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Cancer research
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MODULE 2:
Treatment of early TNBC: what is the current optimal algorithm?

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by SOLTI

COIs disclosure

Employment: Hospital General Universitario Gregorio Marañón & Universidad Complutense de Madrid

Consultant or Advisory Role: Celgene, Novartis, Pierre Fabre, Pfizer, Roche, Astra-Zeneca, Daichii-Sankyo, SeaGen, Gilead, Eisai, MSD, Veracyte and Lilly

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Speaking: Novartis, Roche, Lilly

Travel Grant: Pfizer

Outline

- TNBC epidemiology & biology overview
- Navigating the early TNBC algorithm of treatment
  - Small TNBC tumors
    - Potential for de-escalation based on biology (TILs and histology)
  - Stage II and III TNBC
    - NACT
    - Adjuvant post-NA CT
    - NACT+IO
    - Adjuvant post-NA IO
    - The role of TT in the (neo)adjuvant setting
- Challenges ahead in early TNBC
  - Biomarkers and further steps (new drug development)

TNBC epidemiology & biology

TNBC epidemiology

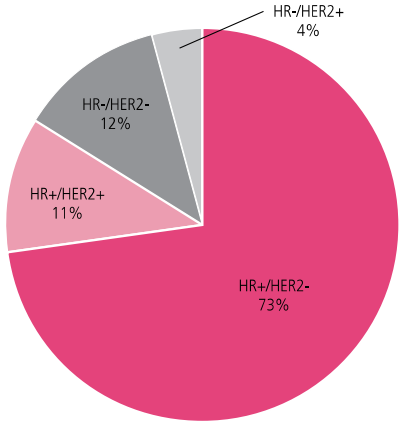
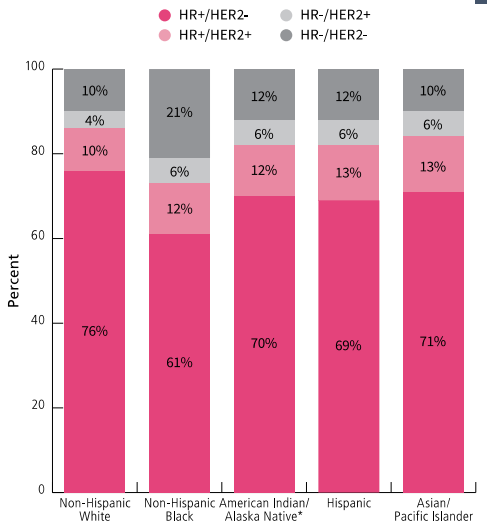
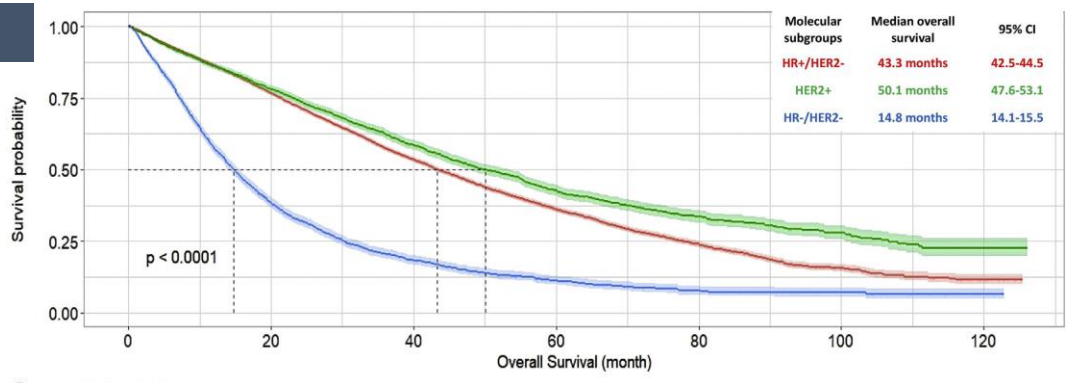


Figure 4. Distribution of Breast Cancer Subtypes by Race/Ethnicity, Ages 20 and Older, US, 2012-2016



ESME Registry (2008-16)

Median OS (95% CI) (months) by year of diagnosis of MBC	
2008	39.1 (36.2-46.5)
2009	42.1 (38.2-50.8)
2010	39.4 (35.9-45.4)
2011	41.1 (35.5-48.3)
2012	50.8 (45.0-55.5)
2013	58.0 (52.0-68.4)
2014	NR (50.6-NR)
2015	NR (55.7-NR)
2016	NR (NR-NR)



5-Year Relative Survival Percent, Female Breast Subtypes by SEER Combined Summary Stage

Subtype	Localized	Regional	Distant
HR+/HER2-	100.0%	90.1%	31.9%
HR-/HER2-	91.3%	65.8%	12.0%
HR+/HER2+	98.8%	89.3%	46.0%
HR-/HER2+	97.3%	82.8%	38.8%
Unknown	96.1%	76.4%	15.6%
Total	99.1%	86.1%	30.0%

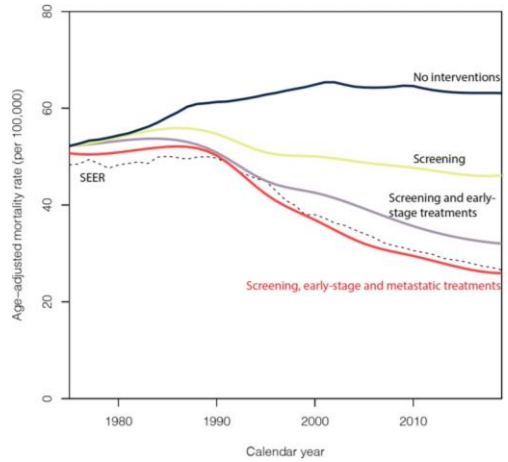
Total 5-yr relative survival

SEER 17 2012–2018 ALL 90.6% vs **TNBC 77.1%**

Contributions of screening, early-stage and metastatic treatment to BC mortality reduction by molecular subtype US (2000-2017)

Overall mortality reduction in 2019

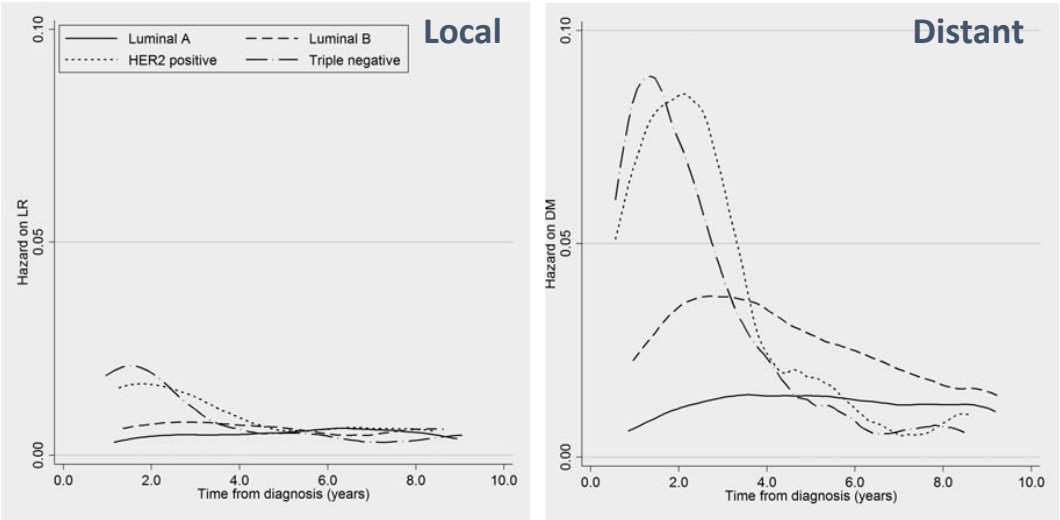
ALL 58% vs ER+/HER2+ 71% vs **TNBC 40%**



https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/breast-cancer-facts-and-figures-2019-2020.pdf; https://seer.cancer.gov/statfacts/html/breast-subtypes.html; Deluche et al EJC 2020; Caswell-Jin et al ASCO 2022

