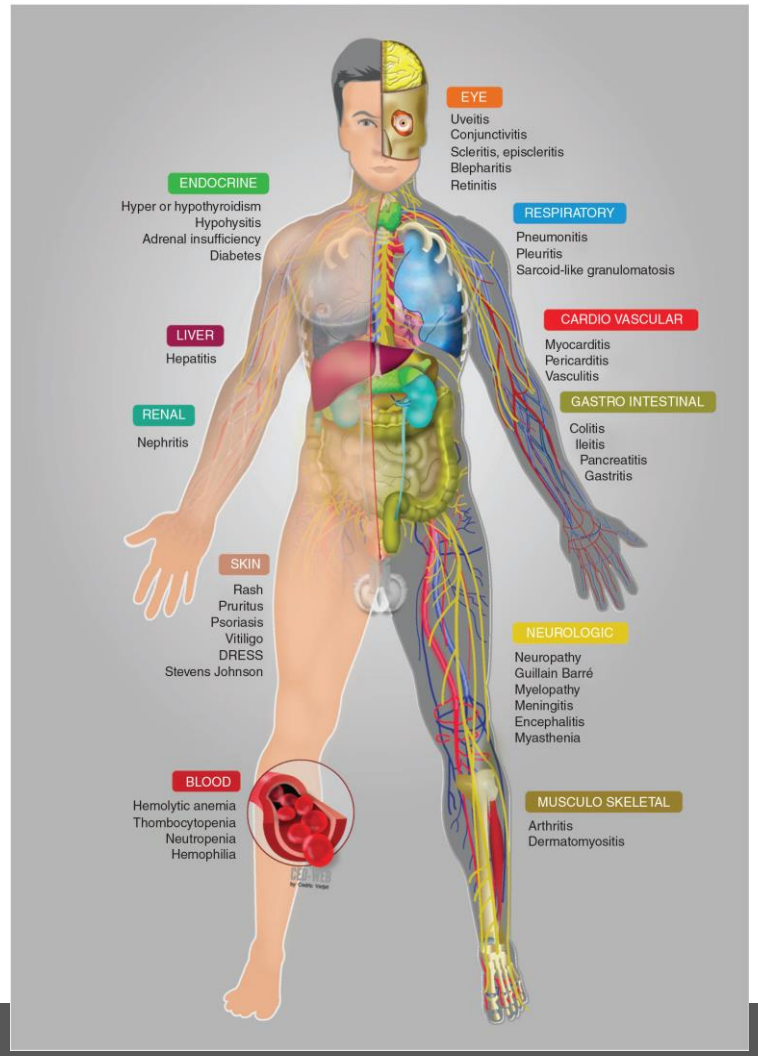


Schmid et al, NEJM 2022; Pusztai, ASCO 2022



Tarantino, npj breast cancer 2022

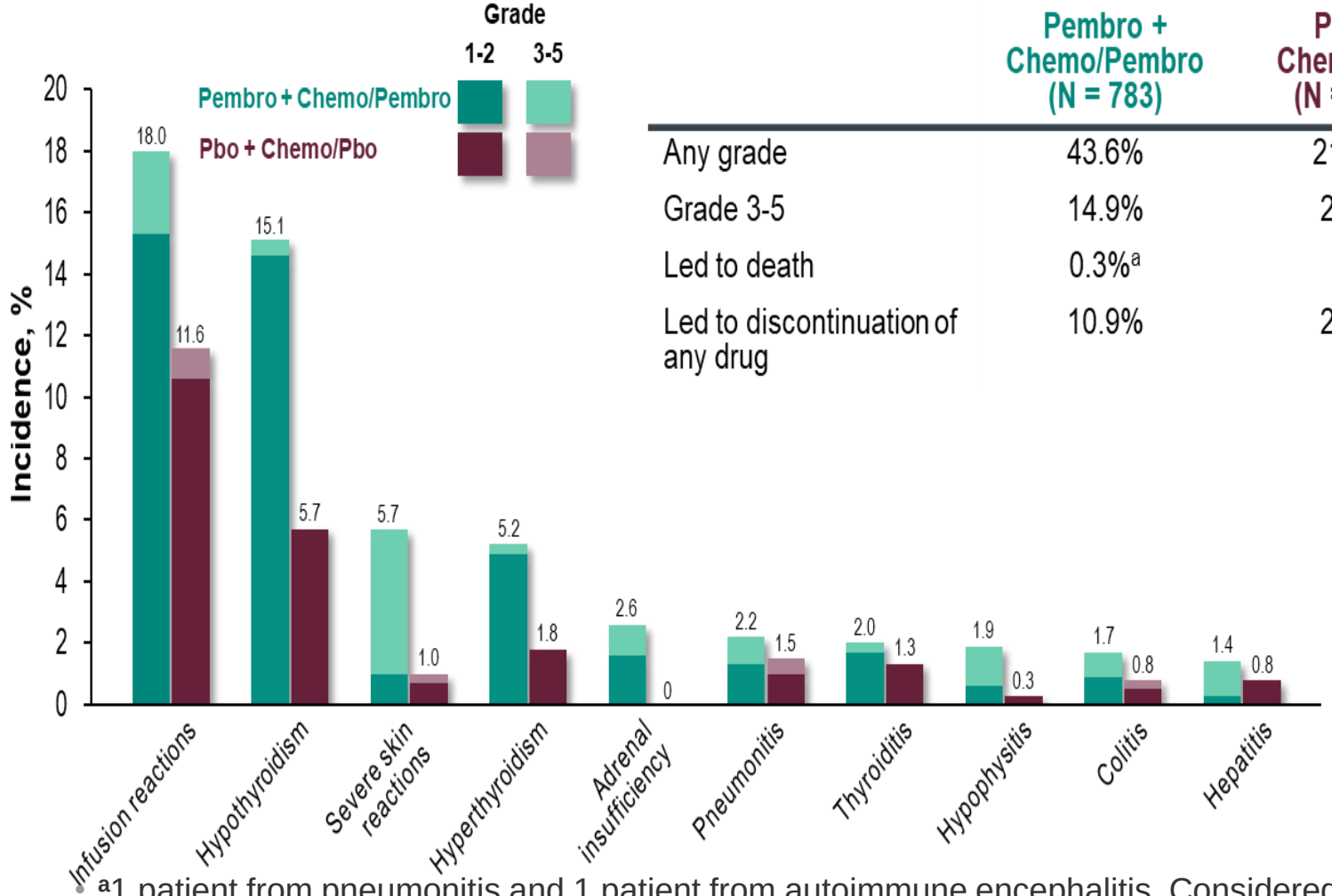
Bagsiden af medaljen – bivirkninger!



- Andet bivirkningsspektrum end kemoterapi og endokrin behandling
- Risiko for livstruende bivirkninger
- Risiko for kroniske bvirkninger
- Pt med eksisterende autoimmune sygdomme?
- Uddannelse af sundhedspersonale og patienter
- Samarbejde på tværs af specialer

Champiat, Ann Oncol 2016

KN522 – immune mediated AEs and infusion reactions



	Pembro + Chemo/Pembro (N = 783)	Pbo + Chemo/Pbo (N = 389)
Any grade	43.6%	21.9%
Grade 3-5	14.9%	2.1%
Led to death	0.3%[a]	0
Led to discontinuation of any drug	10.9%	2.6%

Schmid, ESMO VP 2021

[a]1 patient from pneumonitis and 1 patient from autoimmune encephalitis. Considered regardless of attribution to treatment or immune relatedness by the investigator

