Immunotherapy for Triple Negative Breast Cancer: Optimal Chemotherapy Partners, New Directions, and Managing Toxicity?

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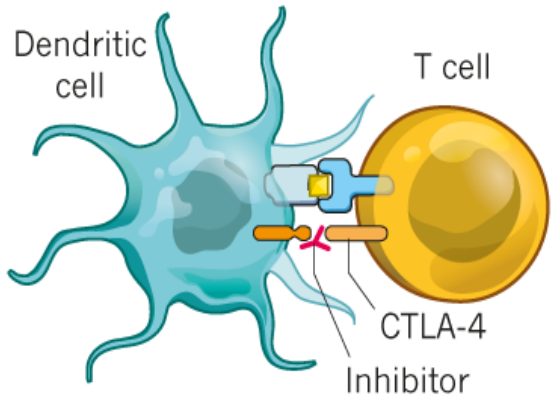
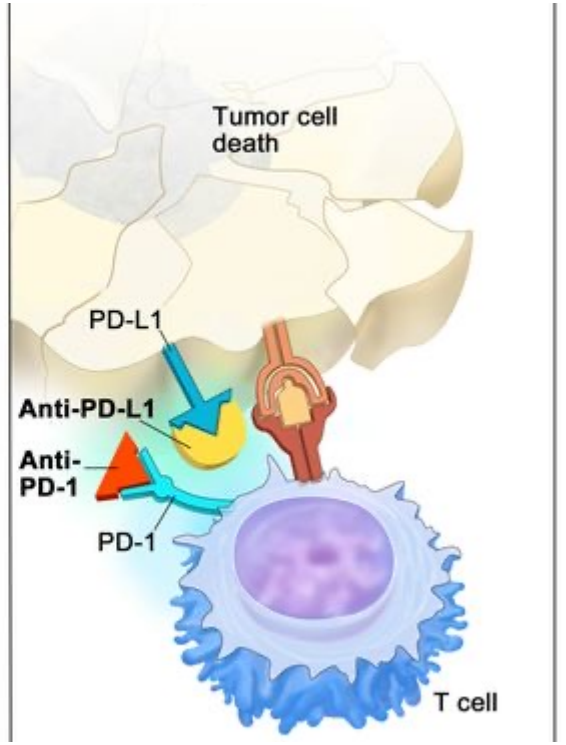
A Cancer Center Designated by the National Cancer Institute

THE UNIVERSITY OF KANSAS CANCER CENTER

Immune Checkpoint Inhibitor (ICI) Therapy

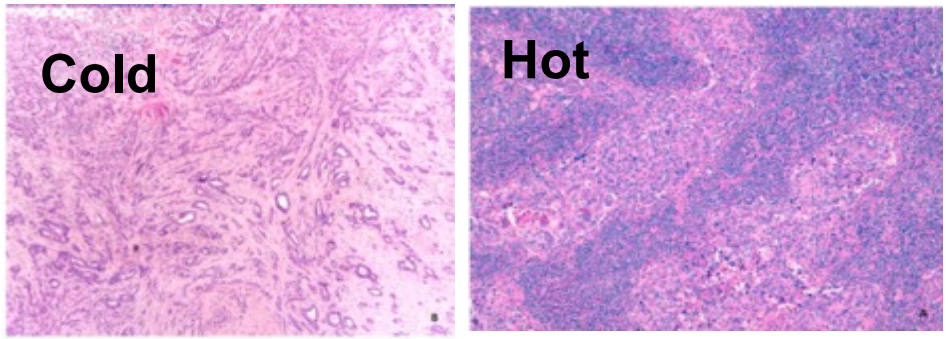
Nobel Prize in Physiology or Medicine, 2018



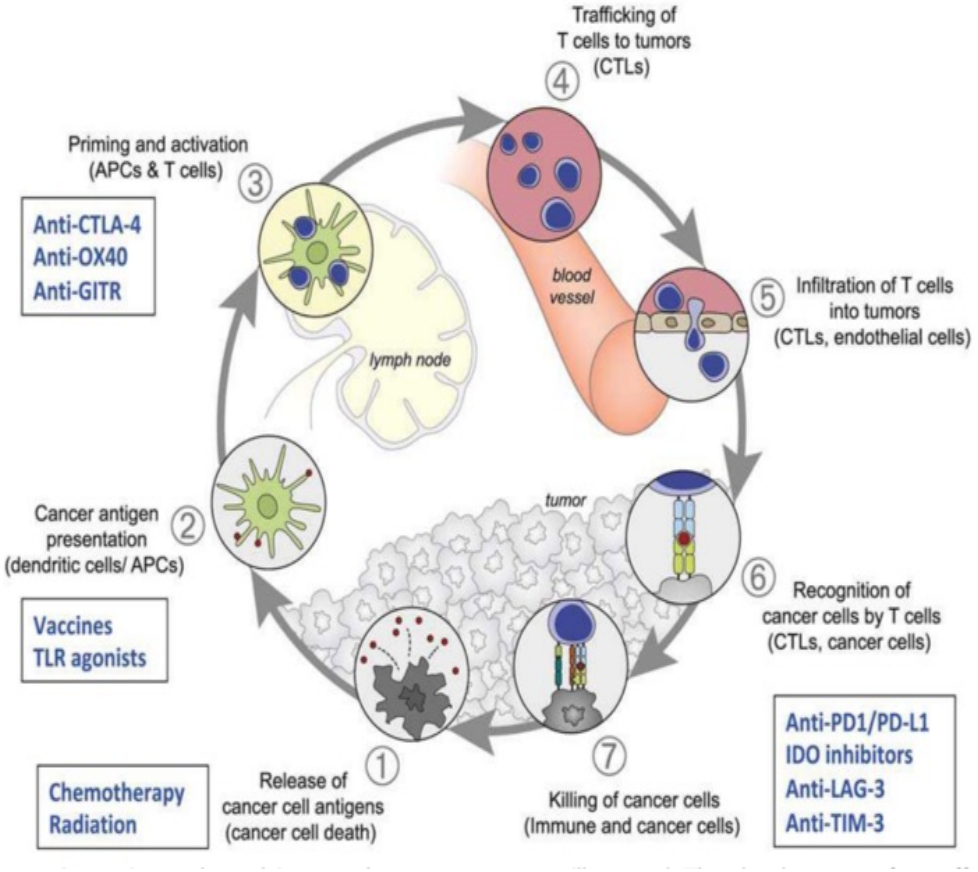


Rationale for Immunotherapy in TNBC

- High TILs in TNBC: evidence of anti-tumor immune response.
  - TIL-enrichment associated with better outcomes/pCR
- PD-L1 expressed mainly in infiltrating immune cells in BC; blocking PD-1/PD-L1 can augment T-cell response
- Chemotherapy can have several immunogenic effects
- Combination with chemotherapy synergistic by targeting different steps in the cancer immunity cycle

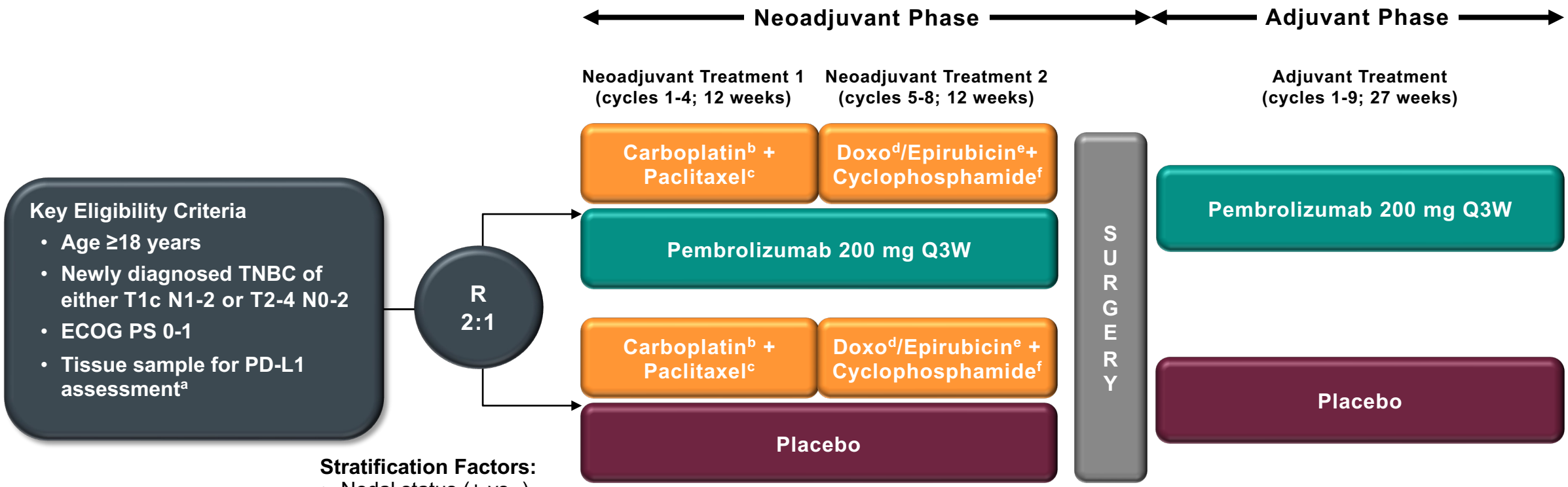


High TILs
CD8+T cells/mRNA
Immune signature



Luen et al, Breast 2016, Stanton et al, Jama Onc 2016, Nanda et al, JCO 2016, Adams et al Ann Oncol 2019, Emens et al, JAMA Onc 2019, Gatti-Mays et al, Nature Breast Cancer 2019, Loi et al, JCO 2019, Adams et al, JAMA Onc 2019, Denkert et al, Lancet Oncol 2018, Page et al, Nature Breast Cancer 2019, Galluzzi et al, Nat Rev Clin Oncol 2020, Chen Immunity 2013

KEYNOTE-522 Study Design (NCT03036488)

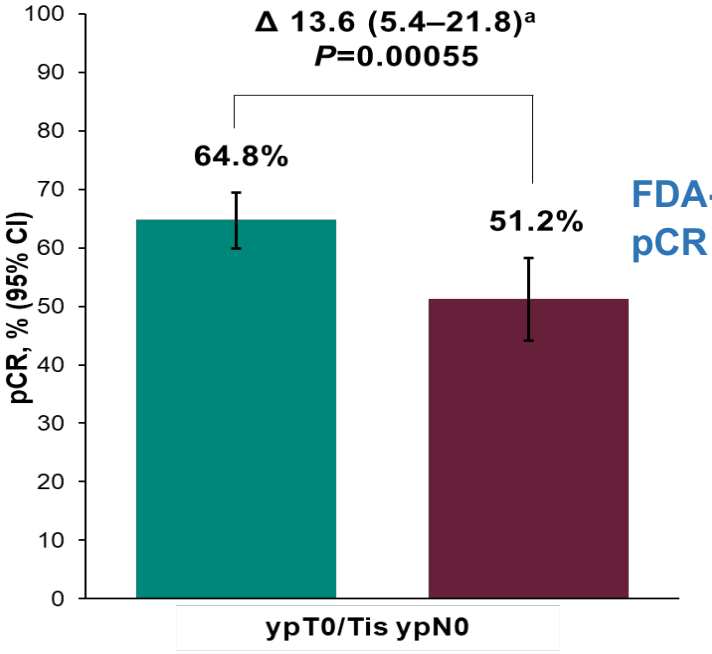


Stratification Factors:
- Nodal status (+ vs -)
- Tumor size (T1/T2 vs T3/T4)
- Carboplatin schedule (Q1W vs Q3W)

- Primary endpoints: pCR (ypT0/Tis ypN0) by local review, EFS by local review
- Secondary endpoints: pCR (ypT0 ypN0 and ypT0/Tis), OS, EFS, AE
- Exploratory endpoints: RCB, pCR by subgroups, EFS by pCR

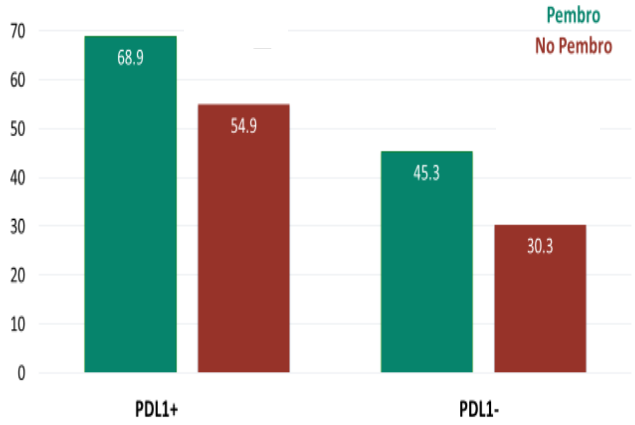
[a]Must consist of at least 2 separate tumor cores from the primary tumor.
[b]Carboplatin dose was AUC 5 Q3W or AUC 1.5 Q1W.
[c]Paclitaxel dose was 80 mg/m^2 Q1W.
[d]Doxorubicin dose was 60 mg/m^2 Q3W.
[e]Epirubicin dose was 90 mg/m^2 Q3W.
[f]Cyclophosphamide dose was 600 mg/m^2 Q3W.