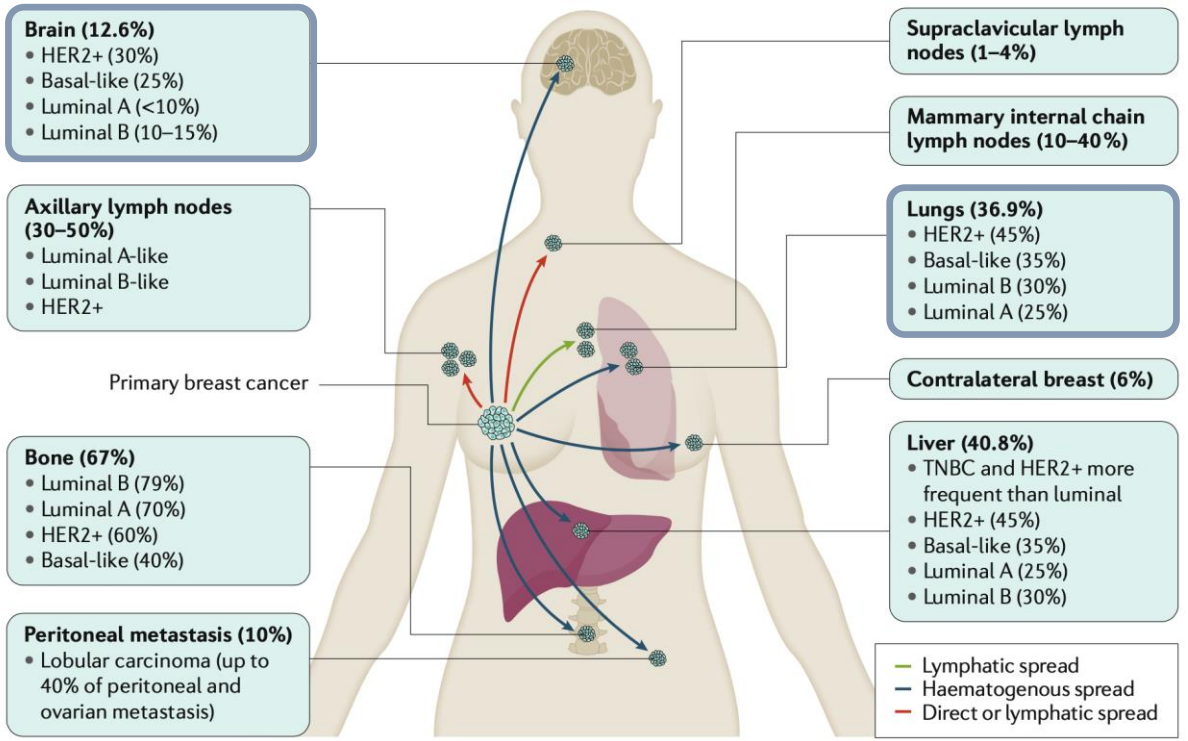
TNBC patterns of recurrence

Hazards of recurrence 10 yrs after diagnosis by BC subtype



- Higher probability of relapse and poorer survival vs non-TNBC
- Higher visceral relapse over first 5 yrs but not with long FU vs HR+BC pattern
- Site-specific recurrence pattern: visceral mets as 1st site (84% vs 61%)

Most common sites of metastasis by BC subtype



Subtype	No. of Patients	Brain Incidence Rate (%)	Brain 95% CI (%)	Liver Incidence Rate (%)	Liver 95% CI (%)	Lung Incidence Rate (%)	Lung 95% CI (%)	Bone Incidence Rate (%)	Bone 95% CI (%)	Distant Nodal Incidence Rate (%)	Distant Nodal 95% CI (%)	Pleural/Peritoneal Incidence Rate (%)	Pleural/Peritoneal 95% CI (%)	Other Incidence Rate (%)	Other 95% CI (%)
Luminal A	1639	2.2	1.6 to 3	7.9	6.7 to 9.4	6.7	5.5 to 7.9	18.7	16.8 to 20.7	4.5	3.5 to 5.6	7.8	6.6 to 9.2	3.8	2.9 to 4.8
Luminal B	893	4.7	3.4 to 6.2	13.8	11.6 to 16.2	13.4	11.2 to 15.8	30.4	27.4 to 33.5	9.6	7.8 to 11.7	14.7	12.5 to 17.2	8.1	6.4 to 10
HER2 positive, ER/PR positive	244	7.9	4.8 to 12	21.3	16.3 to 26.7	17.7	13.2 to 22.8	30.9	25.2 to 36.7	10.5	7 to 14.8	16	11.7 to 21	6.6	3.9 to 10.2
HER2 positive, ER/PR negative	266	14.3	10.4 to 18.8	23.3	18.4 to 28.6	24.1	19.1 to 29.3	30.1	24.7 to 35.7	13	9.2 to 17.4	16.2	12 to 20.9	8.8	5.8 to 12.7
Basal-like	367	10.9	8 to 14.3	9.3	6.6 to 12.5	18.5	14.7 to 22.7	16.6	13 to 20.6	17.2	13.5 to 21.2	12.8	9.6 to 16.5	10.4	7.5 to 13.7
TN nonbasal	318	7.2	4.7 to 10.4	10.7	7.6 to 14.4	12.5	9.1 to 16.5	15.1	11.4 to 19.4	12.3	8.9 to 16.1	9.2	6.3 to 12.7	9.2	6.2 to 12.9
P			< .001		< .001		< .001		< .001		< .001		< .001		< .001

Chen et al Cancer Epidemiol Biom and Prevent 2012; Van Maaren et al IJC 2019; Kennecke et al JCO 2010; Harbeck et al Nat Rev Disease Primers 2019; Foulkes et al. NEJM 2010