Agenda

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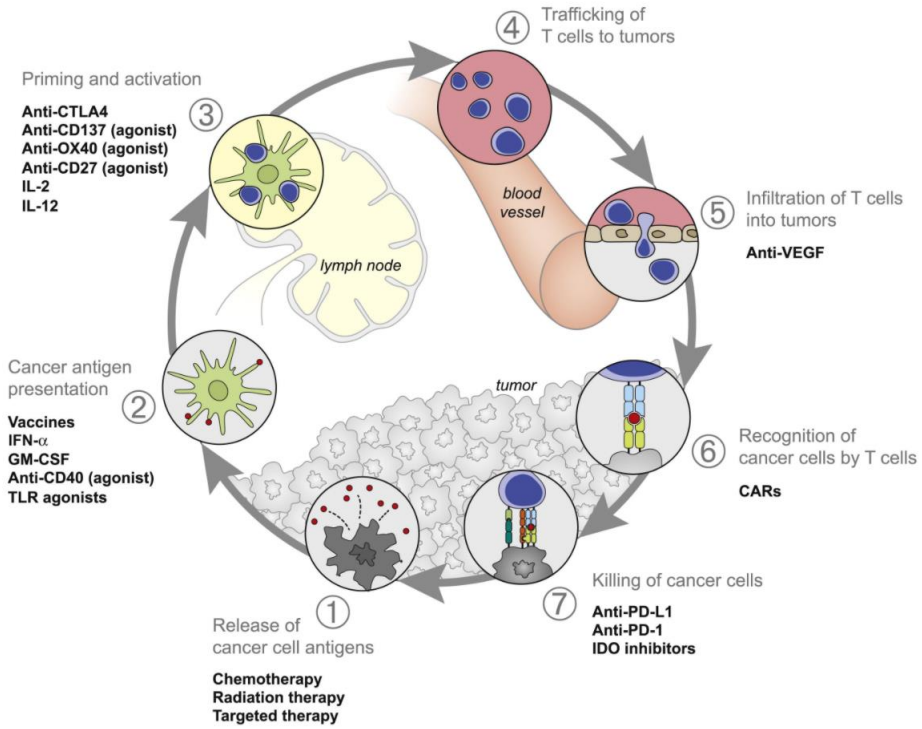
  - ALICE studiet
- Immunterapi til behandling af eTNBC
- **Opsummerering og ”next wave” immunterapi til brystkræft**

Opsummering (1)

- PDL1+ mTNBC
  - PDL1 prædiktiv for repsons
  - CPIs (atezolizumab eller pembrolizumab) + kemoterapi øger OS i 1 linie mTNBC
- eTNBC
  - Tillæg af CPI til neoadjuverende kemoterapi øger pCR og EFS
  - Er adjuverende CPI nødvendig ved pCR
  - Integration med adjuverende capecitabine? PARPi?
- Bivirkninger vs benefit

Opsummering (2)

- Behov for prædiktive markører udover PDL1
  - TILs, TMB, genekspressionsprofiler
  - Mulighed for de-eskalation
- Kombinationsbehandling
  - Optimering af kemobackbone
  - Kombination med PARPi, CDK4/6i, ADCs
- Immunterapi til ER+ og/eller HER2+ sygdom