KEYNOTE-522

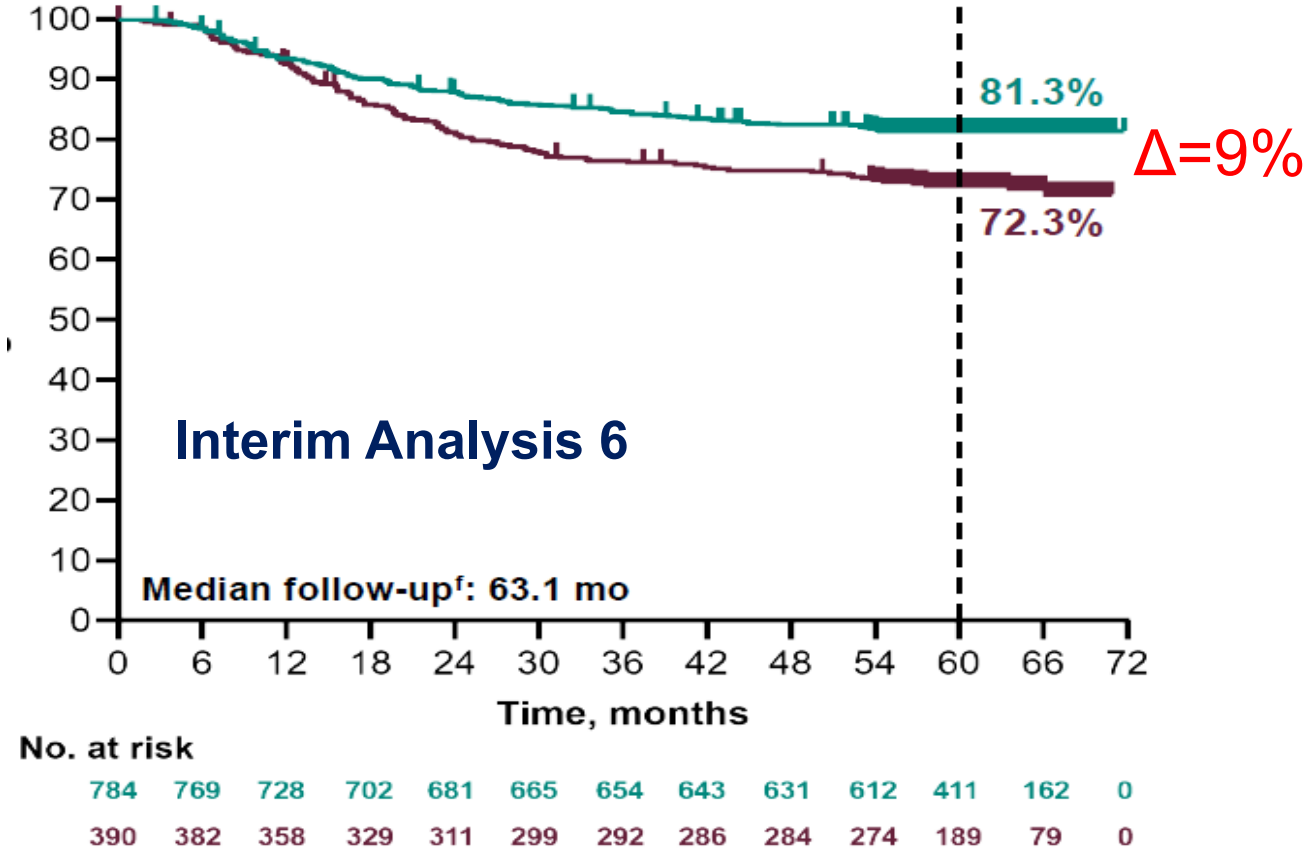


FDA-report
pCR Δ7.5

Keynote-522:
PDL1 Status does NOT predict Benefit from Pembro

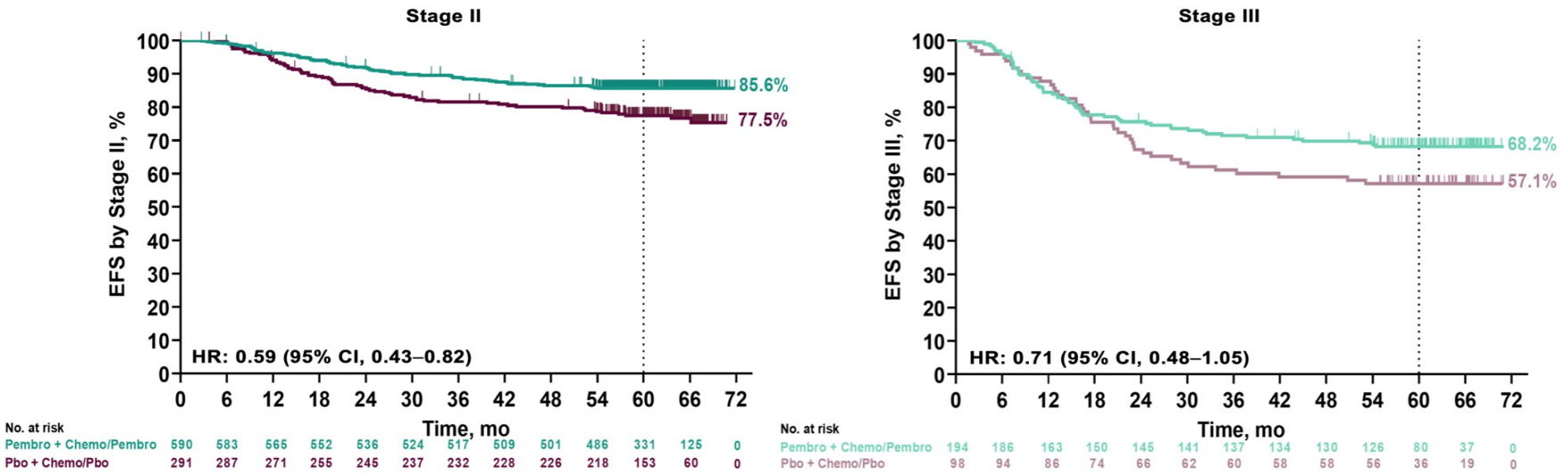


IA6[b]	Events	HR (95% CI)
Pembro + Chemo/Pembro	18.5%	0.63[c] (0.49–0.81)
Placebo + Chemo/Placebo	27.7%	



Schmid et al NEJM 2020 ,Schmid et al NEJM 2022

KEYNOTE-522: subgroup analysis

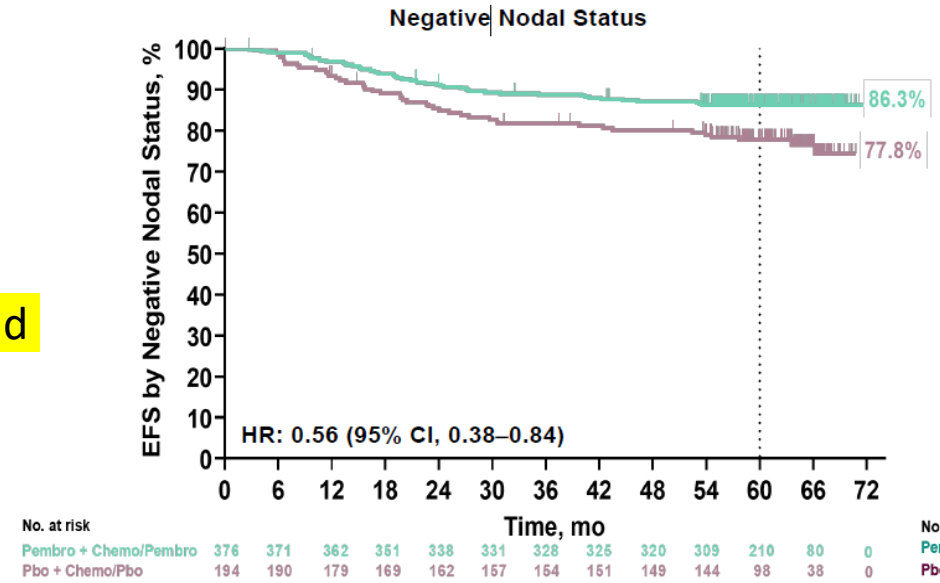


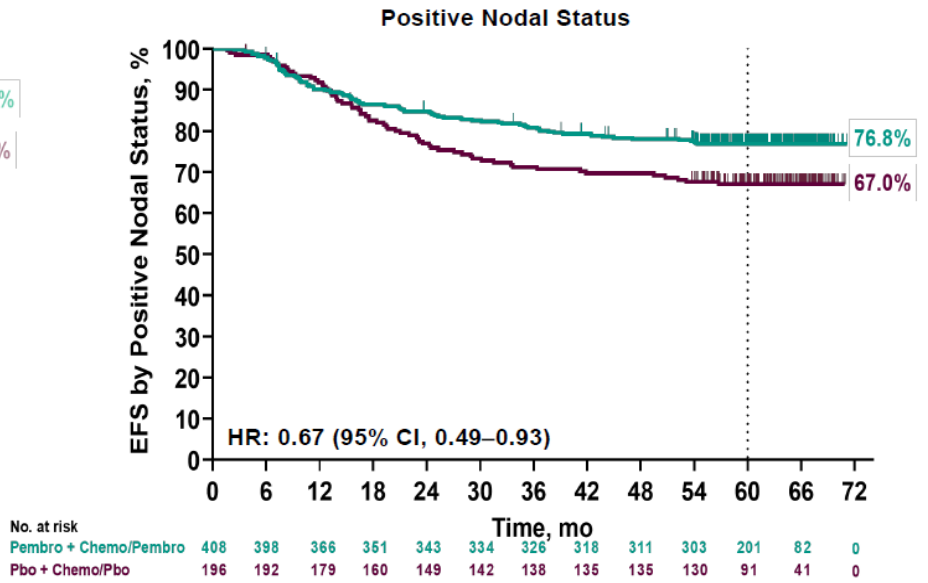
32% of patients with EFS event despite pembrolizumab

Need better therapies for these patients

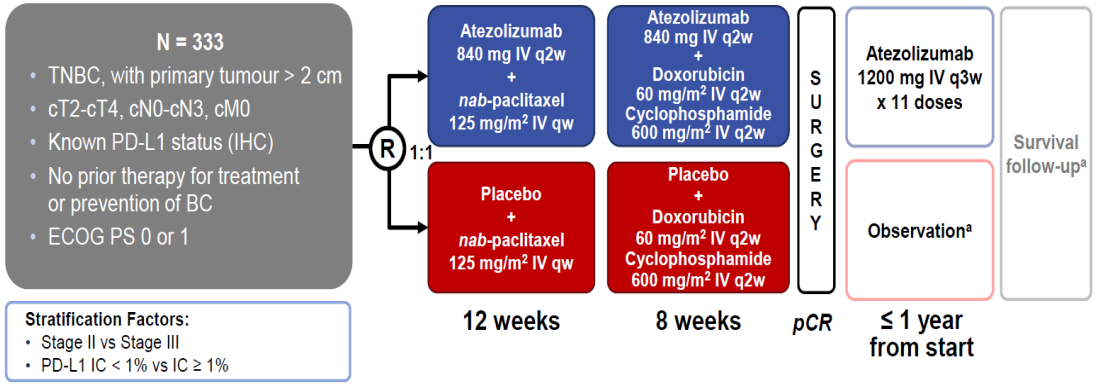
77% of patients with N-ve disease without EFS event with chemotherapy alone

Not all patients need treatment escalation beyond chemotherapy





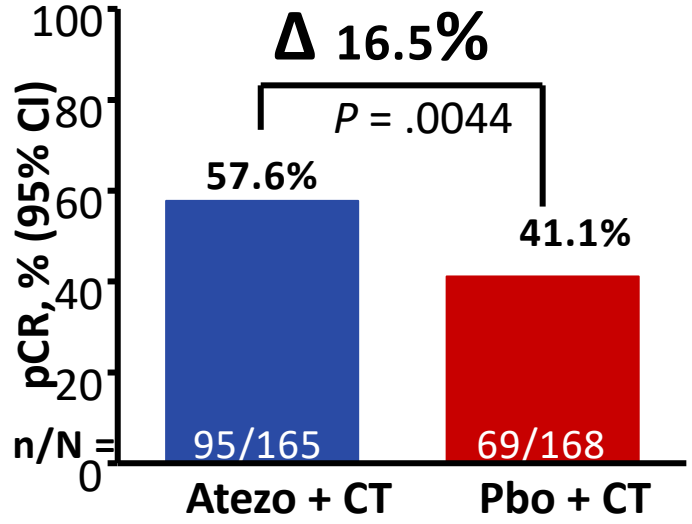
IMpassion031: Addition of Atezolizumab to Neoadjuvant Chemotherapy in Stage II-III TNBC

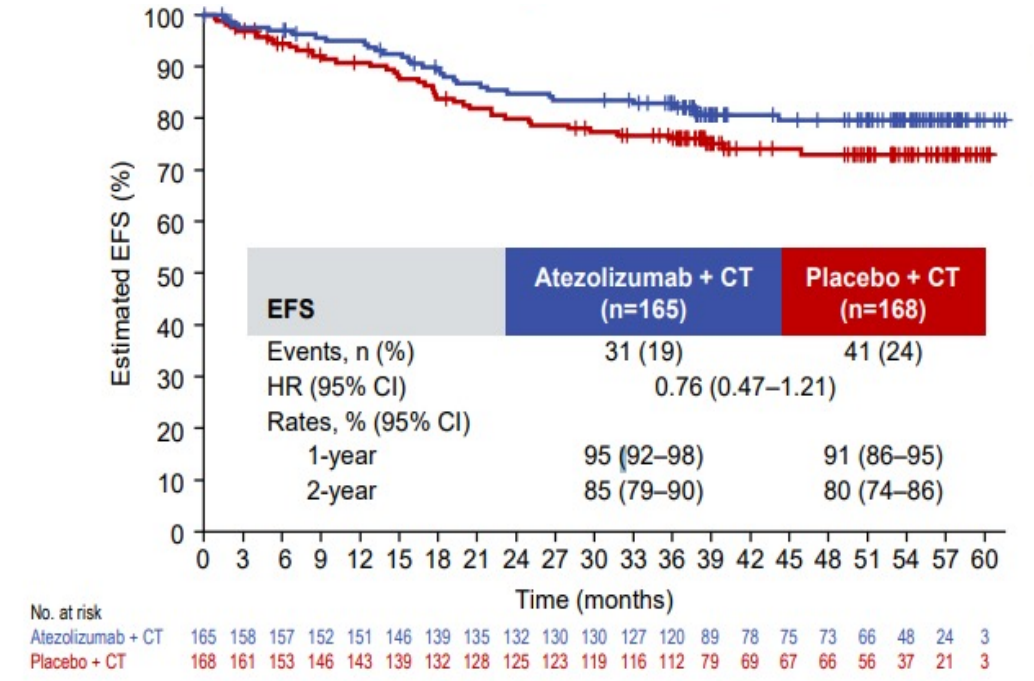


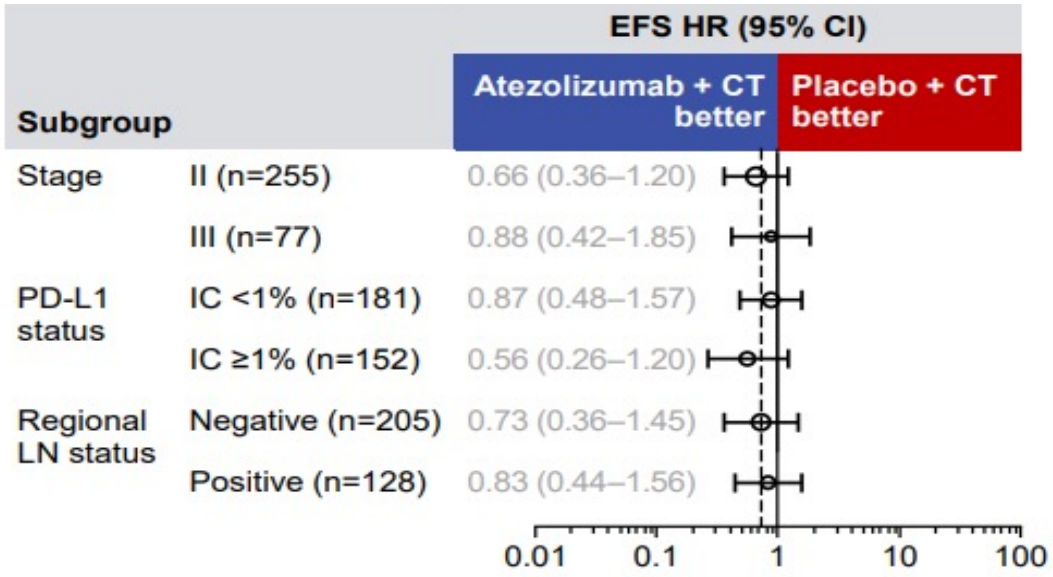
Co-primary endpoints: pathologic complete response (pCR, ypT0/is ypN0) in ITT and PD-L1–positive (IC ≥ 1%) subpopulation

Secondary endpoints: EFS, DFS, and OS in ITT and in PD-L1–positive subpopulation, safety, PROs

Primary end point
pCR
Secondary end point
EFS

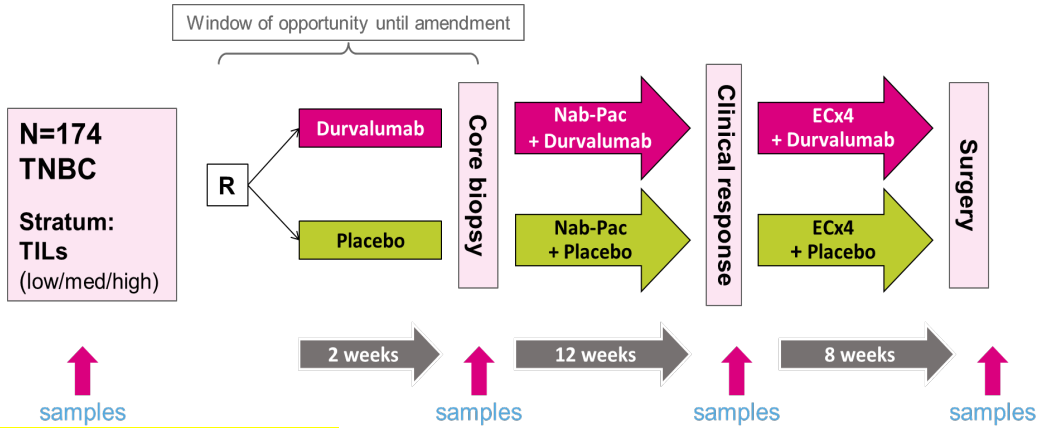






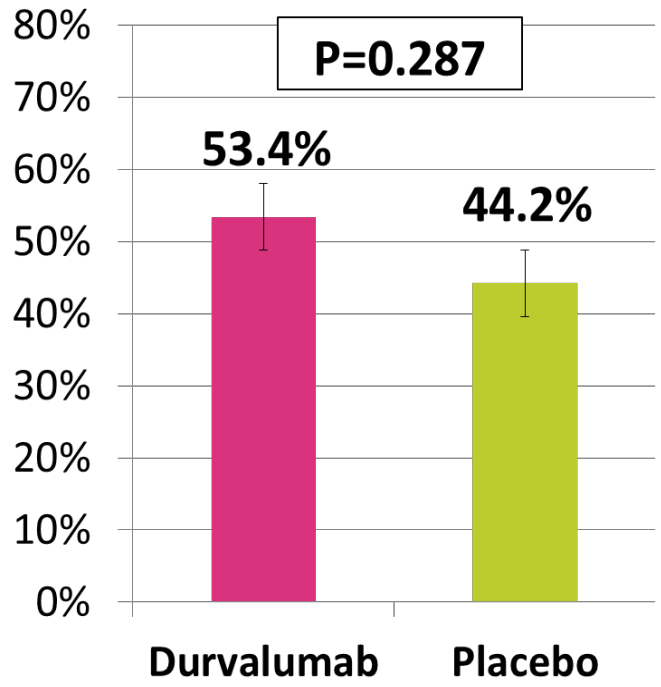
Mittendorf et al Lancet 2020, Barrios et al ESMO Breast 2023

GeparNuevo: Addition of durvalumab to taxane-anthracycline containing chemotherapy