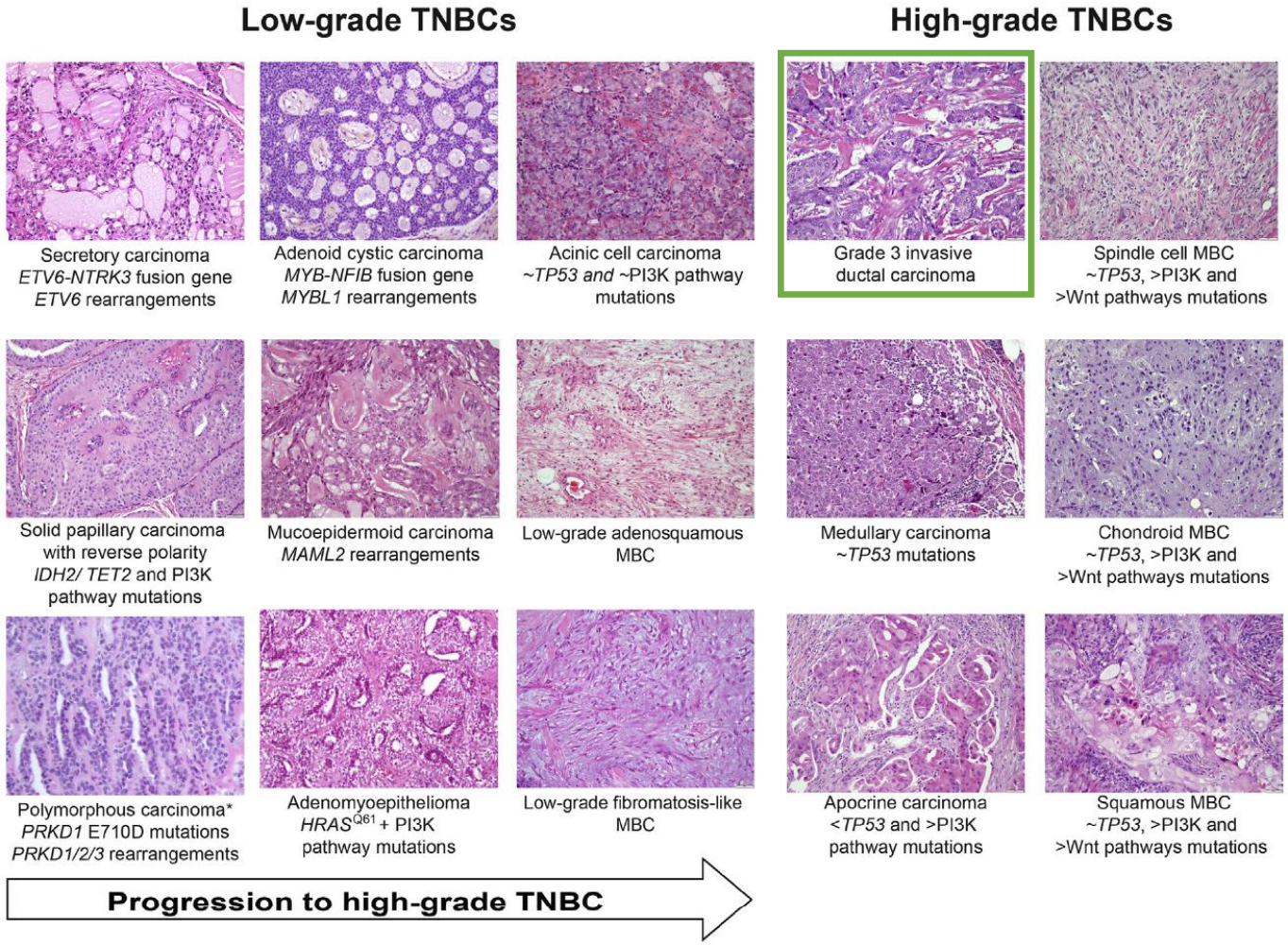
TNBC definition and pathology overview

- TNBC (phenotype) is defined by the **lack of** IHC staining for ER, PR, and HER2 overexpression/HER2 gene amplification
- Controversy regarding prior arbitrary thresholds for positivity for ER and PgR status (<1%)
  - **"ER-low"** category: 1-10% positive tumor cells (ASCO/CAP 2020)
    - ER-low expression in BC is predictive for response to NACT with anticipated pCR comparable to ER-negative BC.
    - ER-low BC appears to resemble ER-negative more than ER-positive BC in terms of prognosis

1%-10% of cells staining

↓

Report as ER Low Positive and add recommended comment‡ (reported data elements should include percentage of cells staining, intensity, and status of controls†)

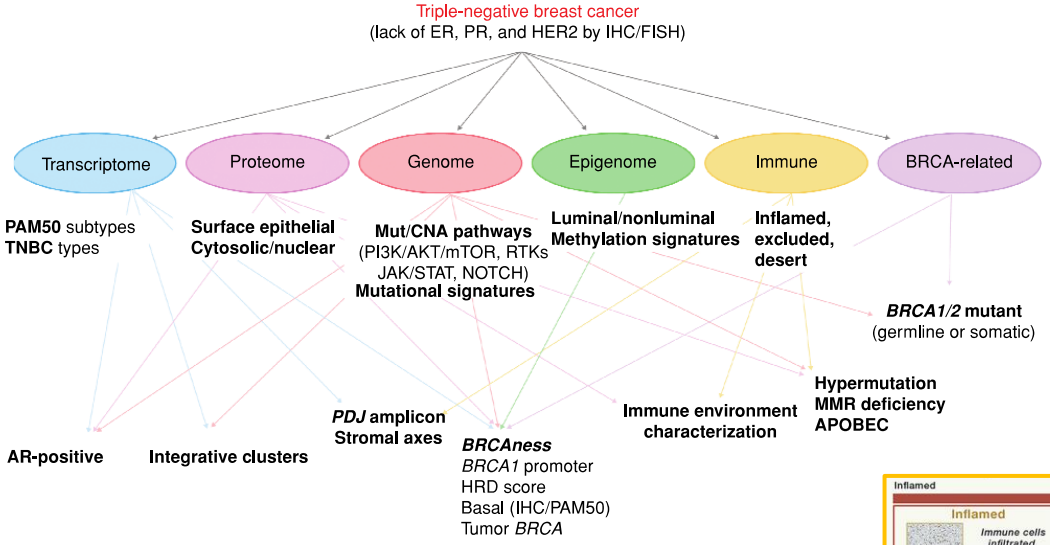


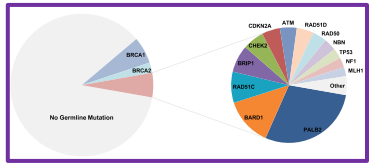
TNBC spectrum of histologic subtypes

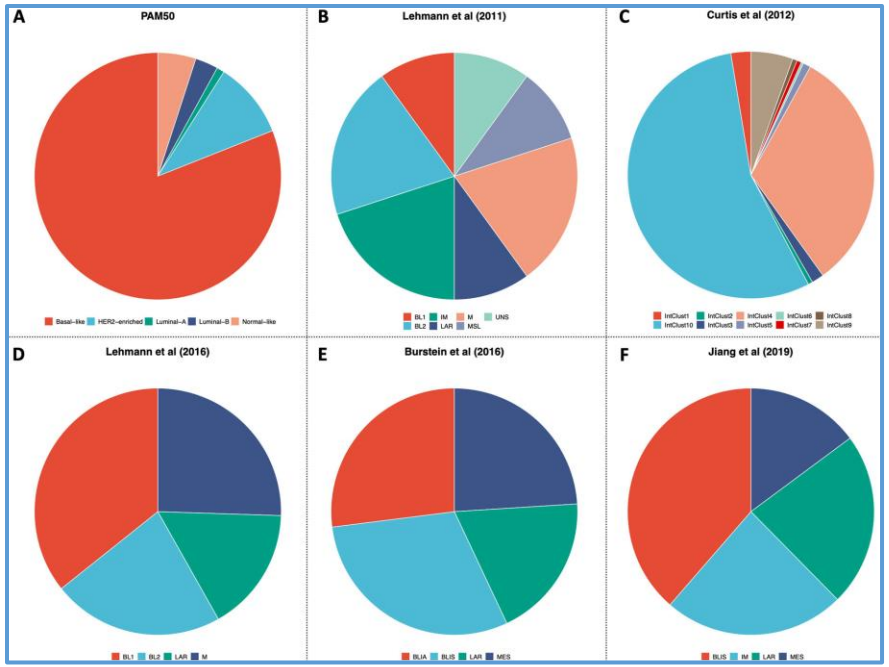
- TNBC use to be high grade (G3), have pushing borders and central necrotic areas, neoplastic cells are arranged in solid sheets or nests, and lymphocytic infiltrates at the periphery of the tumor and within the bulk of the tumor
- Neoplastic cells are atypical and pleomorphic, and have a high mitotic rate
- Sometimes have medullary features and metaplastic elements (squamous or spindle cells)