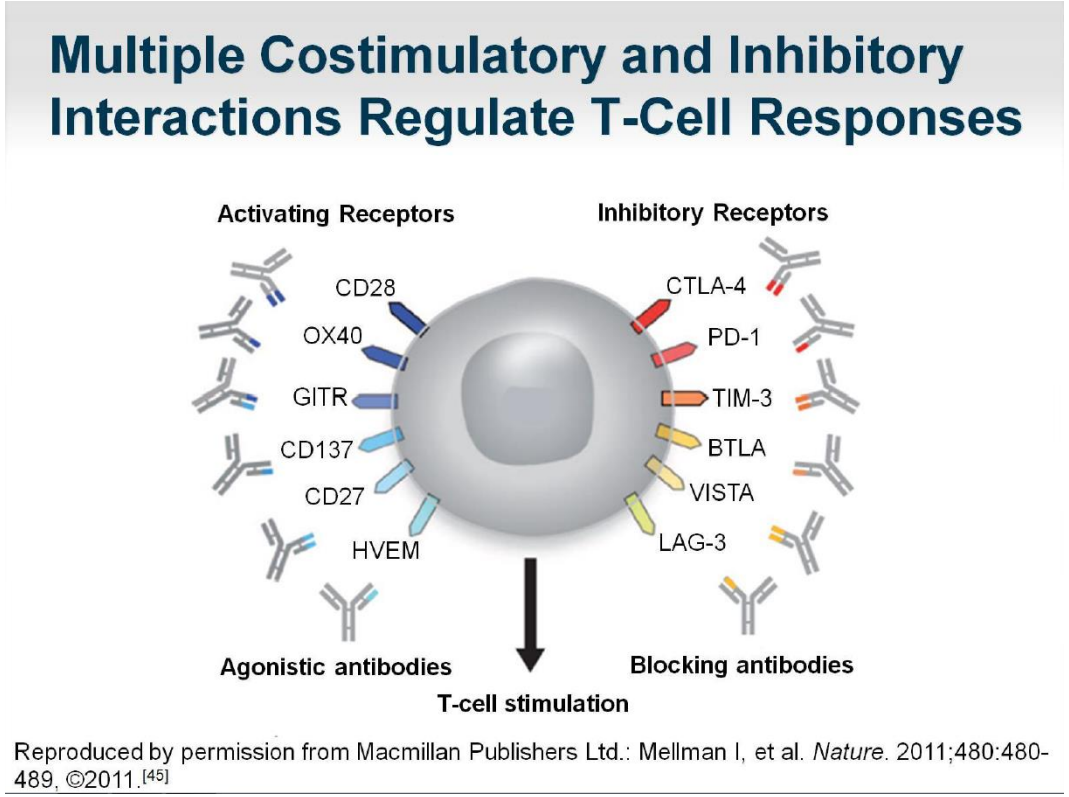


Chen, Immunity 2013

RO7247669
anti-PD-1/anti-LAG-3 bispecific antibody til 1L PDL1+ mTNBC

RO7247669 targets and binds to both PD-1 and LAG-3 expressed on T-cells and inhibits the PD-1- and LAG-3-mediated downregulation of T-cell activation and proliferation.

Synergi?
Forhindre resistens?