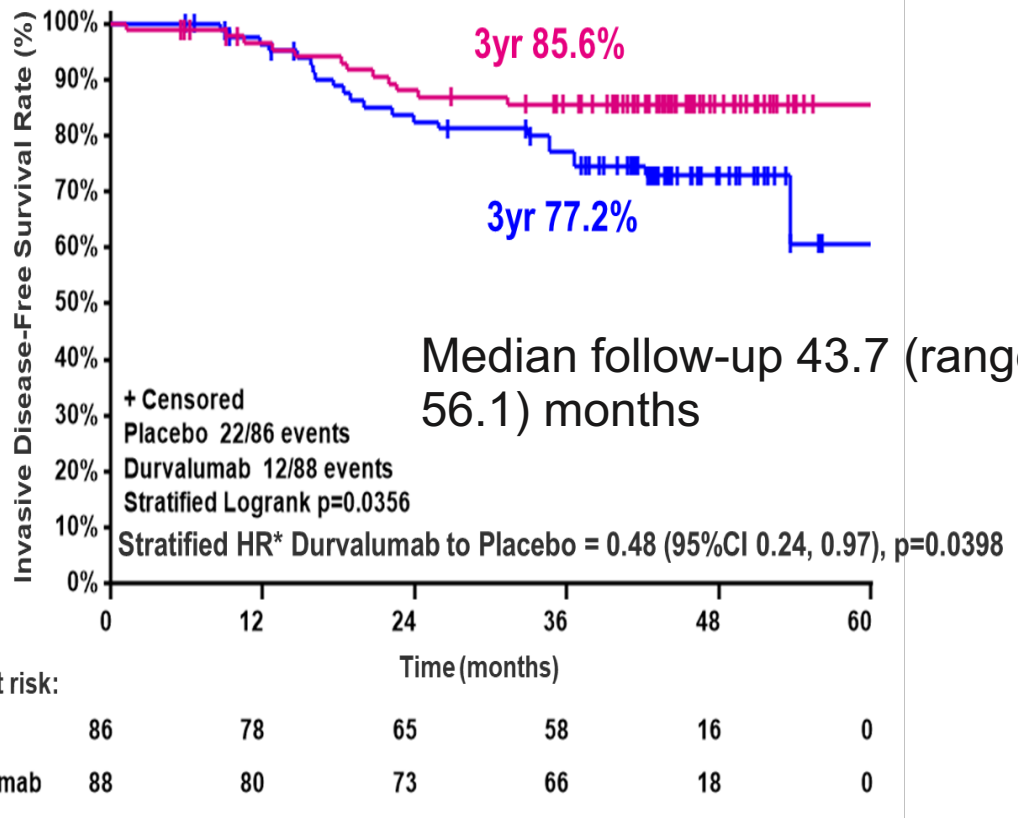


No adjuvnat ICB

pCR: Primary end point



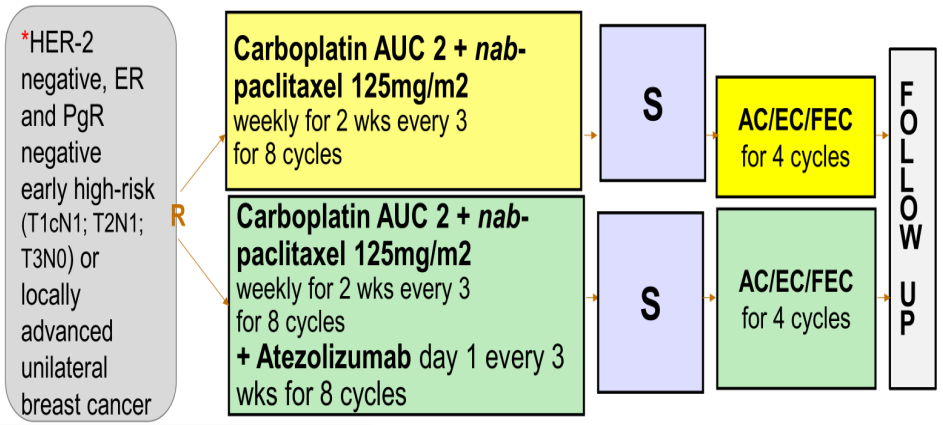
iDFS (secondary end point)



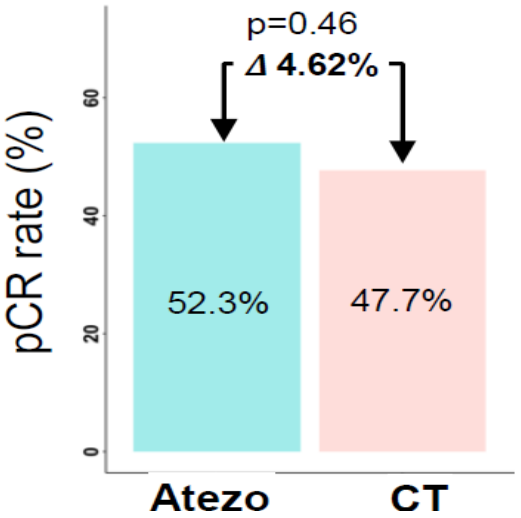
Median follow-up 43.7 (range 4.9-56.1) months

Loibl Annals of Oncology 2019, Loibl S, et al. Annals of oncology 2022

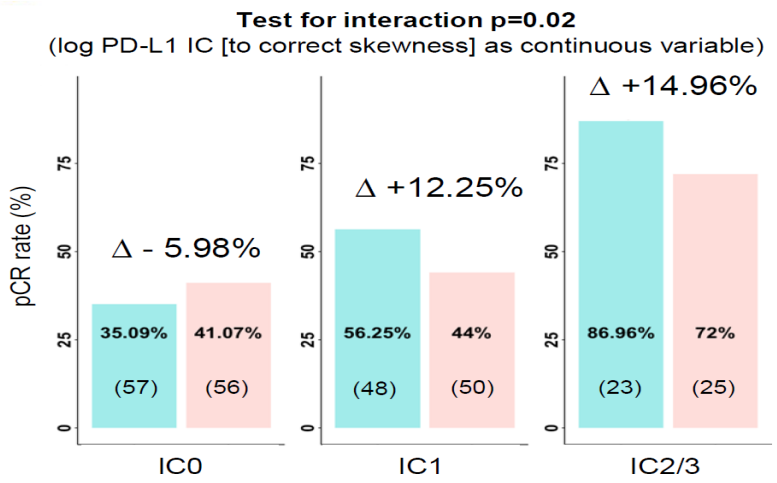
NeoTRIPaPDL1: Atezolizumab plus weekly Carboplatin + Nab-paclitaxel



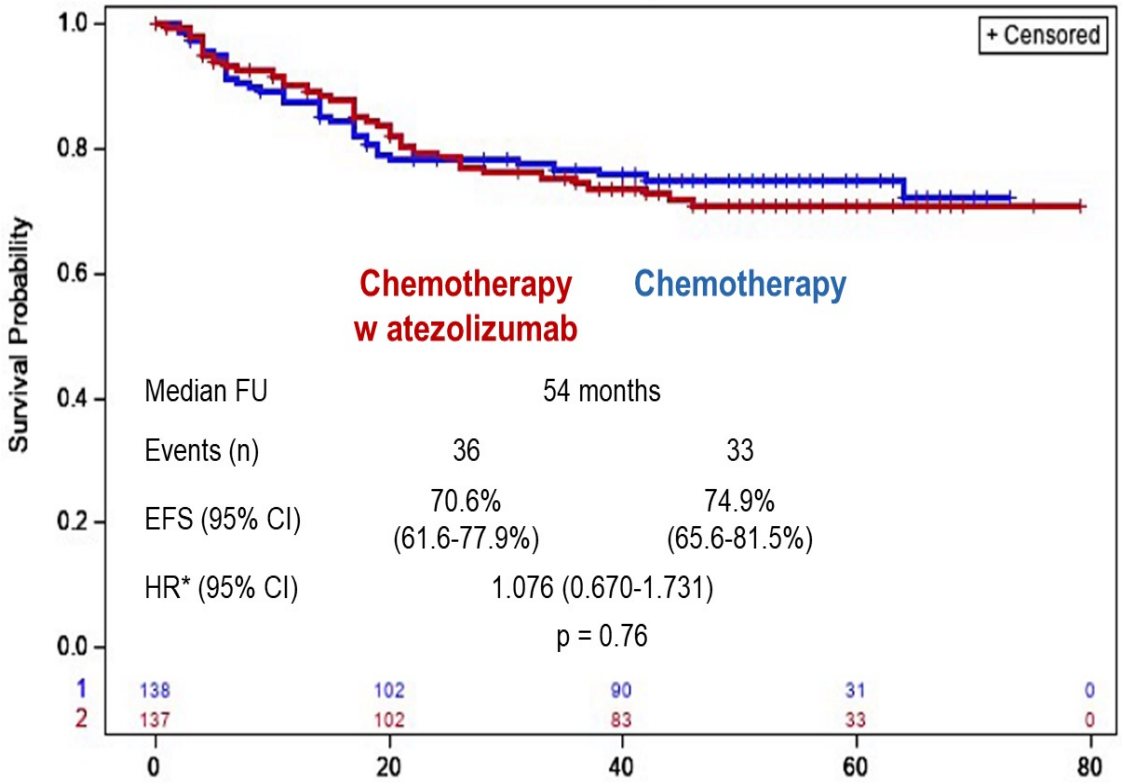
No adjuvnat ICB



PD-L1 status and pCR



EFS



pCR, positive PD-L1, earlier stage as well as higher sTILs were all prognostic and linked to better EFS, but they were not predictive of atezolizumab benefit

Gianni et al Annal Oncol 2022, Gianni et al ESMO 2023

Why no pCR or EFS Benefit in NeoTRIPaPDL1?

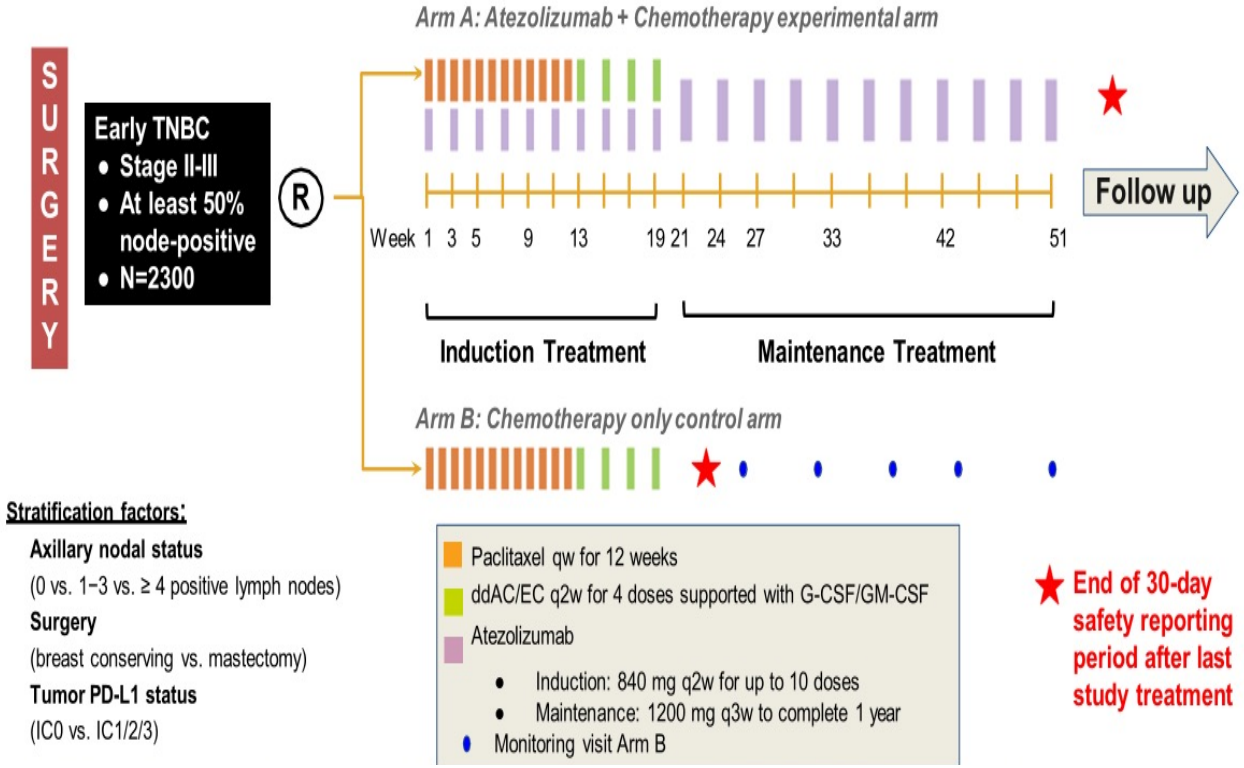
- PDL-1 vs PD-1 inhibitor
  - IMpassion031: pCR better, EFS numerically better with atezolizumab
  - mTNBC: Atezo plus taxane not statistically superior to Taxane (IMpassion130, 131)
- Chemotherapy backbone: no anthracycline
- Anatomic risk of enrolled population:
  - 90% with node positive disease (compared to 30% in Impassosion031)
  - With high anatomical risk would efficacy be more in line with what is observed in mTNBC ?
- Differences in tumour biology: Higher TILs in chemo alone arm
- Chance

Phase II-III Neoadjuvant chemo + ICB trials

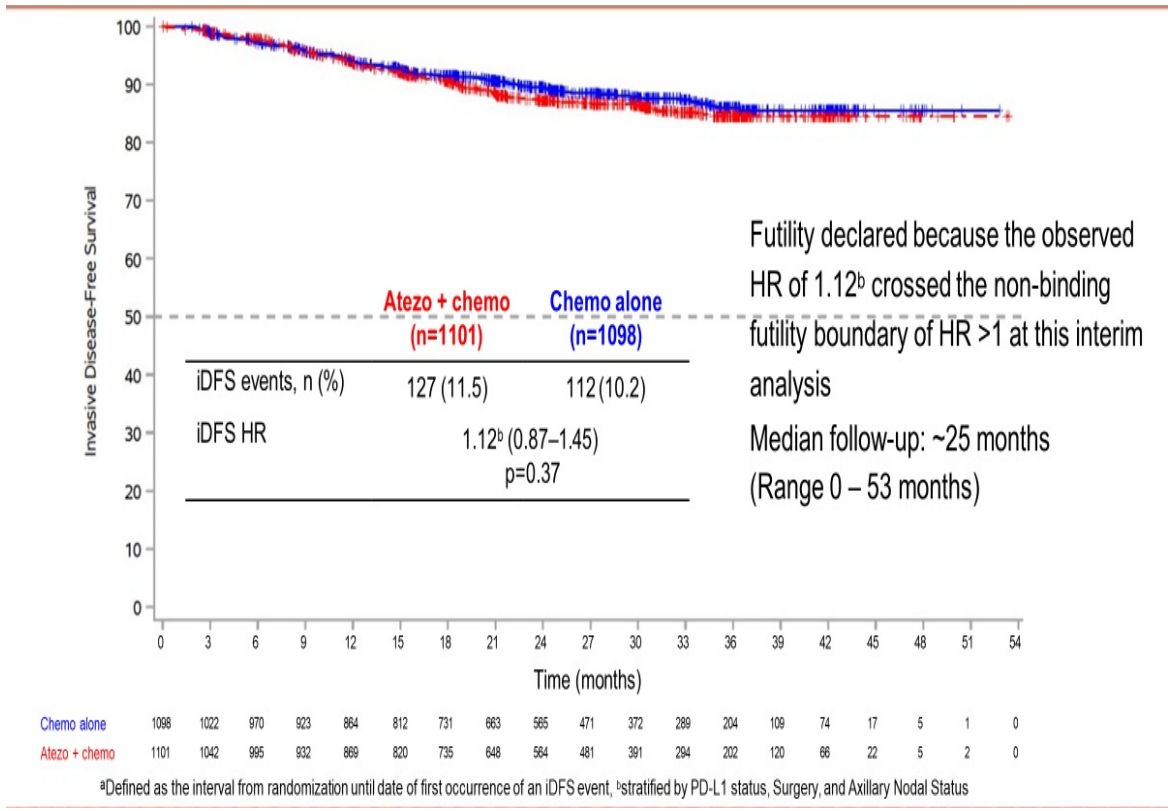
	KEYNOTE-522 (NCT03036488)	GeparNeuvo	IMpassion031 (NCT03197935)	NeoTRIPaPDL1 (NCT02620280)
	N=1174	N=174	N=333	N=280
End points	Co-Primary: pCR and EFS	Primary: pCR Secondary: iDFS, DDFS, OS	Primary: pCR Secondary: EFS	Primary: EFS Secondary: pCR
LN+	51%	33%, stage I: 36%	36%	**87%**
Regimen	Paclitaxel/carbo → AC/EC + pembrolizumab/placebo CbP-AC	nab-paclitaxel→ EC + Durvalumab/placebo nP-EC	nab-paclitaxel →EC + durvalumab/placebo. nP-AC	Wkly carbo/nab-paclitaxel +Atezolizumab/Placebo X 8 cycles CbP
Adj treatment	Pembro/placebo X 27 wks	No ICI	Atezo/placebo X 22 wks	No ICI, EC/AC/FEC
ICI Type	Anti-PD-1	Anti PD-L1	Anti-PD-L1	Anti-PD-L1
Treatment duration	24 weeks	20 weeks	20 weeks	24 weeks
PD-L1+	83% (CPS≥1)	87%(SP263 antibody)	46% (IC≥1%)	56% (IC≥1%)
PCR	ITT: 65 vs 51% (63 vs 55.6%) PD-L1+: 70 vs 55% PD-L1-ve: 45 vs 30%	53 vs 44%$^{n.s}$	ITT: 58 vs 41% PD-L1+: 69 vs 49%$^{n.s}$ PD-L1-ve: 47 vs 34%	ITT: 52 vs 47%$^{n.s.}$ PD-L1+: 56 vs 44% PD-L1-ve: 35 vs 41%
EFS/DFS/OS	5-year EFS 81.3% vs 72.3% HR=0.63, p=0.0003 3-year OS: 89.6% vs 86.9% HR=0.72, p=0.032$^{n.s}$	3-year iDFS: 85.6% vs 77.2% HR=0.48, p=0.0398 3-year OS: 95% vs 83% HR=0.24, p=0.018	2-year EFS: 85% vs 80% (numeric improvement) HR=0.76 (0.47-1.21)	5-year EFS: 70.6% vs 74.9% HR=1.076 p =0.76