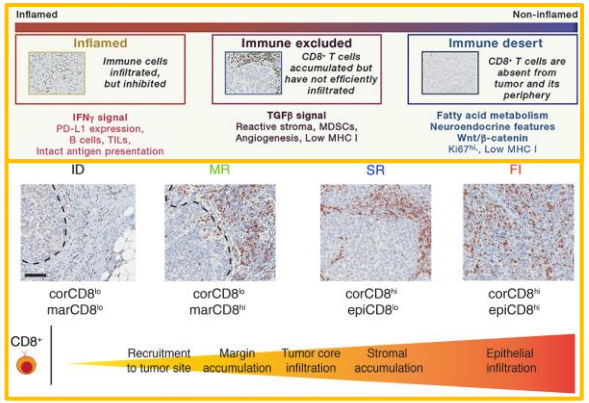
Allison et al JCO 2020; Geyer et al Am J Pathol 2017; Pareja et al npj; Paakkola et al ESMO Open 2021

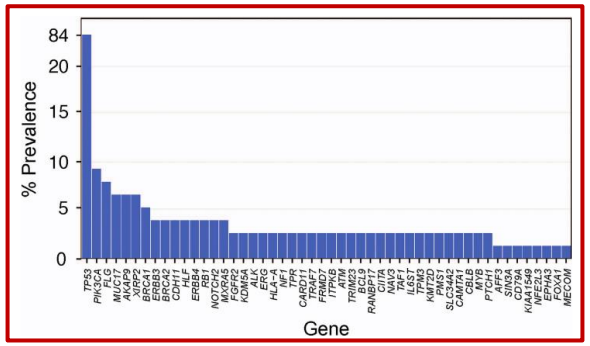
TNBC molecular heterogeneity

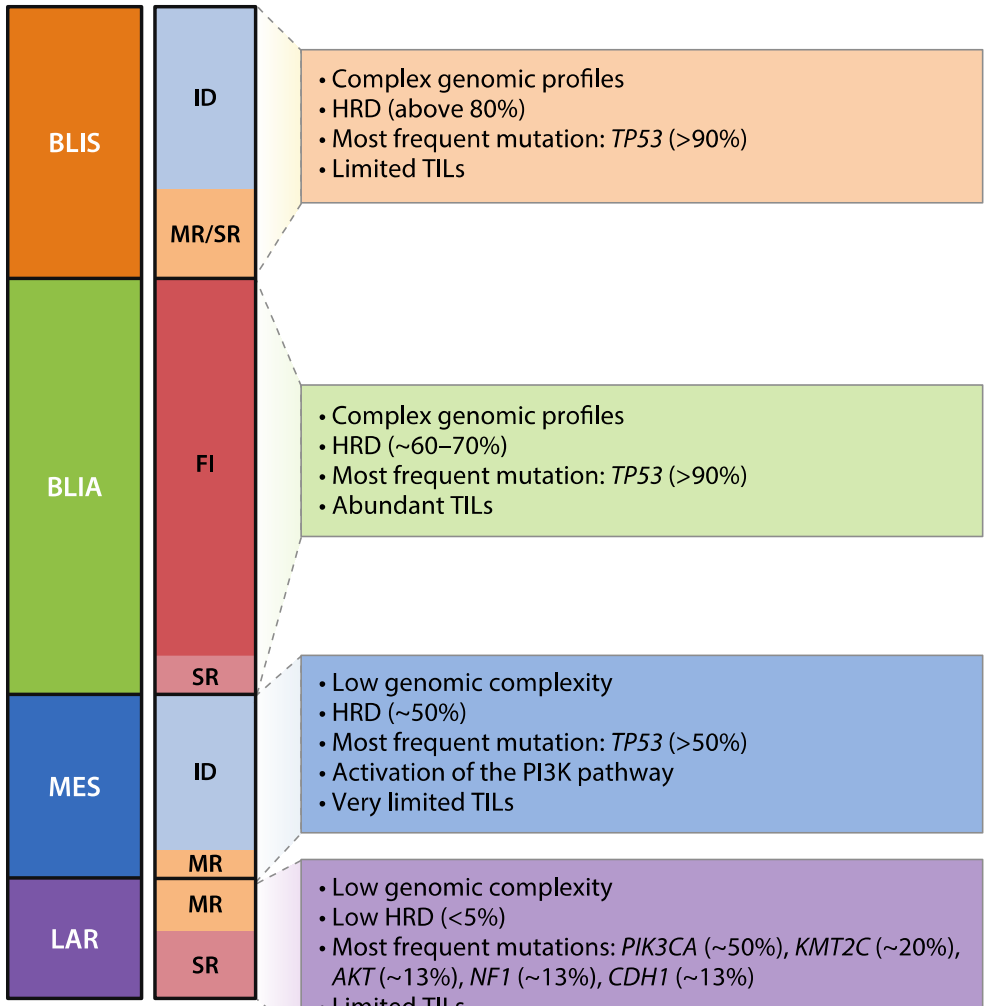






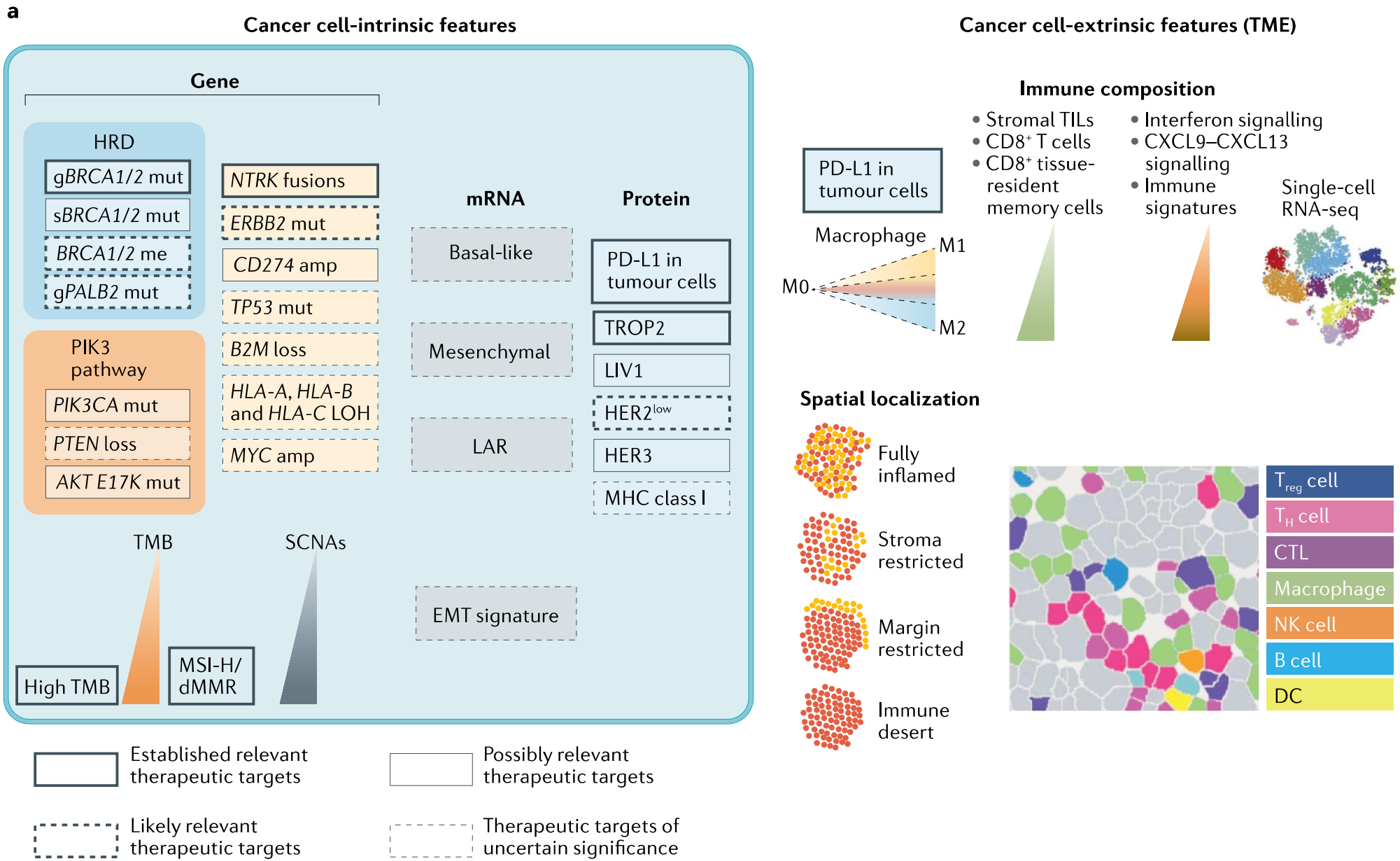






Garrido-Castro et al Cancer Discov 2019; Marra et al npj Breast Cancer 2020; Pareja et al npj Breast Cancer 2016; Derakhshan et al Ann Rev Pathol Mech Dis 2022; Gruosso et al JCI 2019; Hegde et al Immunity 2020; Howard et al Cancer J 2021