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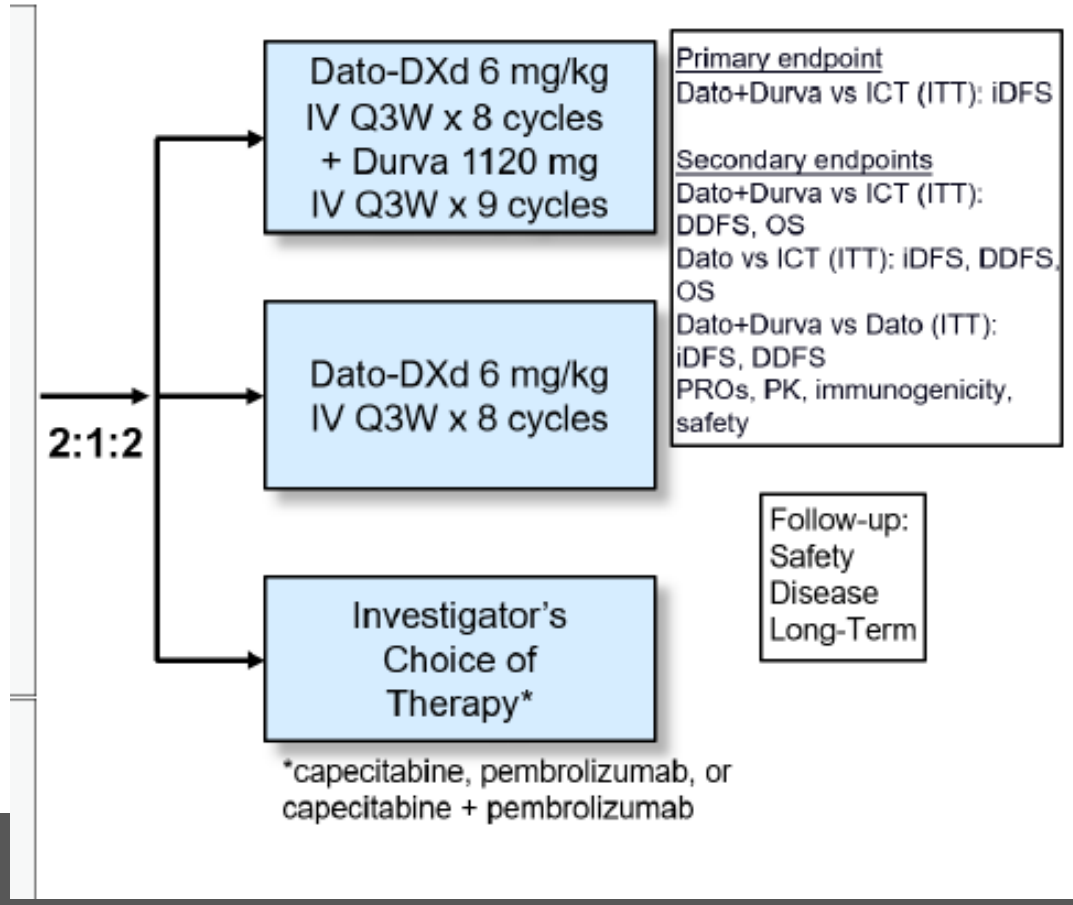
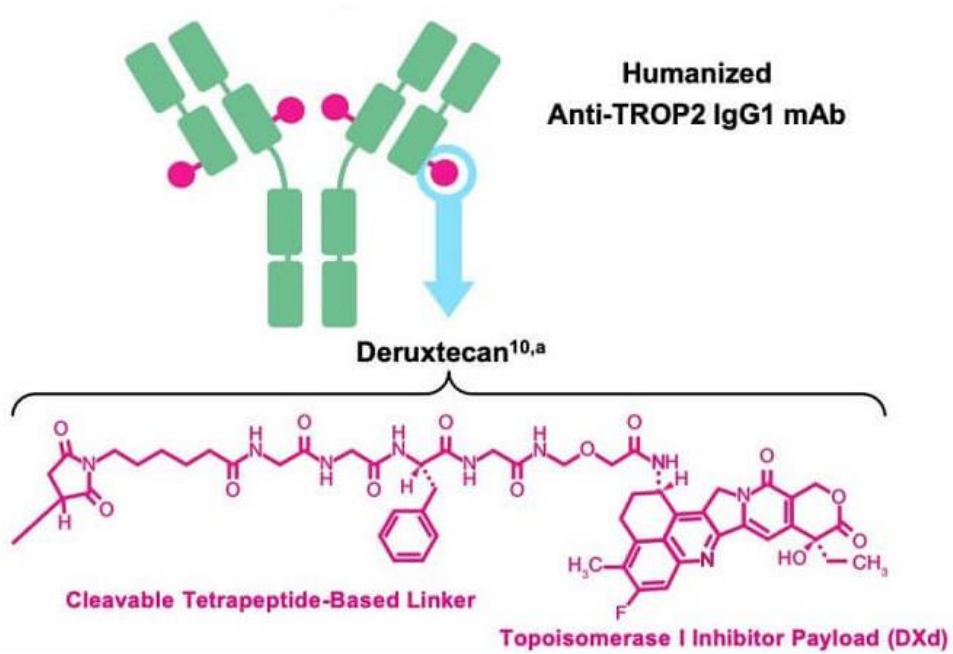
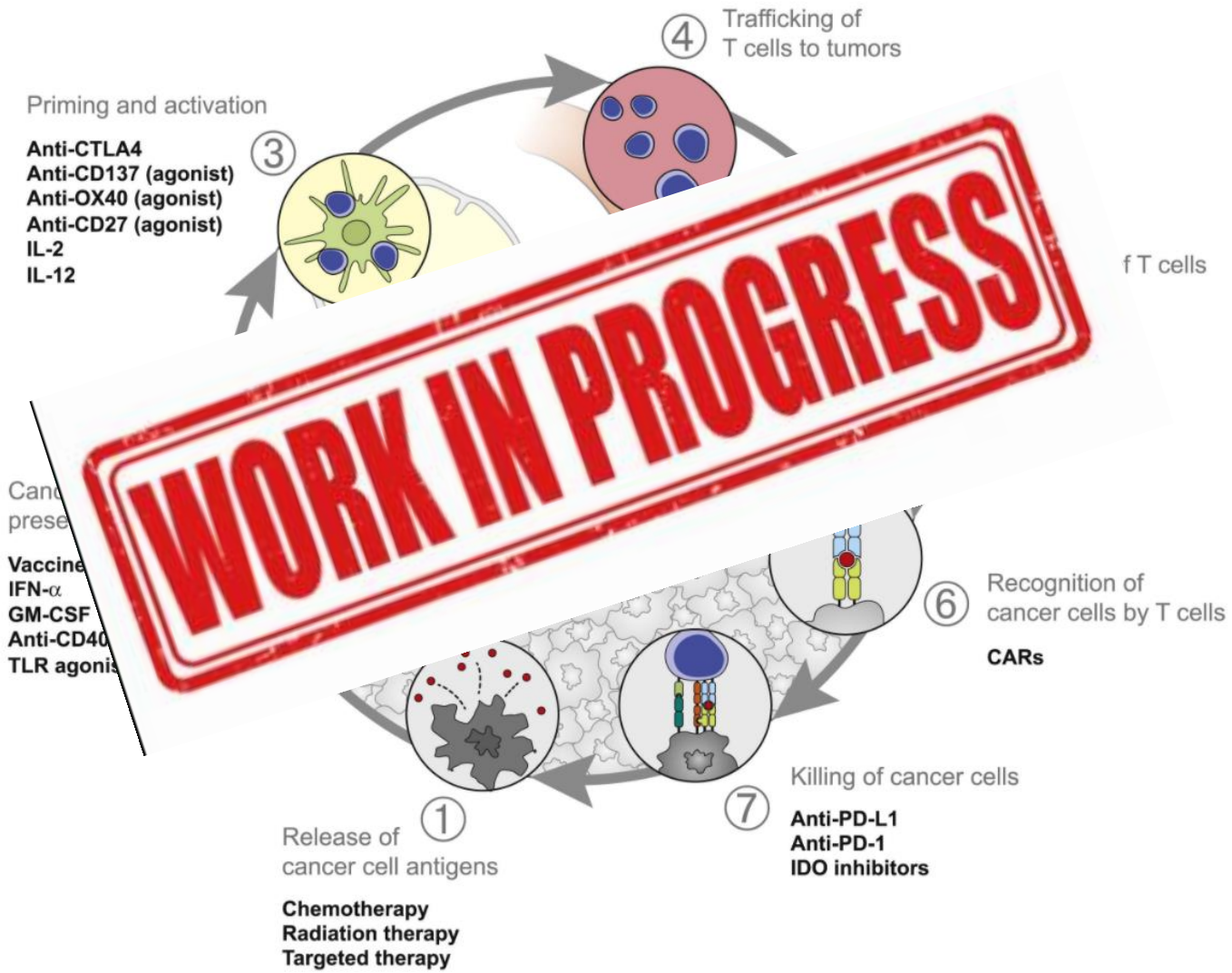
AZ TropionBreast-03
ADC + CPI vs ADC vs standardbeh til eTNBC non-pCR






④ Trafficking of
T cells to tumors
Priming and activation
Anti-CTLA4
Anti-CD137 (agonist)
Anti-OX40 (agonist)
Anti-CD27 (agonist)
IL-2
IL-12
③
f T cells
WORK IN PROGRESS
Canc
prese
Vaccine
IFN-α
GM-CSF
Anti-CD40
TLR agonis
⑥ Recognition of
cancer cells by T cells
CARs
Killing of cancer cells
⑦
Anti-PD-L1
Anti-PD-1
IDO inhibitors
① Release of
cancer cell antigens
Chemotherapy
Radiation therapy
Targeted therapy