Schmid et al, NEJM 2020, Mittendorf et al, Lancet 2020, Gianni et al SABCS 2019, Bianchini et al ESMO 2020, Schmidt et al ESMO 2023, Loibl et al Annals 2022, Gianni et al ESMO 2023

ALEXANDRA/IMpassion030 phase 3 trial : Adjuvant IO (without neoadjuvant component)

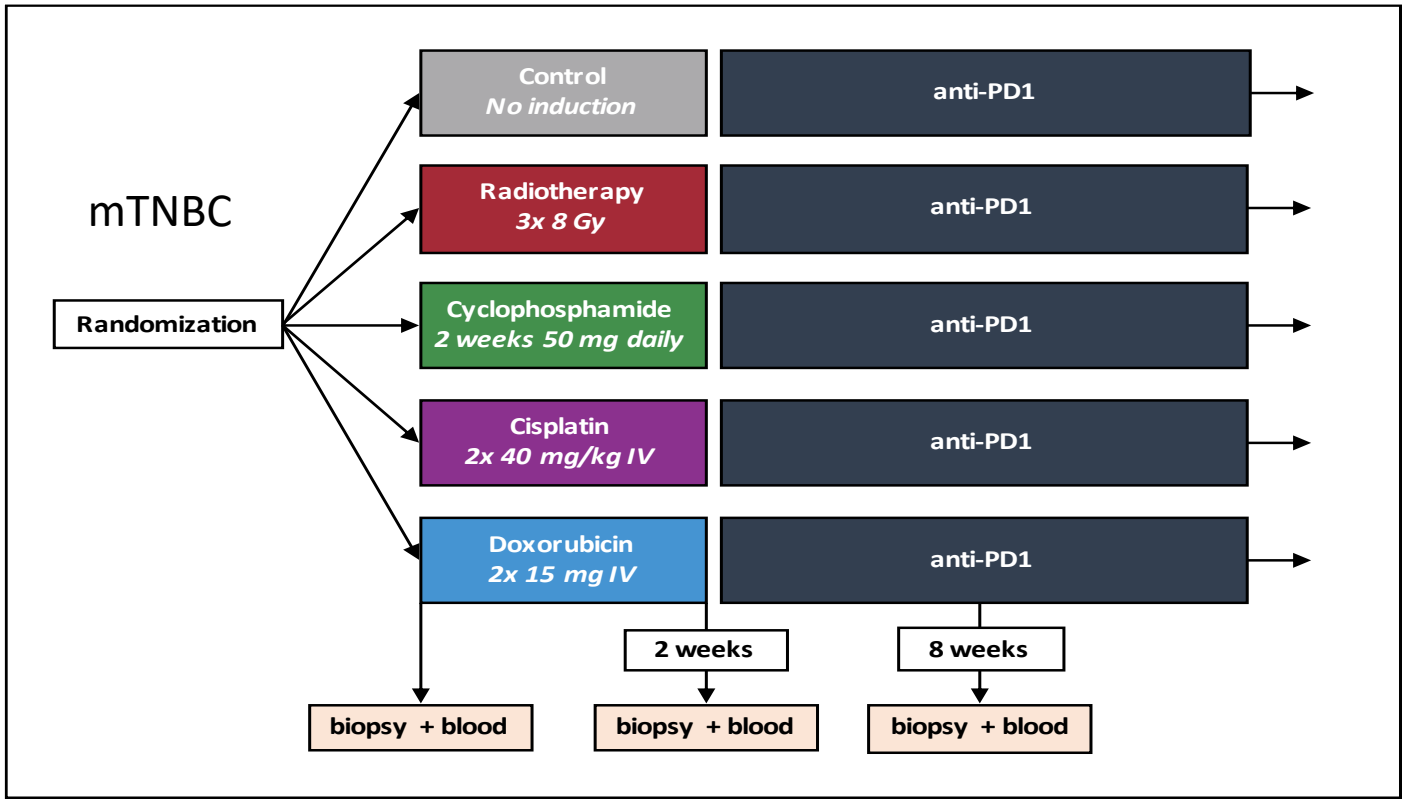


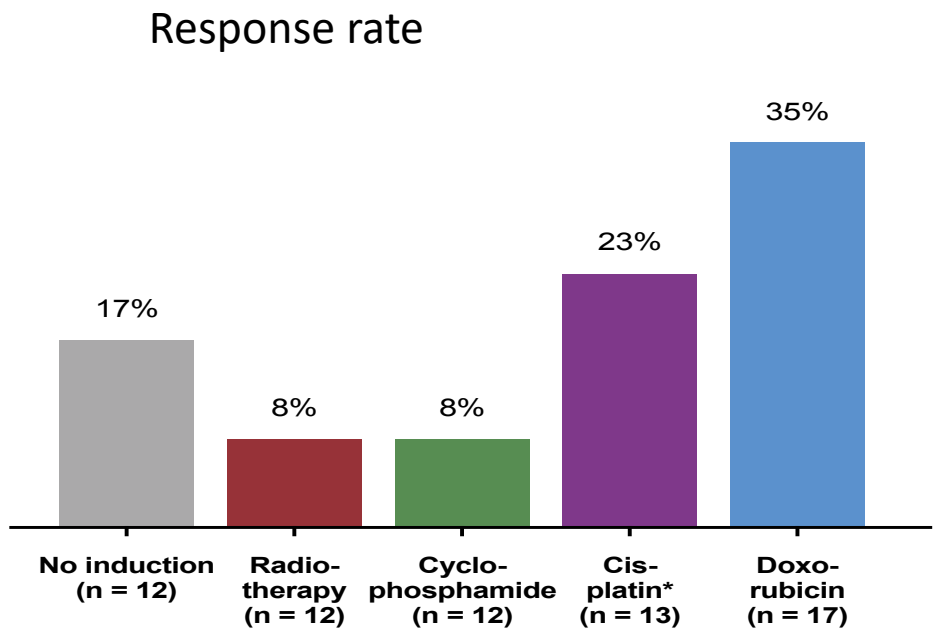
iDFS: Primary End Point



Ignatiadis SABCS 2023

Doxorubicin and Cisplatin induction sensitize to subsequent PD-1 Blockade: TONIC Trial

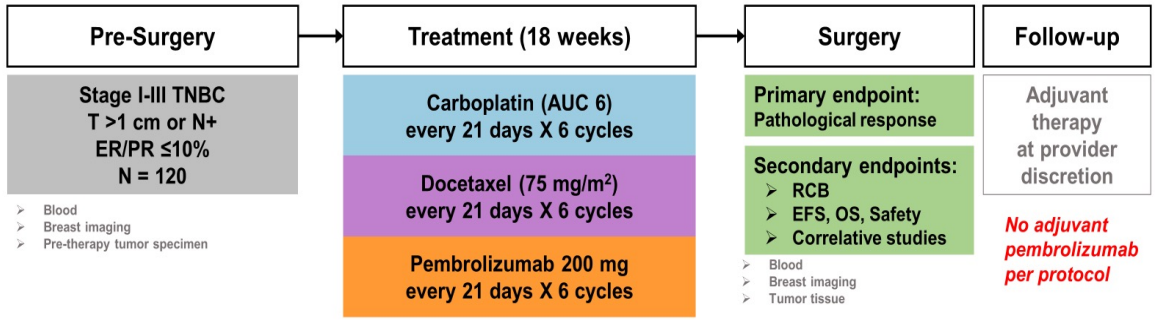


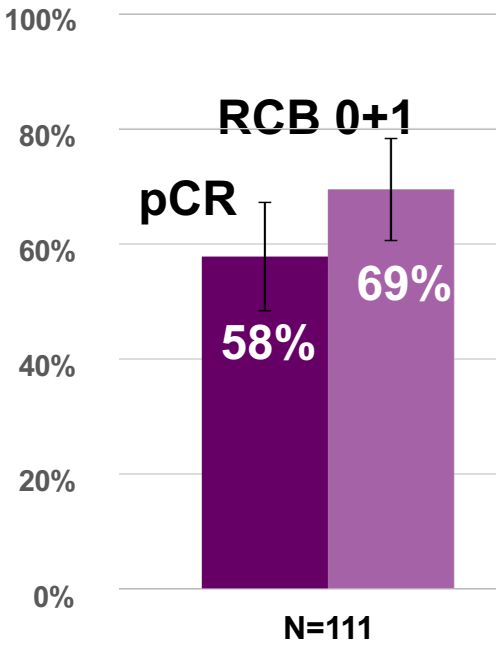


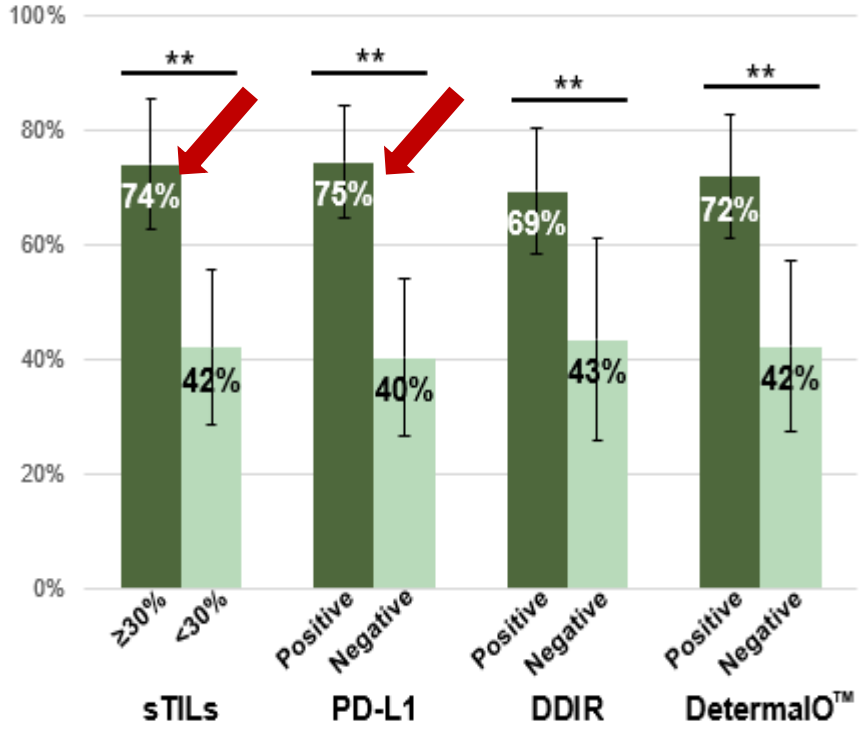
Short term doxorubicin and cisplatin induction led to a more favorable tumor microenvironment (upregulation of immune-related genes involved in PD-1-PD-L1 and T cell cytotoxicity pathways) and increase the likelihood of response to PD-1 blockade

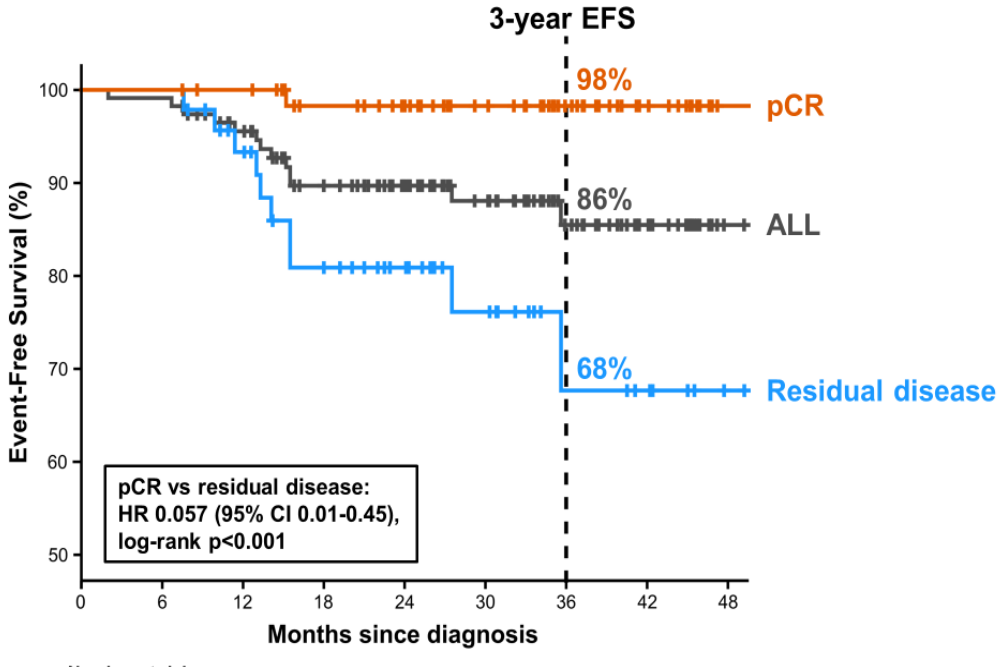
Voorwerk et al, Nature Medicine 2019

NeoPACT: Carboplatin + Docetaxel+ Pemrolizumab





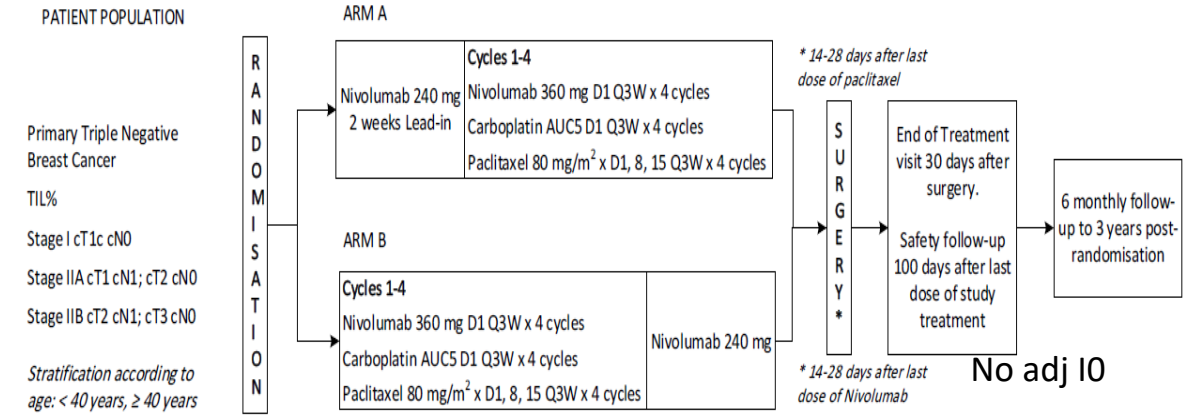




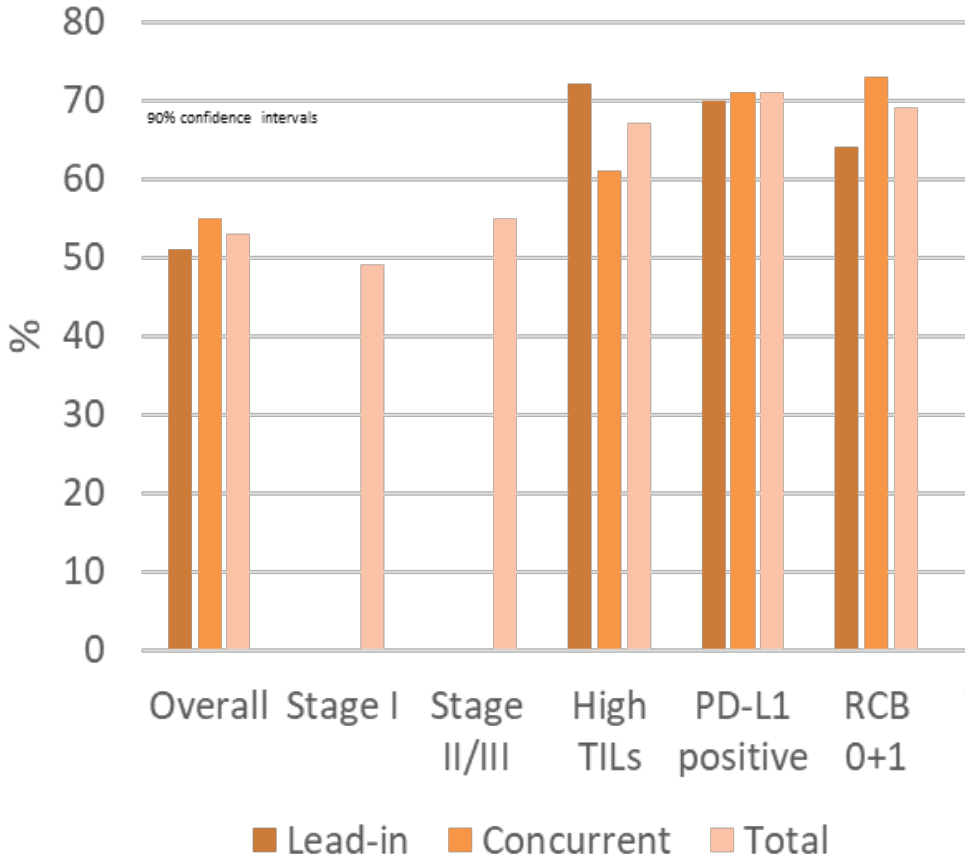
-Immune enrichment assessed by sTILs, PD-L1 or DetermaIO™ signature was noted in almost 50% of patients and was associated with high pCR rates exceeding 70%.
-pCR delta: 30-35% in immune high vs immune low