Molecular features of the TNBC ecosystem



Bianchini et al NRCO 2021

Early TNBC algorithm proposal

Early TNBC algorithm of treatment evolution: where do we start @2020

Early TNBC (ER/PgR- and HER2-)

- pT1pN0
  - pT1a (≤0.5 cm) → No adjuvant CT
  - pT1b (0.5-1 cm) → Consider adjuvant CT (simple regimens*)
  - pT1c (1-2 cm) → Adjuvant CT (simple* or sequential regimens**)
- pT2, pT3 and/or pN≥1 → NACT (sequential regimens)

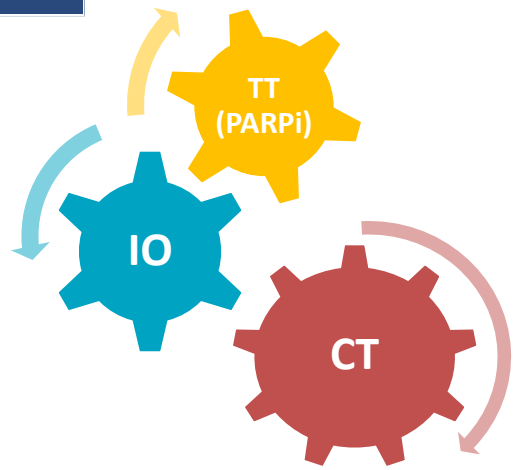
Adding platinum can be discussed in selected patients
Taxane/platinum regimens is an option in patients with contraindication to anthracyclines

Predicting response to NACT (TILs, PD-L1, GEP, HRD, machine learning algorithms)

Prognosis and treatment selection (TILs, RCB, ctDNA, gene signatures)

- pCR (ypT0pN0) → No further treatment
- ypT1–4N0 or ypN≥1 → Capecitabine (6-8 cycles)

Clinical trials (CT, ICI, PARP-I, new drugs)



PRINCIPLES OF PREOPERATIVE SYSTEMIC THERAPY

National Comprehensive Cancer Network®

Known Benefits of Preoperative Systemic Therapy
- Facilitates breast conservation
- Can render inoperable tumors operable
- Treatment response provides important prognostic information at an individual patient level, particularly in patients with TNBC or HER2-positive breast cancer
- Identifies patients with residual disease at higher risk for relapse to allow for the addition of supplemental adjuvant regimens, particularly in patients with TNBC or HER2-positive breast cancer.
- Allows time for genetic testing
- Allows time to plan breast reconstruction in patients electing mastectomy
- Allows time for delayed decision-making for definitive surgery

Opportunities
- May allow SLNB alone if initial cN+ becomes cN0 after preoperative therapy
- May provide an opportunity to modify systemic treatment if no preoperative therapy response or progression of disease
- May allow for more limited radiation fields in patients with cN+ who become cN0/pN0 after preoperative therapy
- Provides excellent research platform to test novel therapies and predictive biomarkers

Cautions
- Possible overtreatment with systemic therapy if clinical stage is overestimated
- Possible undertreatment locoregionally with radiotherapy if clinical stage is underestimated
- Possibility of disease progression during preoperative systemic therapy

Candidates for Preoperative Systemic Therapy
- Patients with inoperable breast cancer:
  - IBC
  - Bulky or matted cN2 axillary nodes
  - cN3 nodal disease
  - cT4 tumors
- In select patients with operable breast cancer
  - Preoperative systemic therapy is preferred for:
    - HER2-positive disease and TNBC, if ≥cT2 or ≥cN1
    - Large primary tumor relative to breast size in a patient who desires breast conservation
    - cN+ disease likely to become cN0 with preoperative systemic therapy
  - Preoperative systemic therapy can be considered for cT1c, cN0 HER2-positive disease and TNBC
- Patients in whom definitive surgery may be delayed.

Non-candidates for Preoperative Systemic Therapy
- Patients with extensive in situ disease when extent of invasive carcinoma is not well-defined
- Patients with a poorly delineated extent of tumor
- Patients whose tumors are not palpable or clinically assessable

Marra et al Cancer J 2021; Burstein et al Ann Oncol 2021; Loibl et al Lancet 2021; NCCN guidelines v4.2022

Navigating the early TNBC algorithm of treatment

Early TNBC

pT1a pN0

No CT?

pT1b-c pN0

Adjuvant CT

≥T2 and/or ≥N1

NACT — **Sequential Regimens anthra/taxanes Including Platinums (escalation/de-escalation)**

NACT+ICIs — **Atezo/Durva/Pembrolizumab**

No pCR

Pembrolizumab — Adjuvant postNA ICIs

Capecitabine — Adjuvant postNA CT

Olaparib (gBRCAmut) — Adjuvant postNA TT

Clinical Trials?

pCR

No further Systemic Therapy?

Adjuvant postNA ICIs — **Pembrolizumab?**

Clinical Trials?

Early TNBC treatment: small tumors (T1N0)

ASCO

Recommendation 3.2. Patients with cT1a or cT1bN0 TNBC should not routinely be offered neoadjuvant therapy outside of a clinical trial (Type: evidence-based; benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

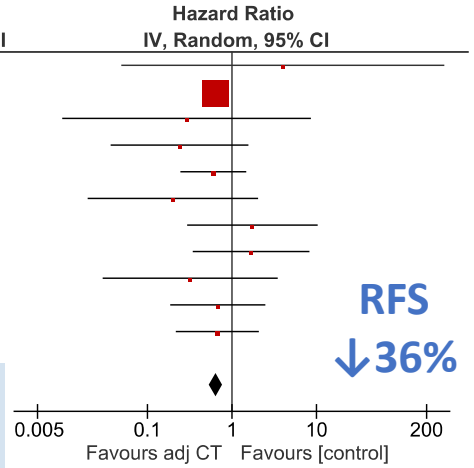
BCC 2021

T1a	Chemotherapy—case by case
T1b	TC chemotherapy
T1c	AC/T chemotherapy

Adjuvant CT pT1ab N0M0 TNBC: systematic review & meta-analysis

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
An 2020 pT1a	1.3838	2.2345	0.2%	3.99 [0.05, 318.41]
An 2020 pT1b	-0.4463	0.0962	86.9%	0.64 [0.53, 0.77]
Bao 2018	-1.2379	1.718	0.3%	0.29 [0.01, 8.41]
Colonna 2015	-1.4271	0.9475	0.9%	0.24 [0.04, 1.54]
de Nonneville 2017	-0.5108	0.4467	4.0%	0.60 [0.25, 1.44]
Ho 2012 pT1a	-1.6094	1.1748	0.6%	0.20 [0.02, 2.00]
Ho 2012 pT1b	0.5539	0.8969	1.0%	1.74 [0.30, 10.09]
Olszewski 2013	0.5188	0.8003	1.3%	1.68 [0.35, 8.06]
Ren 2019	-1.1394	1.2077	0.6%	0.32 [0.03, 3.41]
Vaz-Luis 2014 pT1a	-0.3857	0.6506	1.9%	0.68 [0.19, 2.43]
Vaz-Luis 2014 pT1b	-0.4005	0.5682	2.5%	0.67 [0.22, 2.04]
Total (95% CI)			**100.0%**	**0.64 [0.54, 0.77]**

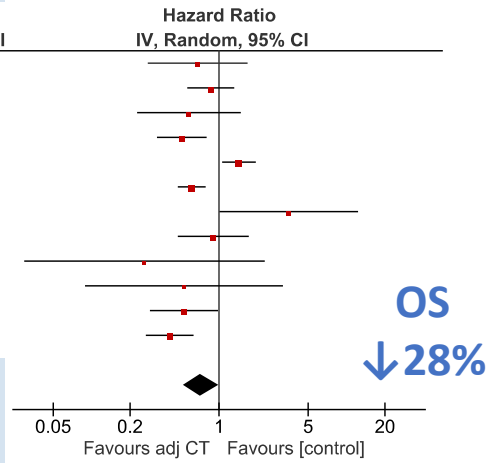
Heterogeneity: Tau² = 0.00; Chi² = 6.00, df = 10 (P = 0.82); I² = 0%
Test for overall effect: Z = 4.94 (P < 0.00001)



RFS ↓36%

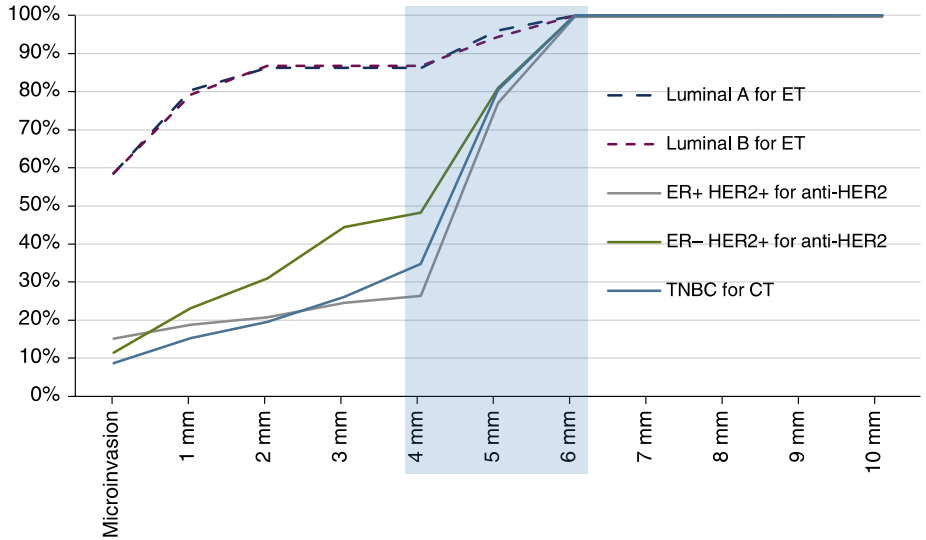
Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Du 2020 T1a	-0.3857	0.4527	6.7%	0.68 [0.28, 1.65]
Du 2020 T1b	-0.1508	0.2098	11.4%	0.86 [0.57, 1.30]
Fu 2020 pT1a	-0.5447	0.4719	6.4%	0.58 [0.23, 1.46]
Lan 2021 pT1b	-0.6733	0.2221	11.2%	0.51 [0.33, 0.79]
Oladeru 2020 pT1a	0.3577	0.148	12.7%	1.43 [1.07, 1.91]
Oladeru 2020 pT1b	-0.4943	0.1223	13.1%	0.61 [0.48, 0.78]
Steenbruggen 2020 pT1a	1.2585	0.632	4.4%	3.52 [1.02, 12.15]
Steenbruggen 2020 pT1b	-0.1054	0.3207	9.1%	0.90 [0.48, 1.69]
Vaz-Luis 2014 pT1a	-1.3471	1.1018	1.8%	0.26 [0.03, 2.25]
Vaz-Luis 2014 pT1b	-0.6349	0.9046	2.6%	0.53 [0.09, 3.12]
Zhai 2020 BCS	-0.6349	0.3077	9.3%	0.53 [0.29, 0.97]
Zhai 2020 other surgeries	-0.8916	0.2131	11.4%	0.41 [0.27, 0.62]
Total (95% CI)			**100.0%**	**0.72 [0.53, 0.99]**

Heterogeneity: Tau² = 0.18; Chi² = 42.29, df = 11 (P < 0.0001); I² = 74%
Test for overall effect: Z = 2.04 (P = 0.04)



OS ↓28%

Size threshold for initiating systemic therapy by tumor type and treatment



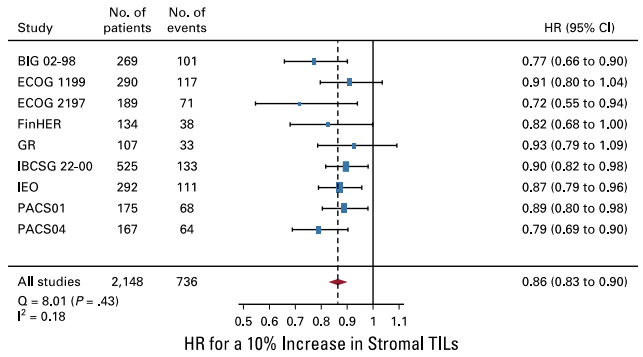
- 14 retrospective studies (N= 15047 pts, 1996-2016), median FU 3-8 yrs
  - 14-84% received CT (11 studies not specified)
- Only pT1b subgroup is associated with OS in regression analysis
- Other clinical factors (pT1b substage, grade, TILs, BC subtype, post-operative RT and advanced age/comorbidities) may modulate benefit-to-risk ratio of adjuvant CT and choice of agents in this subgroup

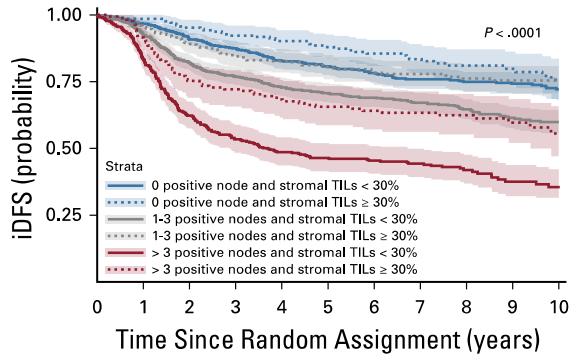
Burstein et al Ann Oncol 2021; Korde et al JCO 2021; Petrelli et al EJC 2021; Vaz-Luis et al JCO 2014; Theriault et al Clin Breast Cancer 2010

Early TNBC treatment: small tumors & TILs biomarker beyond the TNM staging system

Prognostic Value_all CT treated [sTILs in eTNBC pool analysis; N=2148 pts, 9 studies]