Sharma et al JAMA Oncology 2023

Randomized Phase II Study of Neoadjuvant Nivolumab (N) 2 week lead-in followed by 12 weeks of concurrent N+carboplatin plus paclitaxel (CbP) vs concurrent N+CbP in TNBC: (BCT1902/IBCSG 61-20 Neo-N)



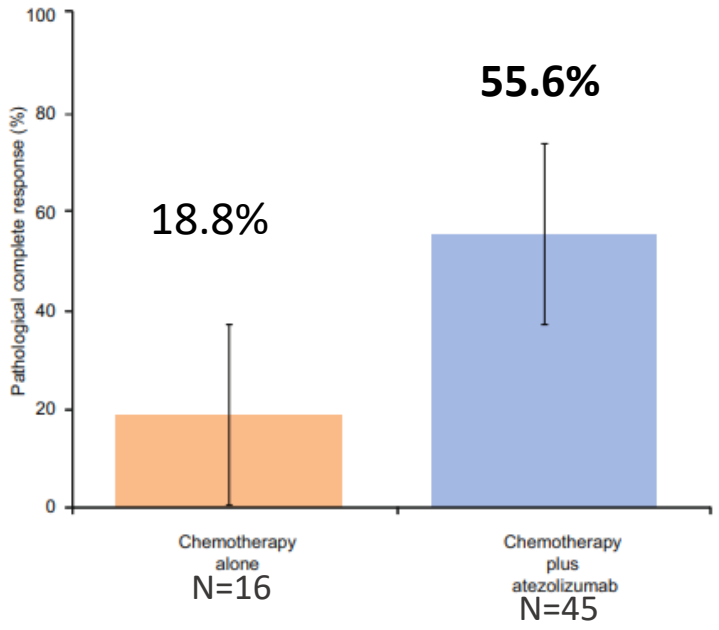
N=108, Stage I-II evaluable at 14 centers
35% stage I, 43-51% PDL1+

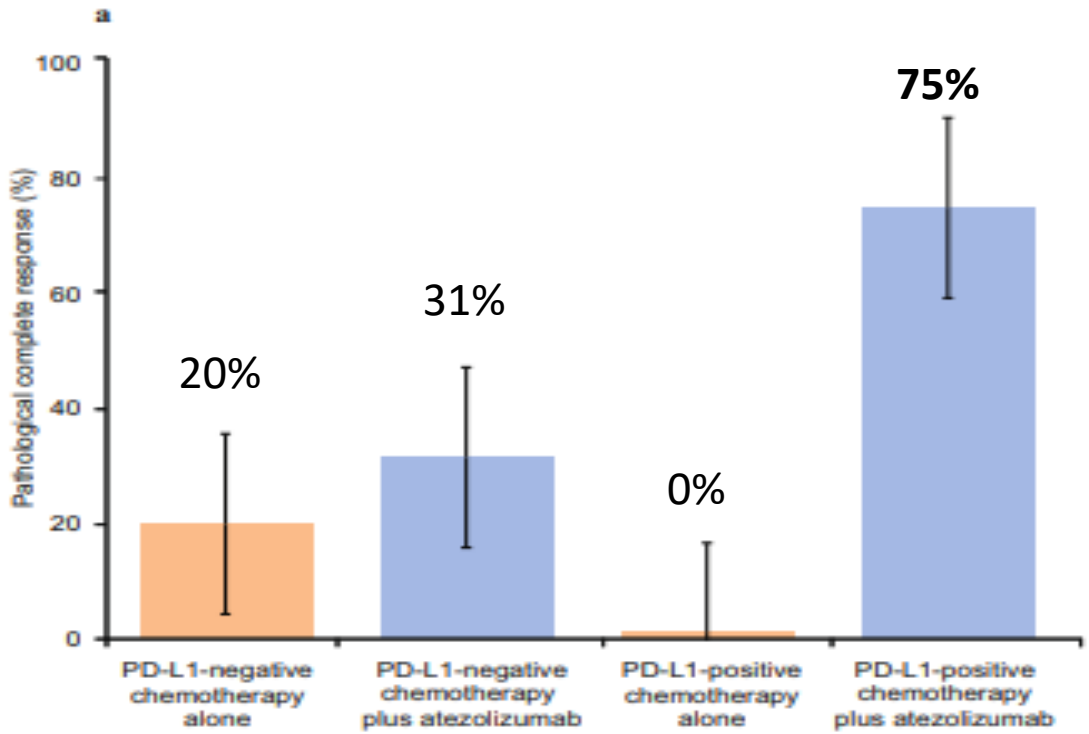


- pCR rates: 53% (90%CI 44-61%)
  - Lead-in: 51% (90%CI 39-63%)
  - Concurrent: 55% (90%CI 43-66%)
  - PD-L1 **71% positive vs 33% negative**; sTILs 67% high vs 47% low
- No evidence of pCR advantage with Lead-in Nivo
- Patients with immune enriched tumors, identified by high sTILs or PD-L1 positivity, had high pCR rates with 12 weeks of treatment;
- EFS pending

Loi et al SABCS 2023

Randomized phase 2 study of neoadjuvant carboplatin and paclitaxel with or without atezolizumab -NCI 10013

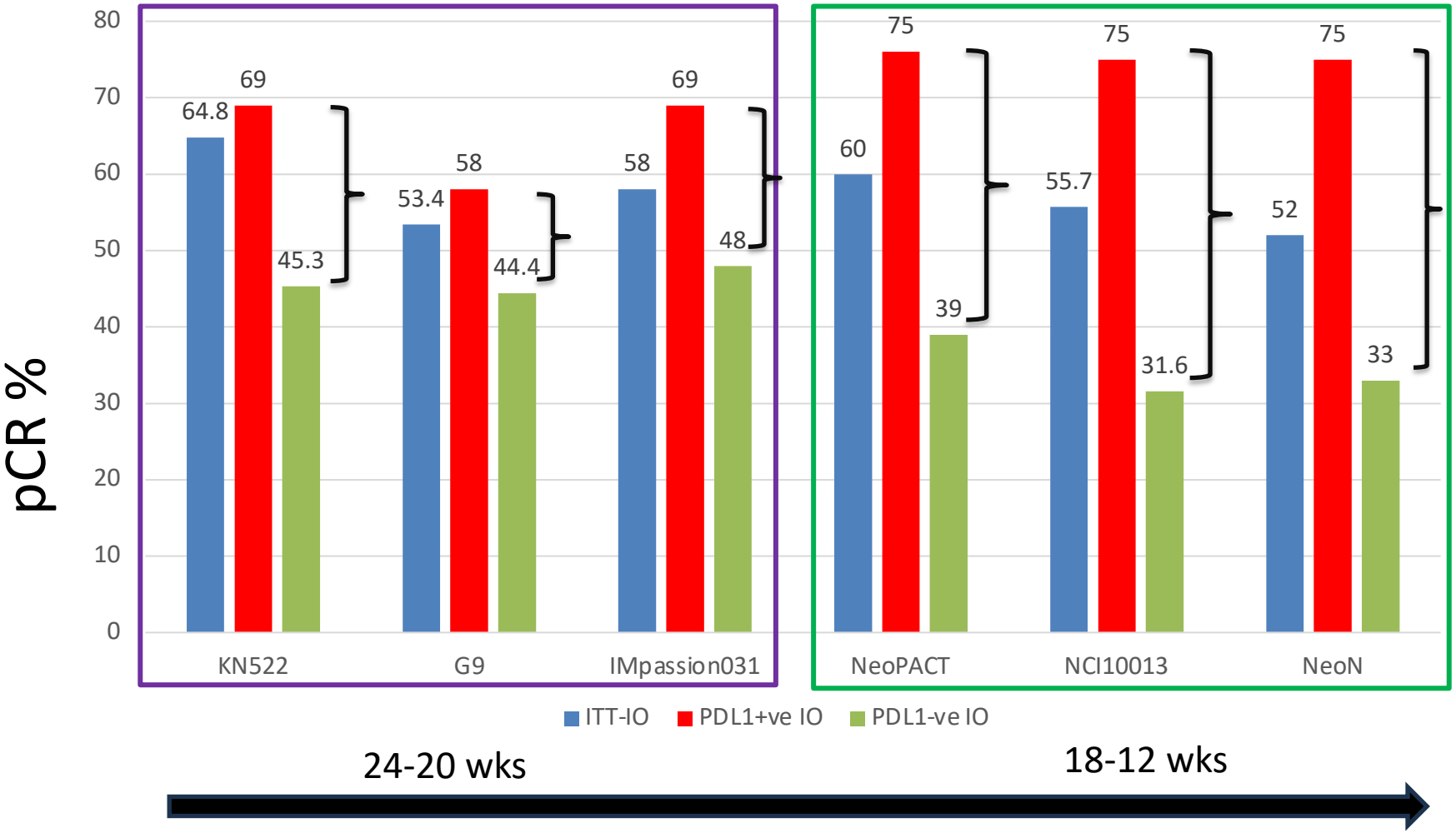




- Carboplatin AUC5 every 3 weeks ×4 cycles plus paclitaxel 80 mg/m2 every week ×12 weeks (Arm A), + atezolizumab 1200 mg every 3 weeks ×4 cycles (Arm B).
- 50% N+, 63% stage II, 37% stage III , No stage I,
- 45% PDL-1+ (SP142)

Ademuyiwa et al NPJ Breast 2022

Immune enriched vs poor eTNBC chemoimmunotherapy trials ordered by chemotherapy duration

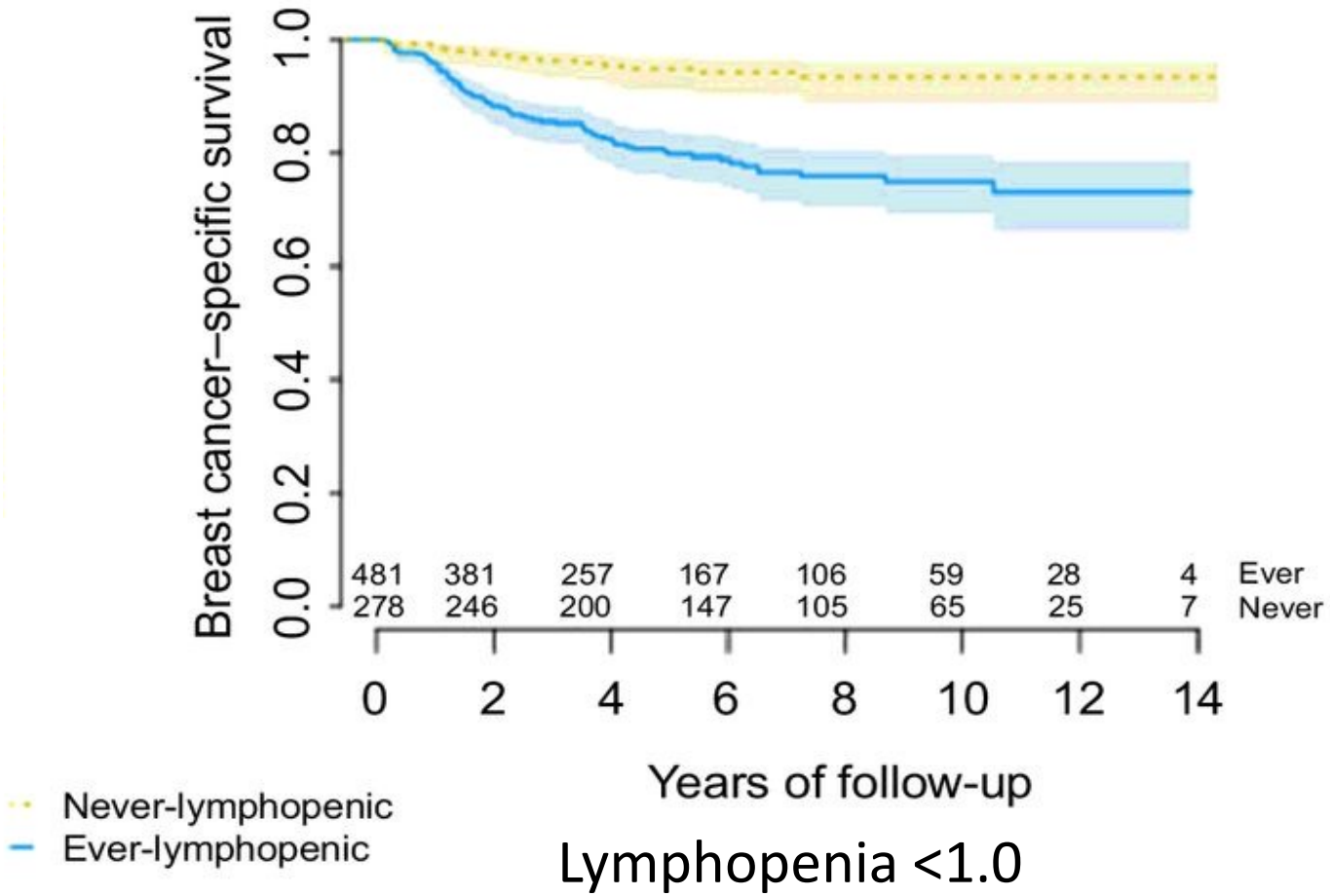


Trial (IO arm)	PDL1 pos vs neg % increase
KN522	23.7%
G9	13.6%
Impassion031	21%
NeoPACT	37%
NCI10013	43.4%
NeoN	42%

In immune enriched tumors, in setting of less chemotherapy, PD-(L) 1 inhibitors can have large effects with pCR rates of 75%
In immune enriched tumors in setting of intense chemo+IO why are pCR rates not exceeding 70%?