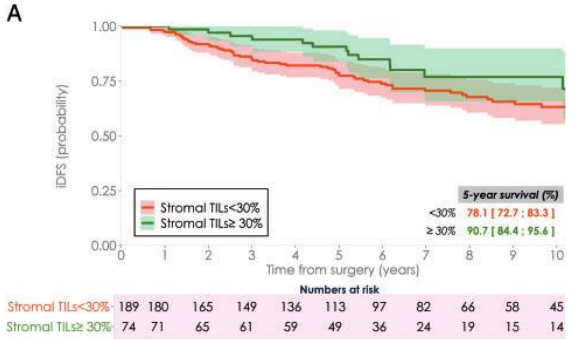
- 33% N0, average 23% TILs
- 55.7% anthras and 44.23% Anthras+taxane
- sTILs were significantly lower with older age, larger tumor size, more nodal involvement and lower histologic grade
- ***Each 10% ΔsTILs corresponded to a of HR 0.87 for iDFS, 0.83 for D-DFS and 0.84 for OS***
- N0 ≥30% sTILs 3yr iDFS 92% ; DDFS 97% and OS 99%

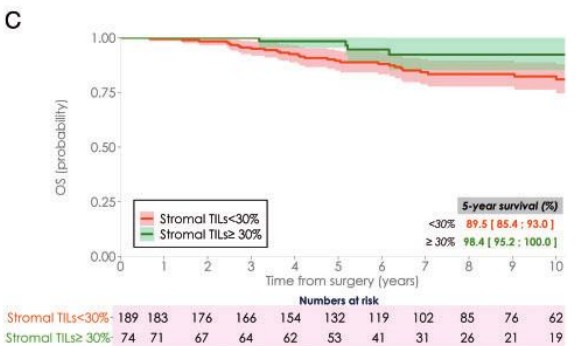




Prognostic Value no-CT [sTILs in eTNBC series; N=476 pts, 4 centres]

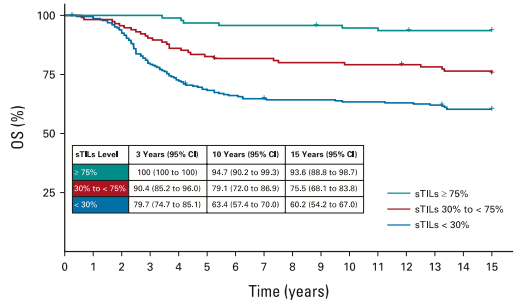
- 83% N0, median level 10% TILs
- sTILs independent prognostic value for iDFS and OS
- ***Each 10% Δ sTILs corresponded to a HR 0.90 for iDFS, 0.86 for D-DFS and 0.88 for OS***
- Stage I with >30% sTILs 5yr iDFS 91% ; DDFS 97% and OS 98%





PARADIGM study group, no-CT [N=441 pts, Netherlands Cancer Registry]

- Pts <40 years, diagnosed with T any N0M0 (85.9% G3, median 20% TILs)
- ***Each 10% Δ sTILs corresponded to an aHRs 0.81 for OS and 0.74 for DMFS***
- Pts >30% and <75% TILs 10yr OS 80% and DRFS 84% & Pts >75% TILs 10yr OS 95% and DRFS 98%



Park et al Ann Oncol 2019; Loi et al JCO 2019; De Jong et al JCO 2022; Loi et al npj Breast Cancer 2022

Early TNBC treatment: potential for de-escalation “rare histologies”

- **Adenoid cystic and other salivary carcinomas**
- **Secretory carcinoma**
- **Rare low-grade forms of metaplastic carcinoma[u]**

→ **ER-negative and PR-negative, HER2-negative[x]** → **Limited available data support local therapy only with consideration for systemic/targeted therapies only in pN+ disease**

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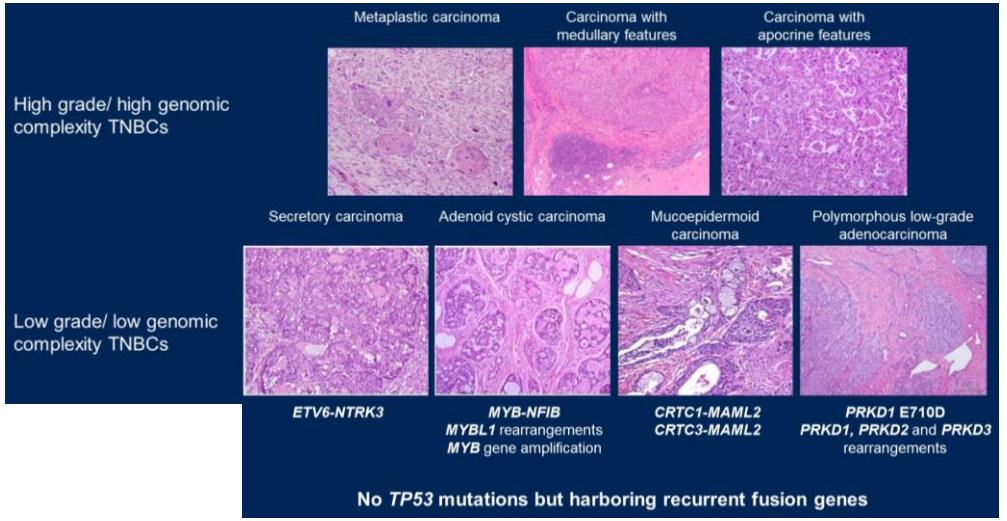
Invasive Breast Cancer

[u] There are rare subtypes of metaplastic carcinoma (eg, low-grade adenosquamous and low-grade fibromatosis-like carcinoma) that are considered to have a favorable prognosis without adjuvant systemic therapies.



Benefit of adjuvant CT in special histology subtypes of TNBC

- 15 retrospective studies systematic review (1970-2015), median FU 51 mo
  - Adenoid cystic, apocrine and medullary TNBCs better prognosis (5yr-OS rates >92% and 10yr-DFS rates >95%) compared to TNBC NOS
  - Lobular and metaplastic TNBCs the poorest prognosis (5yr-OS rates <85%)
- 2019 St Gallen consensus emphasized that special BC histologies may need different considerations, encouraging participation to clinical trials and recommending more research to estimate the clinical magnitude of benefits from adjuvant treatments
- Benefit of adjuvant CT in pts with special histology TNBC is variable, valuably important in more aggressive special types and negligible in more indolent tumors at earlier stage

Proposal of research areas of de-escalation in eTNBC adjuvant setting

TNBC histology special type	Clinical setting for chemotherapy de-escalation	LoE	GoR[a]	Research areas for treatment individualization
Adenoid cystic	Stage 1, Grade 1	IV	C	Use of adjuvant androgens modulators; predictive role or TILs
Medullary	T < 10 mm, pN0	IV	C	Predictive role of presence, numerosity and geo-spatial pattern of TILs
Apocrine	pN0	IV	C	Use of adjuvant androgens modulators
Metaplastic, low-grade[b]	pN0	IV	C	Predictive role of the primary tumor dimension on CT benefit
Metaplastic, high-grade	None	IV	C	Treatment intensification and benefit of alternative CT schedules[c]; implementation of window-of-opportunities trials in NAT

Geyer et al Am J Pathol 2017; Dieci et al Oncologist 2014; Trapani et al BCRT 2021; Reish-Filho J ASCO 2022 & Derakhsham et al Ann Rev Pathol Mech Dis 2022; Srivastava et al npj Breast Cacner 2022

Early TNBC algorithm of treatment: adjuvant chemotherapy

Early TNBC

- **pT1a pN0** → No CT?
- **pT1b-c pN0** → Adjuvant CT

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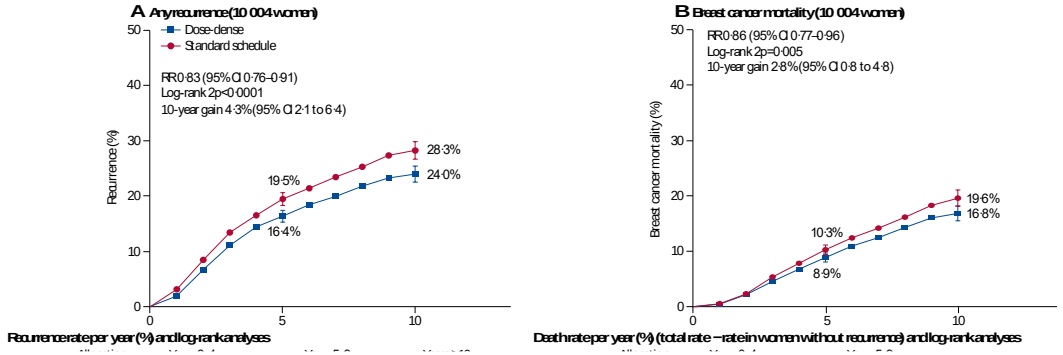
PREOPERATIVE/ADJUVANT THERAPY REGIMENS[a]