Lower Absolute Lymphocyte Counts Predict higher Mortality in 1463 Early-Stage Triple-Negative Breast Cancer patients

On multivariable analysis, the main predictor of developing lymphopenia
was neoadjuvant/adjuvant chemotherapy use



Afgahi A et al Clin Cancer Res. 2018 doi:10.1158/1078-0432.CCR-17-1323

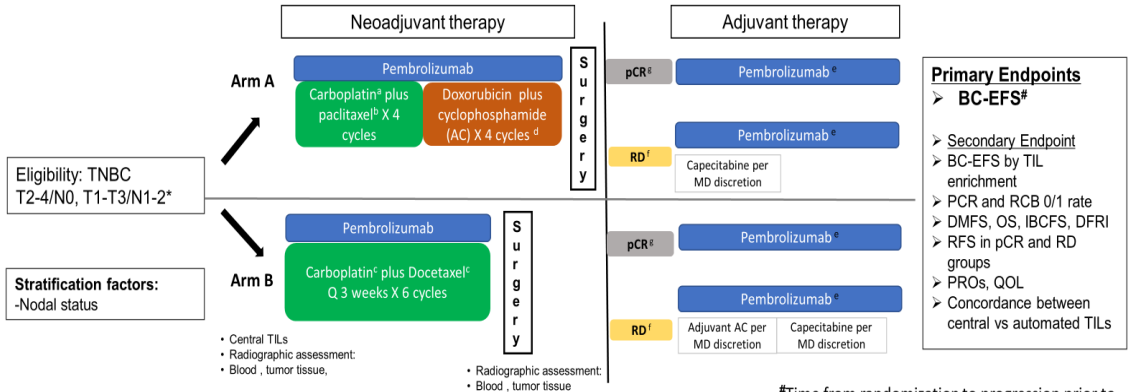
Optimal Chemotherapy partner/s

- Dependent on immune upregulation and to some degree on anatomical stage
- Immune enriched (stage I and II?)
  - Shorter duration of anthracycline-free chemoimmunotherapy
- Stage III, immune deplete
  - KN-522, ADC + IO , Adoptive cellular therapy (ACT)

S2212: Shorter Anthracycline-free Chemoimmunotherapy Adapted to pathological Response in Early TNBC (SCARLET)

Randomized non-inferiority trial

Hypothesis: In patients with early stage TNBC, carboplatin-taxane chemoimmunotherapy is non-inferior to taxane-platinum-anthracycline-based chemoimmunotherapy



*T4/N+ , any N3 and inflammatory breast cancer excluded
[a]Carboplatin QW or Q3W, [b] Paclitaxel QW.
[c] Carboplatin Q3W, Docetaxel Q3W
[d] AC every 2 or 3 weeks
[e] Total duration of neo plus adjuvant pembrolizumab = 51 weeks
[f] Adjuvant Olaparib per MD discretion in gBRCA+ allowed
[g] No Further Adjuvant chemotherapy.

N=2400

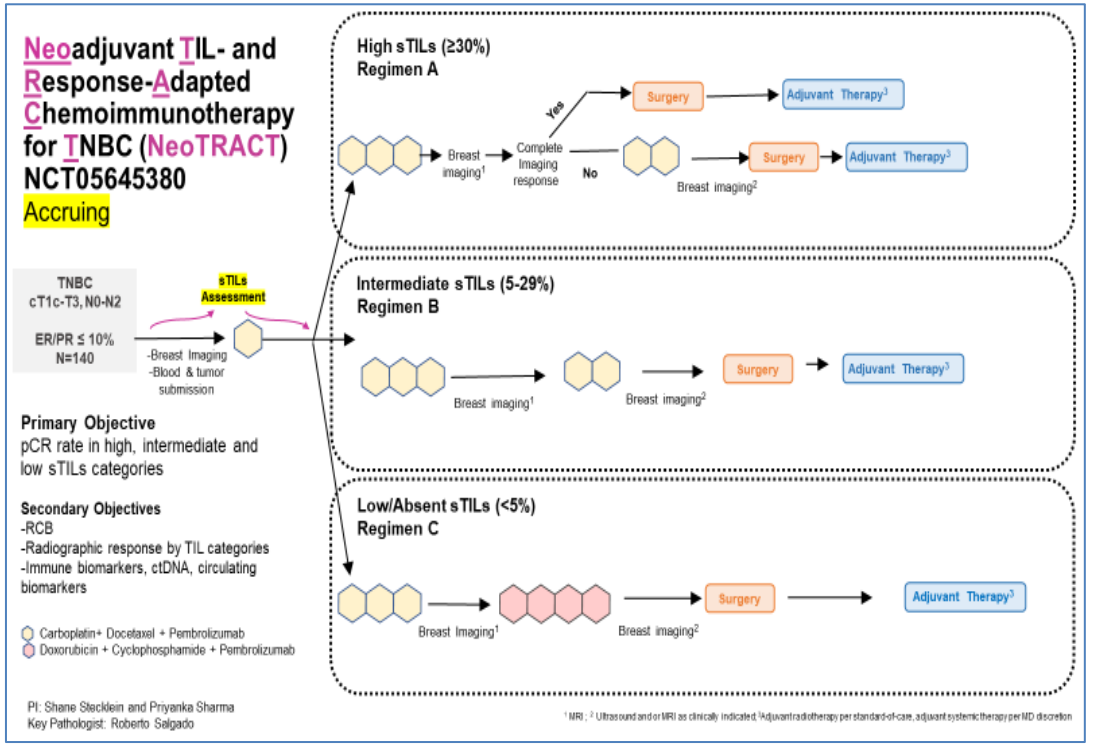
PI: Priyanka Sharma and Zahi Mitri

NCT05929768

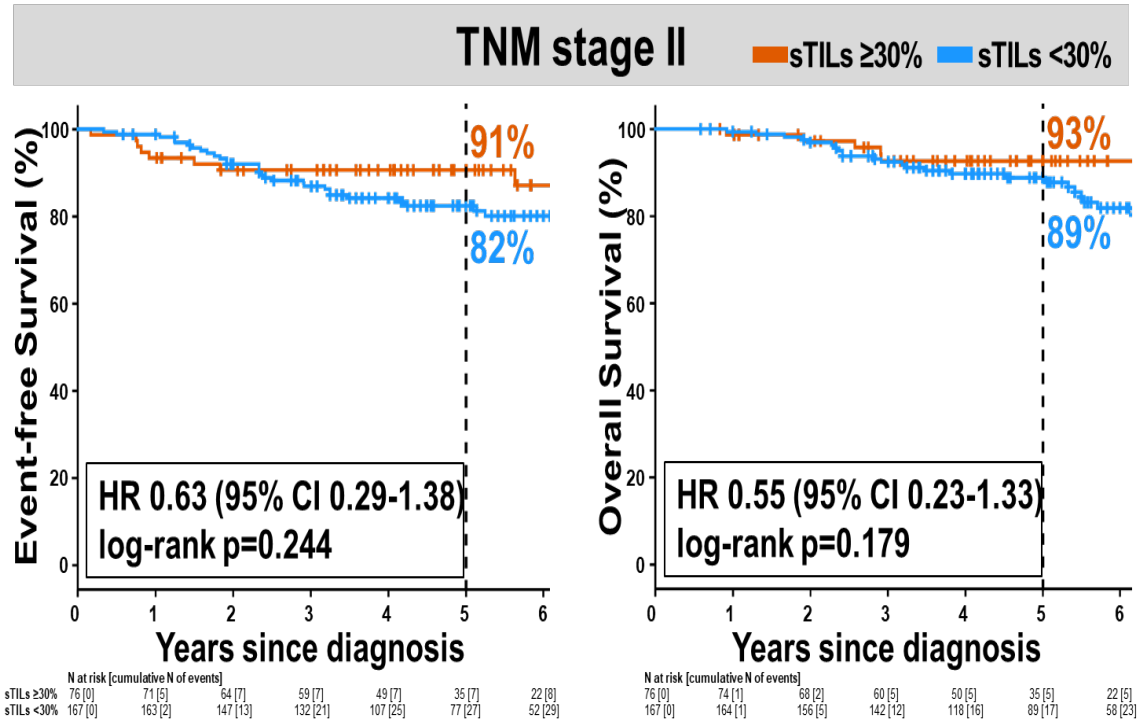
#Time from randomization to progression prior to surgery, invasive recurrence after surgery, new contralateral BC, or death due to any cause (**adjusted for nodal status and TIL enrichment**)

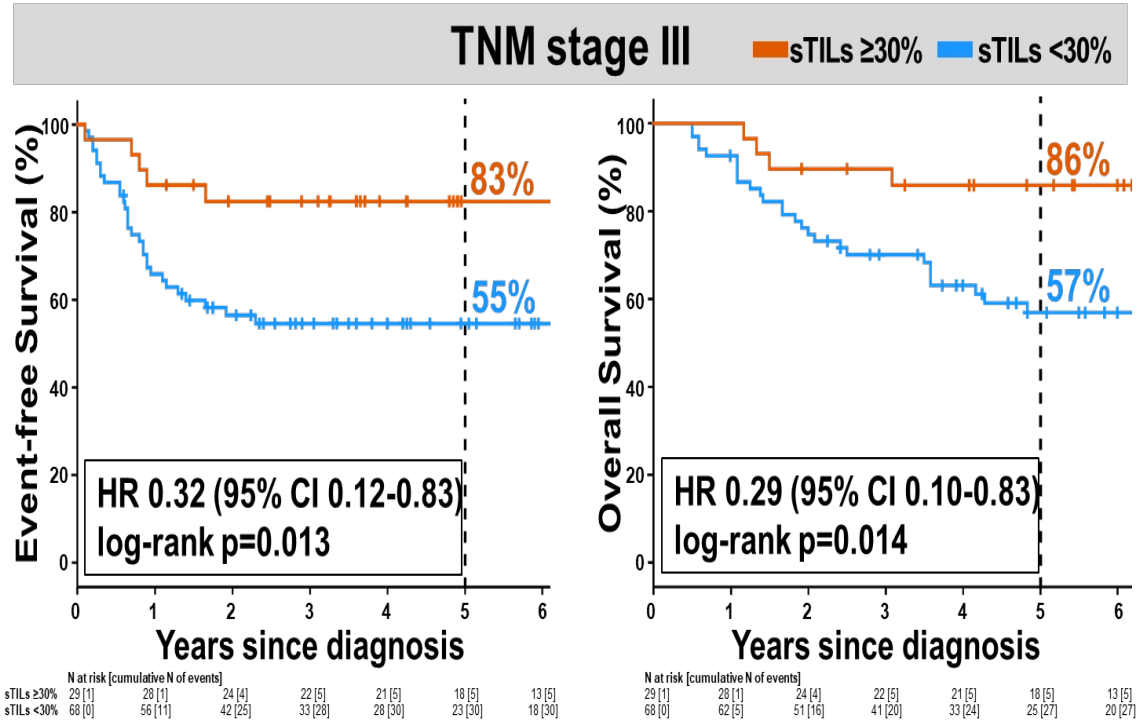
SWOG CANCER RESEARCH NETWORK

sTILs are integral marker for primary and secondary end point analysis



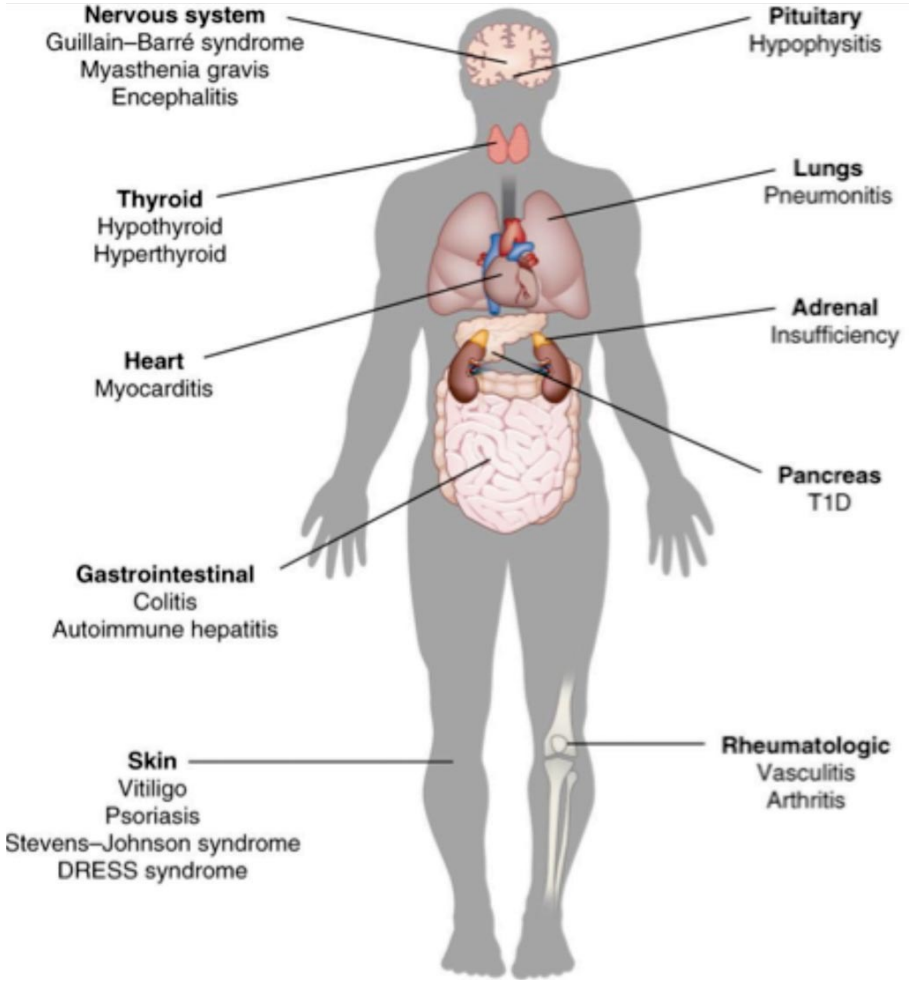
Do all patients with stage II-III eTNBC need chemo-immunotherapy ?





- A pooled analysis of two multi-site studies (NCT02302742, NCT01560663) of 474 patients with stage I (T>1cm)–III TNBC who received six cycles of neoadjuvant carboplatin (AUC 6) plus docetaxel (75 mg/m^2) (CbD).
- 5y OS of 93% with NACT alone in in patients with stage II disease and ≥30% sTILs (31% of patients with stage II disease had ≥30% sTILs). ? incremental benefit of adding immunotherapy in this subgroup

Safety of neoadjuvant immune check point inhibitors in early stage TNBC



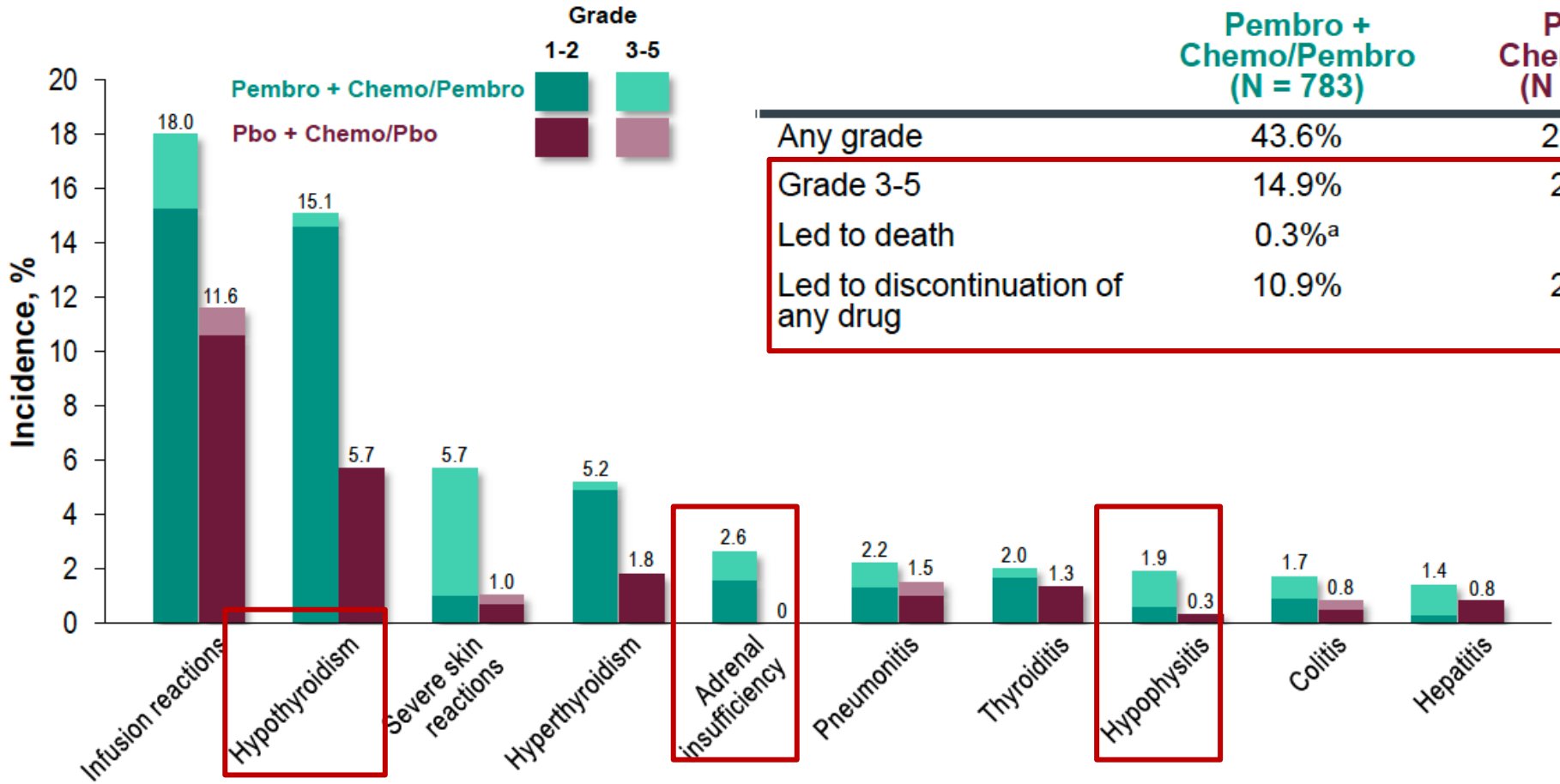
D'Abreo and Adams. Nat Rev Clin Oncol 2019, Brahmer et al, J Clin Oncol 2018

irAE incidence in eTNBC

- Any grade: 40-44%
- **Grade 3-5: 14-15%**

- **Mechanisms of irAEs are not well understood.**
- **Interplay between multiple factors including:**
  - **Clinical and demographic features**
  - **Auto-antibodies**
  - **Blood counts**
  - **Immune cells: T/B-cells, Tregs**
  - **Cytokines**
  - **Microbiome**
  - **Genetic factors: HLA, IL7 SNP**

Immune-Mediated AEs and Infusion Reactions in Combined Phases



	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%

Immune-Mediated AEs and Infusion Reactions with Incidence ≥10 Patients

Diabetes
Renal dysfunction
Inflammatory arthritis
Skin darkening

Immune AEs can happen post completion of IO
Females have a higher incidence of irAEs

KN522 Schmid et al

irAE: Post KN-522 data

Real World data
N=577 (17 sites), 18.2% Blacks

Adverse drug events(ADE) causing dose reduction	37.6%
ADE leading to early discontinuation	39.5%
irAE, all grades	71%
irAE ≥ 3 higher	**33.5%**

	Blacks	White	p
pCR	52.3%	55.9%	0.6
≥ 3 higher irAE	20.9%	33.8%	0.01
Hospitalization rate	39%	36%	0.5

TART
-1800days)
STOPPING ICI
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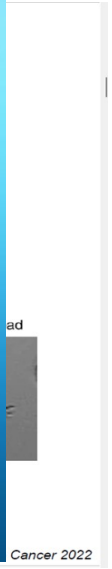


Hofherr et al SABCS 2023, Jacob et al SABCS 2023

irAE in early stage TNBC

- irAEs rates with KN-522 regimen in real world probably higher than noted in pivotal trials
- Rates ? differ by race in breast cancer: Race/ethnicity data on irAEs from large trials remain limited
- Up to 25% of patients may experience delayed irAEs: Diagnosis requires continued heightened awareness and prompt treatment.
- Future work is needed to identify clinical and molecular biomarkers that better predict individual patient's risk for irAE.

Biomarkers of irAEs	Effect on irAEs	References
Clinical Factors		
Sex	↑ in females (?)	Unger et al. 2022; Micelli et al. 2023; Hu et al. 2022
Pre-existing autoimmune conditions	↑ irAEs	Placais,et al. 2022
Auto-antibodies		
Thyroid auto-antibodies	↑ thyroid-specific irAEs	Daban et al. 2023; Kimbara et al. 2018
Other auto-antibodies	Unclear	Izawa et al. 2022
Blood cell counts		
Absolute eosinophil count	↑ irAEs	Zhou et al. 2023
Neutrophil/lymphocyte ratio	↑ irAEs (baseline) ↓ irAEs (on-treatment)	Zhou et al. 2023
Platelet/lymphocyte ratio	↑ irAEs	Zhou et al. 2023
Circulating cytokines		
IL-1, IL-8, IL-13, IFN-α… (at baseline or early during treatment)	↑ irAEs	Lim et al. 2019; Botticelli et al. 2023
Intestinal microbiome		
Bacteroides intestinalis	↑ irAEs (ileitis)	Andrews et al. 2021; Lam et al. 2021
HLA		
HLA-DRB1	↑ irAEs (pruritus)	Hassan Ali et al. 2023
HLA-DQB1	↑ irAEs (colitis)	Hassan Ali et al. 2023

None is currently used in clinical practice

Overview of the Management of irAEs

Early recognition and prompt management

ASCO

- **Grade 1:**
  - Continued CPI with close monitoring
- **Grade 2:**
  - Suspend CPI
  - Consider resuming once ≤ G1
  - Corticosteroids may be administered
- **Grade 3:**
  - Suspend CPI
  - Initiate high-dose corticosteroids; taper over at least 4 to 6 weeks
  - Some refractory cases may require infliximab or other immunosuppressive therapy
- **Grade 4:**
  - Permanent discontinuation recommended

sitc

Society for Immunotherapy of Cancer

- **Grade 1:**
  - Continue immunotherapy
  - Corticosteroids not usually indicated
- **Grade 2:**
  - Hold CPI during corticosteroid use
  - Taper corticosteroids once ≤ G1
  - Restart CPI once resolved to ≤G1 and off corticosteroids
- **Grade 3:**
  - Hold CPI
  - Taper corticosteroids once ≤ G1
  - Discontinue immunotherapy if symptoms do not improve in 4 to 6 weeks
- **Grade 4:**
  - Discontinue immunotherapy
  - Corticosteroids can be used

Neoadjuvant immunotherapy response biomarkers

- PD-L1 not predictive X
  - Consistent findings from most studies (except NeoTRIP)
- TILs, TMB, many immune signatures also not predictive X
  - Predict response to neoadjuvant chemo-immunotherapy but NOT preferential response to addition of check point inhibitor
- DETERMA IO score ?
  - Measures both tumor gene expression and the tumor immune microenvironment
  - Preferential benefit from Chemo+Atezo vs Chemo in NeoTRIP and high pCR in NeoPACT
- MHC-II expression on tumor cells ?
  - Predictive of pCR with durvalumab + NAC and pembrolizumab + NAC in cross trial comparisons
- CD8+TCF1+Ki67+ ?
  - High CD8+TCF1+Ki67+ density linked to increased pCR and EFS with the addition of atezolizumab to chemotherapy in NeoTRIP
- ImSig Proliferation in immune low tumors ?
  - NeoPACT and neoSTOP analysis

Sinn BV, et al. *Clin Cancer Res* 2021;27:2584-2591, Gonzalez-Ericsson et al Clin Cancer Res 2021 , Bianchini et al ESMO 2021, Sharma et al JAMA oncology 2022, Stecklein et al ASCO 2023, Giani et al ESMO 2023

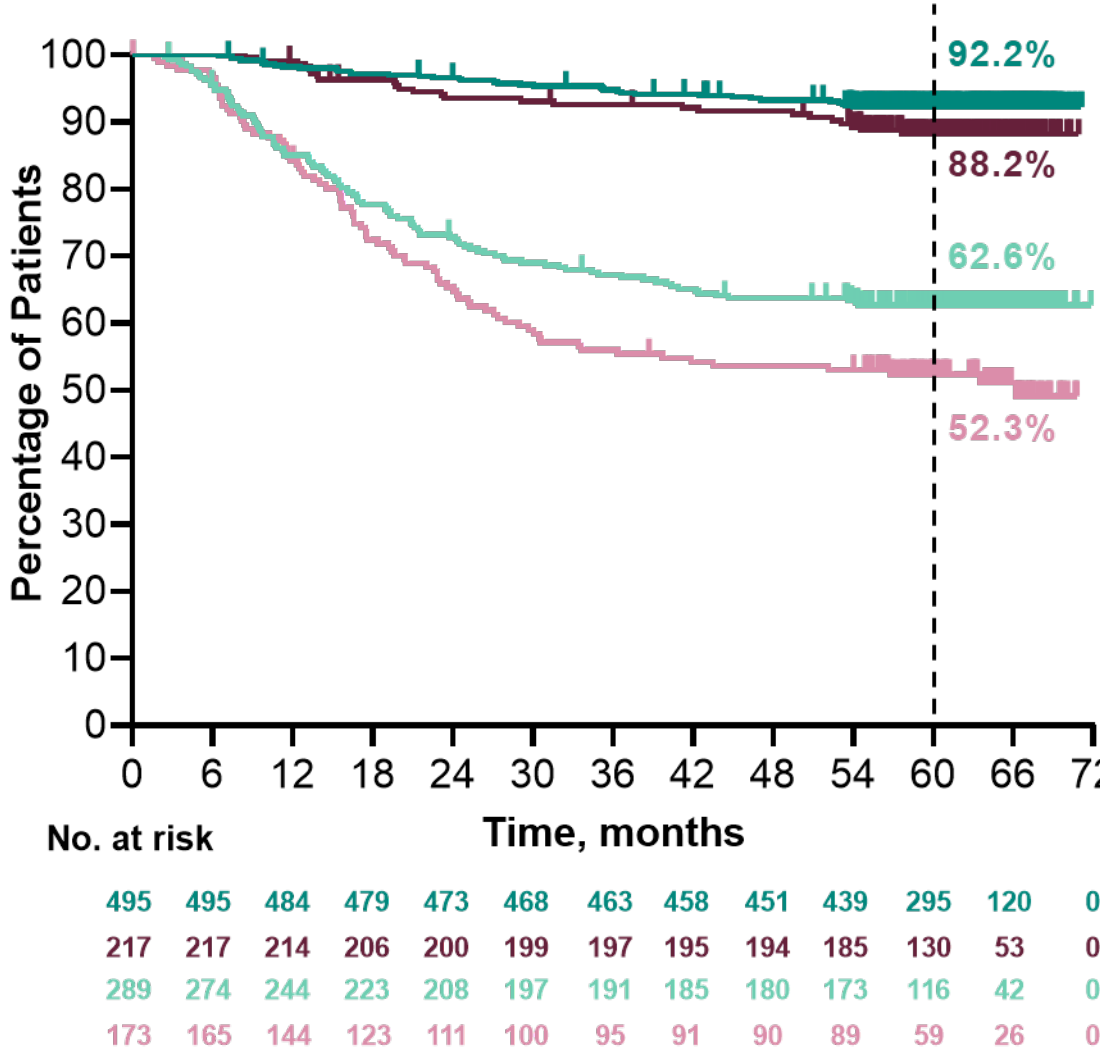
Neo-adjuvant immunotherapy in TNBC: Current state

- Addition of immune check point inhibitor to NACT improves EFS/iDFS
  - Modest improvement in pCR leading to bigger EFS improvements
  - Overall survival data pending
  - Individual patient selection biomarkers remain elusive
- In immune enriched tumors 12-18 weeks of taxane-platinum based chemoimmunotherapy leads to high (>70% pCR rates)
  - ? Can Longer/more intense regimens be detrimental in immune enriched tumors

Knowledge Gaps

- Do all patients need 4-drug poly-chemotherapy when immunotherapy is part of NAST?
  - Can we de-escalate chemotherapy? S2212
  - I-SPY 2.2: Ongoing arms assessing novel agents/combinations to allow early de-escalation
- Role of adjuvant ICB
  - In setting of PCR (OptimICE-PCR)
  - In setting of Residual disease (SWOG 1418)
- Do all patients need chemotherapy plus immunotherapy?
  - Can we identify patients who do not need/unlikely to benefit from ICB?
- Patient perspective
  - Long term side effects of ICB in curative setting, toxicity predictors, impact on fertility
- Pathological response to guide adjuvant de/escalation strategies
  - pCR is associated with excellent long-term outcomes: serves as a guide for de-escalation strategies
  - Residual disease is associated with high risk of recurrence (despite adjuvant capecitabine): escalation strategies
- Early identification of patients unlikely to achieve optimal response with neoadjuvant treatment
  - Tissue, Imaging +/- Machine learning/AI, Circulating biomarkers (ctDNA)
  - Neoadjuvant testing of novel more effective therapies

KEYNOTE-522: EFS by PCR

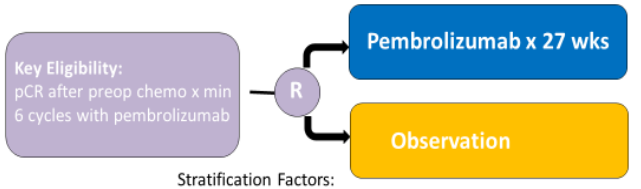


? Benefit from adjuvant ICB

38% event rate despite neo+adjuvant ICB

OptimICE-pCR

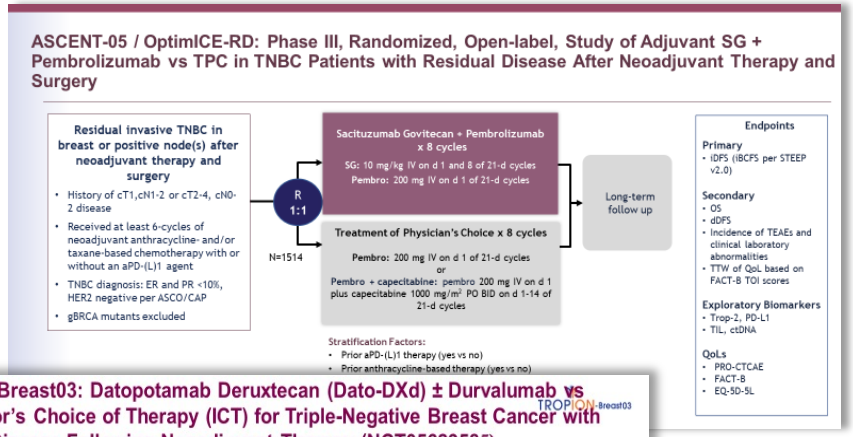
A Randomized, Open-label, Phase 3 Study of Adjuvant Pembrolizumab Versus Observation in Triple Negative Breast Cancer with pCR After Surgery and Neoadjuvant Chemotherapy and Checkpoint Inhibitor Therapy

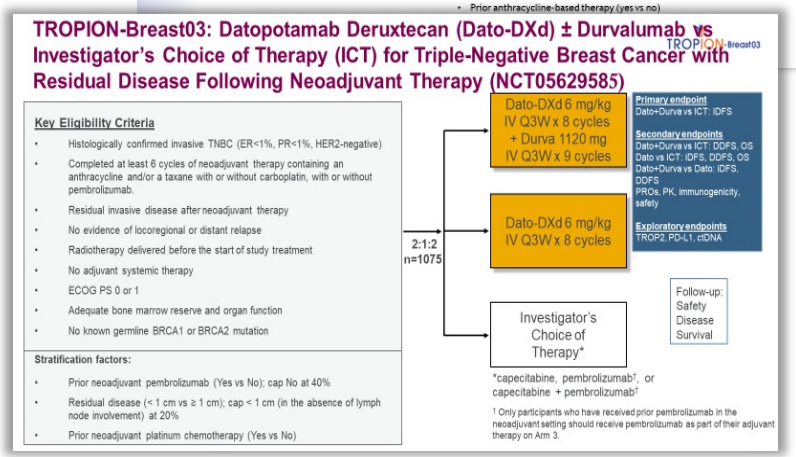


Stratification Factors:
- Baseline nodal status
- Receipt of anthracycline chemotherapy: yes vs. no

- **Primary Objective:**

To evaluate whether observation results in a non-inferior RFS compared to adjuvant pembrolizumab in early-stage TNBC patients who achieve a pCR after neoadjuvant chemotherapy with ICI therapy



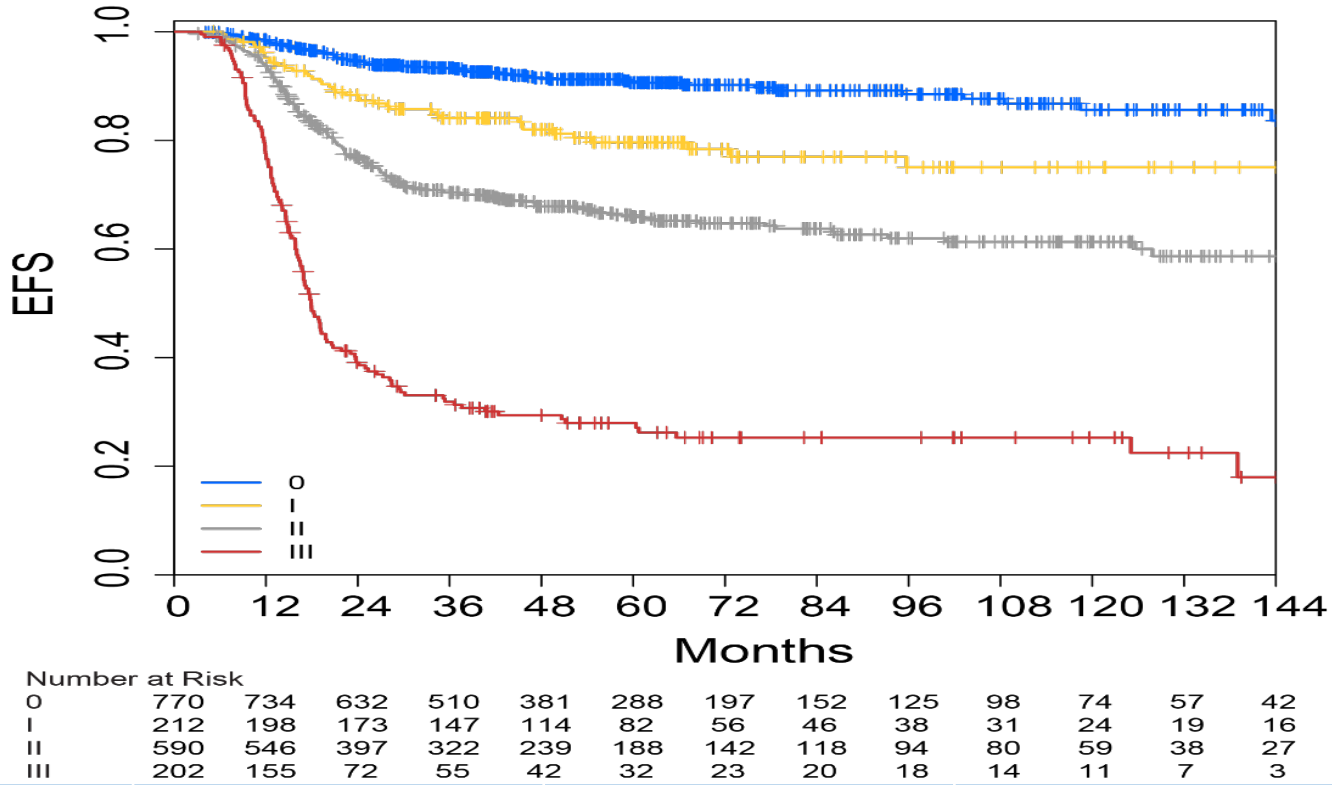


Schmid et al ESMO plenary 2021

ICB, immune checkpoint blockade.

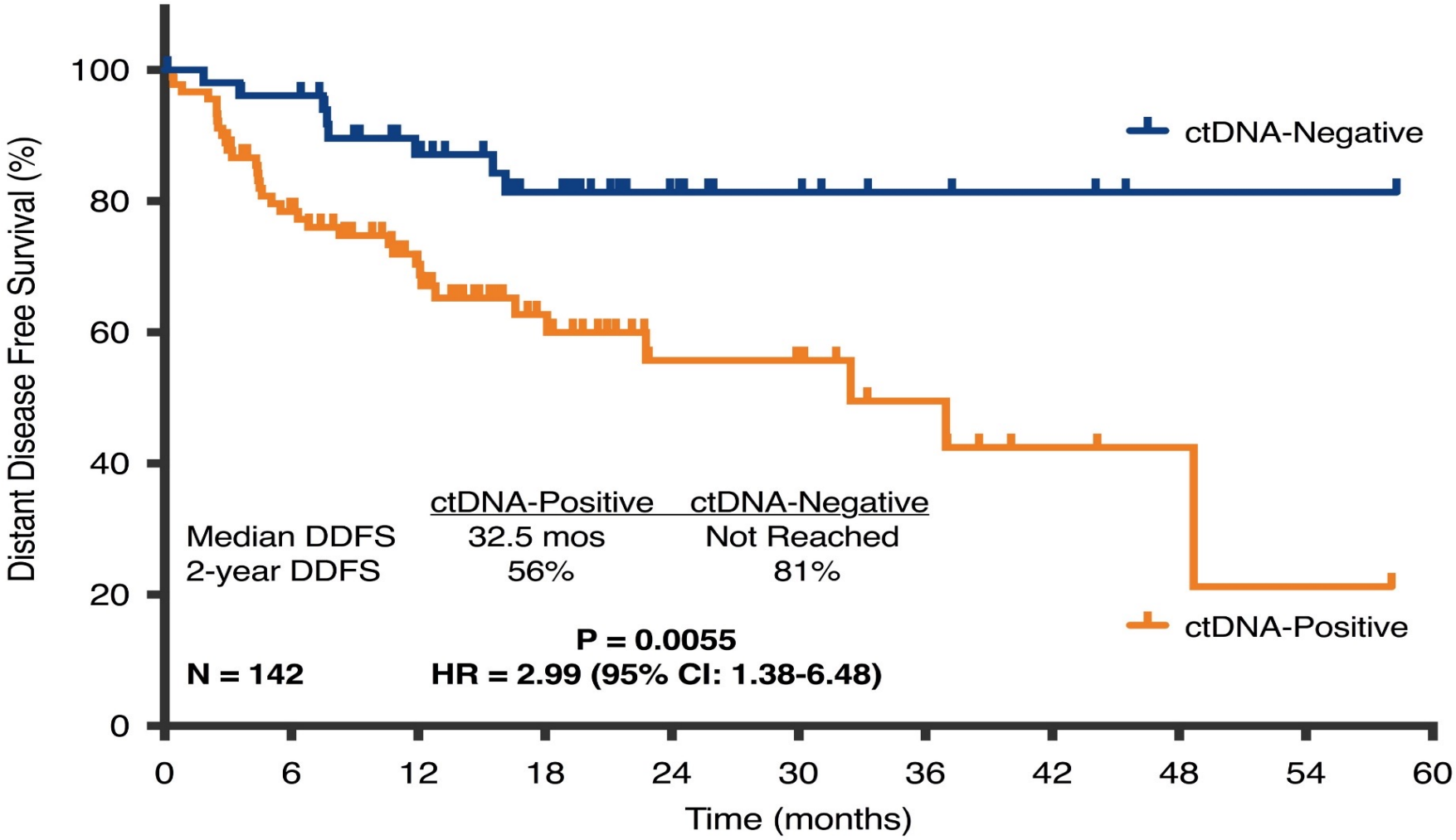
Refining Risk in patients with residual disease

Symmans et al Lancet Oncology 2021



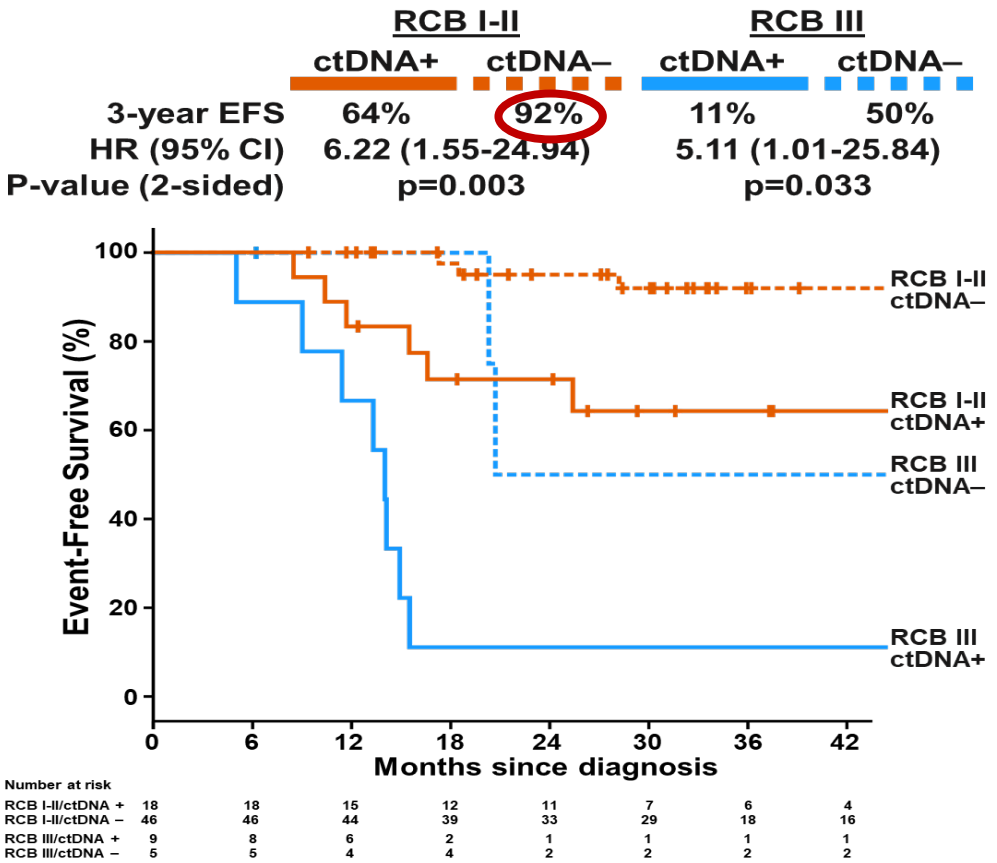
Phenotype	Outcome	pCR=RCB-0	RCB-I	RCB-II	RCB-III
HR-/HER2- (N=1774)	Frequency (%)	43%	12%	33%	11%
	5 yr EFS (95% CI)	91% (88%-93%)	80% (74%-86%)	66% (62%-70%)	28% (22%-35%)
	10 yr EFS (95% CI)	86% (81%-90%)	75% (68%-83%)	61% (57%-66%)	25% (19%-33%)

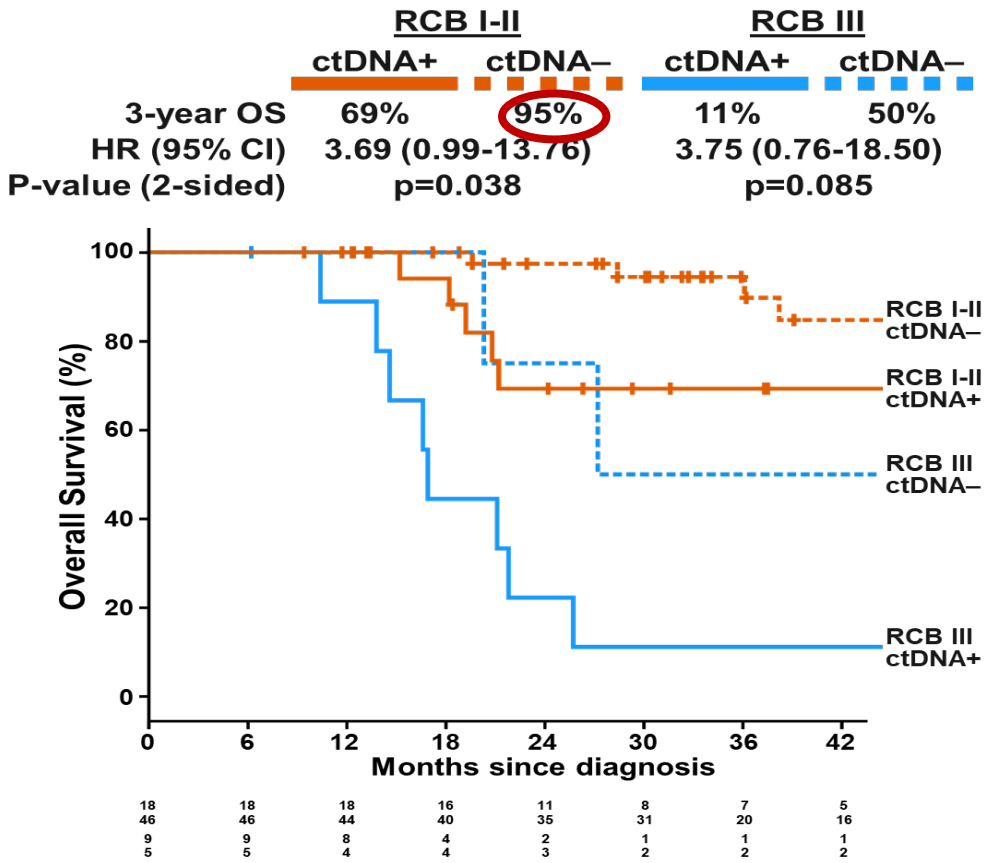
Association of ctDNA with outcomes in patients with residual disease



Radovich, M.,*JAMA oncology 2020*

Combined impact of post treatment ctDNA and RCB on outcomes **in** patients with residual disease



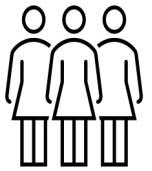


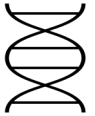
- Overall, 3-year EFS: 46% vs 84% (ctDNA+ vs ctDNA-)
- ctDNA status discriminates outcomes in patients with RCB I-II
- RCB III has poor outcome regardless of ctDNA status

Stecklein et al NPJ 2023

Closing the gap:Optimal systemic therapy in eTNBC

- Patient selection, DEI
- Optimizing chemotherapy backbone
- Tailoring therapy de/escalation to response
- Risk-Benefit, QOL, Long term toxicity
- Predictive biomarkers or response and toxicity
- Patient advocacy and community engagement





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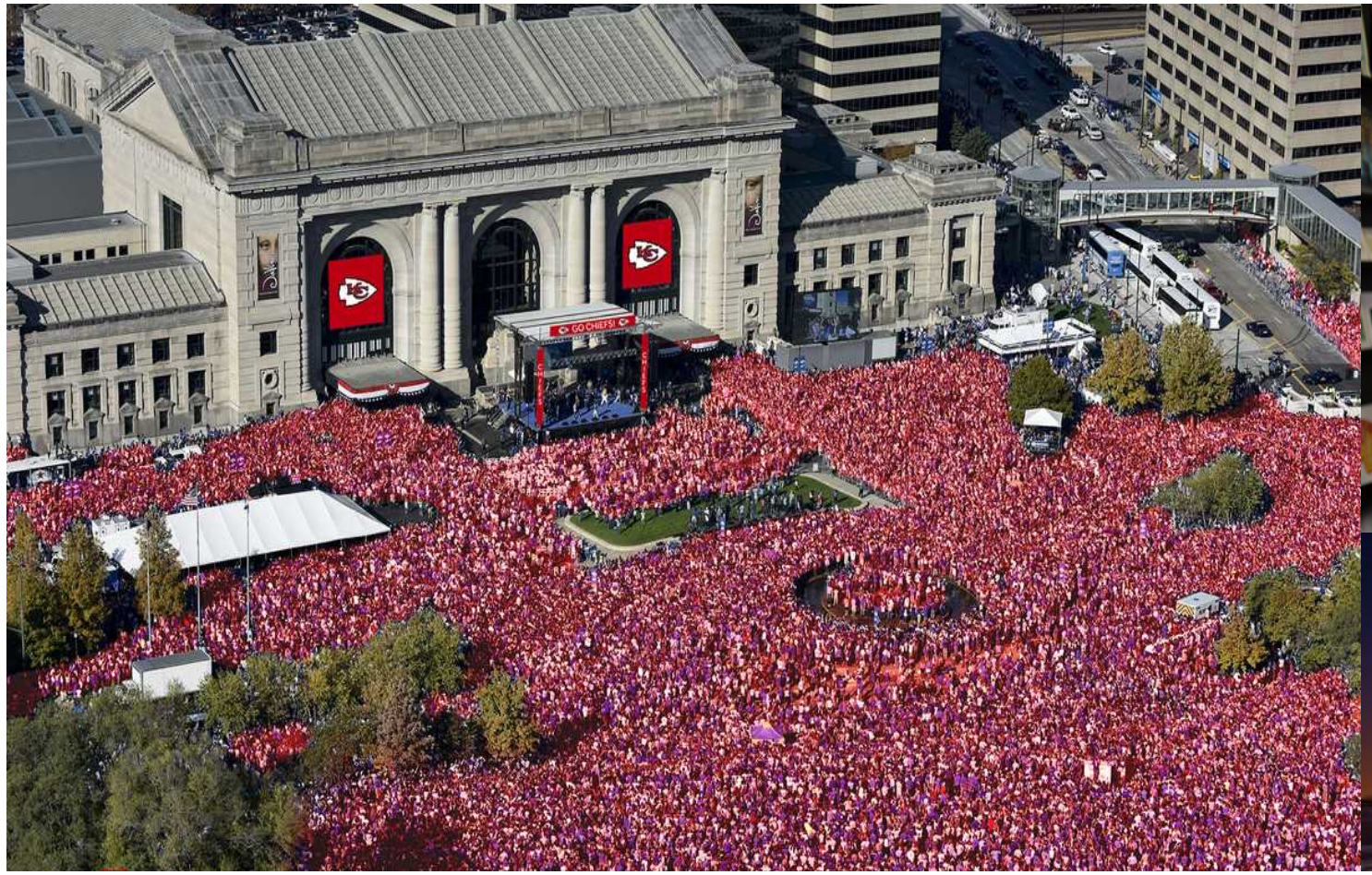

EXTRA SLIDES