HER2-Negative[b]	
Preferred Regimens: • Dose-dense AC (doxorubicin/cyclophosphamide) followed by paclitaxel every 2 weeks[c] • Dose-dense AC (doxorubicin/cyclophosphamide) followed by weekly paclitaxel[c] • TC (docetaxel and cyclophosphamide) • Olaparib, if germline *BRCA1/2* mutations[d,e] • High-risk[f] triple-negative breast cancer (TNBC): Preoperative pembrolizumab + carboplatin + paclitaxel, followed by preoperative pembrolizumab + cyclophosphamide + doxorubicin or epirubicin, followed by adjuvant pembrolizumab • TNBC and residual disease after preoperative therapy with taxane-, alkylator-, and anthracycline-based chemotherapy:[e] Capecitabine	
Useful in Certain Circumstances: • Dose-dense AC (doxorubicin/cyclophosphamide) • AC (doxorubicin/cyclophosphamide) every 3 weeks (category 2B) • CMF (cyclophosphamide/methotrexate/fluorouracil) • AC followed by weekly paclitaxel[c] • Capecitabine (maintenance therapy for TNBC after adjuvant chemotherapy)	**Other Recommended Regimens:** • AC followed by docetaxel every 3 weeks[c] • EC (epirubicin/cyclophosphamide) • TAC (docetaxel/doxorubicin/cyclophosphamide) • Select patients with TNBC:[g] ▸ Paclitaxel + carboplatin[g] (various schedules) ▸ Docetaxel + carboplatin[g] (preoperative setting only)

- CT benefit is larger in ER- vs ER+ (5yr-DFS absolute difference 22.8% vs 7.0% and 5yr-OS absolute difference 16.7% vs 4.0%) *[CALGB & US BC Integroup N=6,644 pts N+]*
- Poli-CT regimens comparison *[EBCTCG Meta-analysis N=100,000 pts, 123 RCTs]*
  - **Anthras vs no-CT** ↓27% risk of recurrence and ↓21% risk of BC death (82% N+) and ER poor (73% N+)
  - **Anthras/Taxanes vs Anthras** ↓16% risk of recurrence and ↓14% risk of BC death (100% N+)
- Anthras/Tax vs Taxane no anthras comparison *[EBCTCG Meta-analysis N=18,203pts, 16 RCTs]*
  - 15% proportional and 2.5% absolute reduction @10 yrs in risk of invasive recurrence for AT vs T, larger reduction with concurrent schedules, and did not differ by ER status

Dose-Dense CT *[EBCTCG Meta-analysis N=37298 pts, 26 RCTs]*



- *ER- (66% N+) 10yr recurrence gain 3.7% vs ER+ (84% N+) 10yr gain 3.1%*

Marra et al Cancer J 2021; Gray et al Lancet 2019; Burstein et al Ann Oncol 2019; Berry et al JAMA 2006, EBCTCG Lancet 2012; Braybrooke et al SABCS 221

Early TNBC algorithm of treatment: adjuvant chemotherapy (CT)

Early TNBC

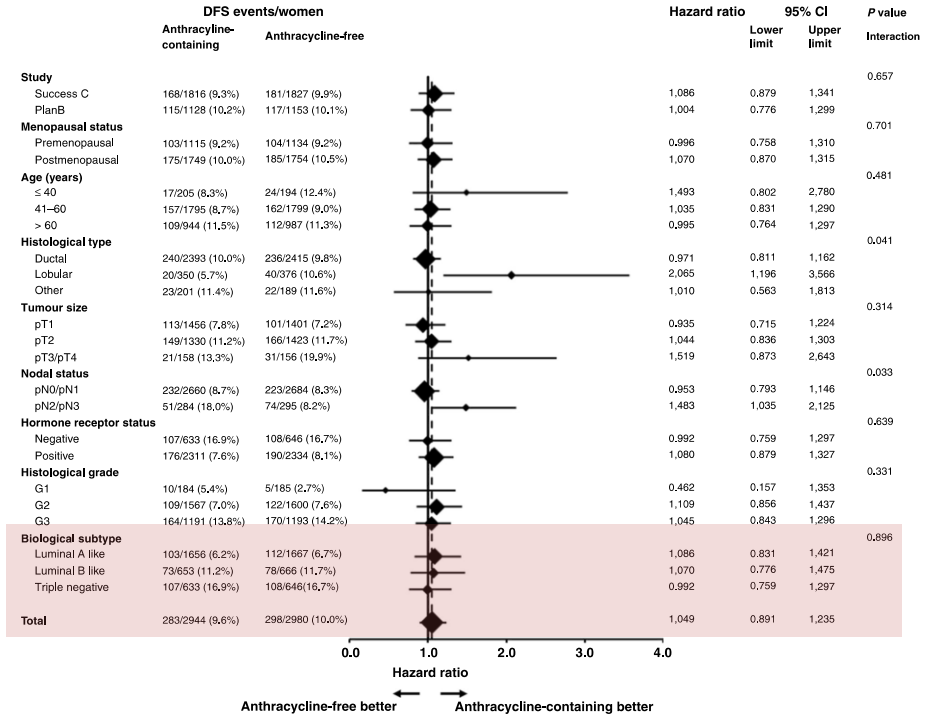
pT1a pN0 → No CT?

pT1b-c pN0 → Adjuvant CT

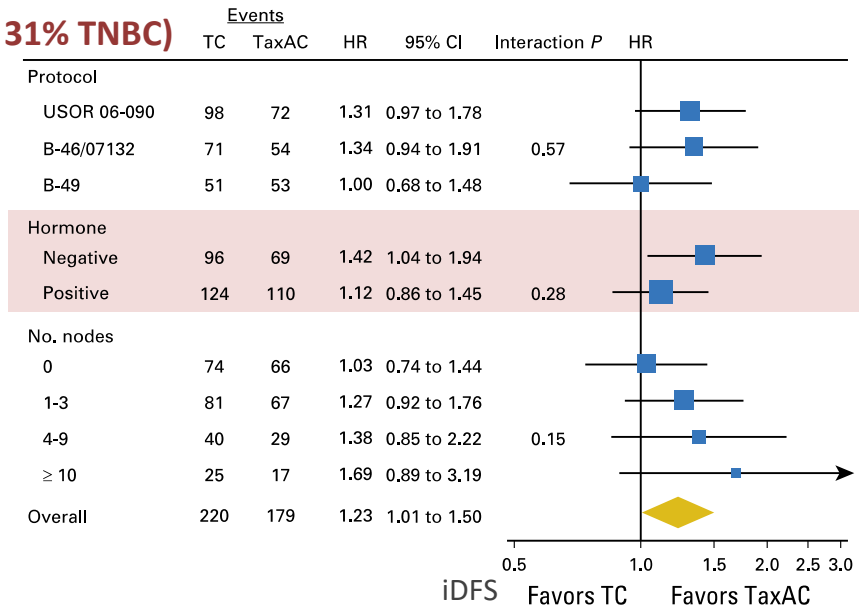
Adjuvant CT (Anthra-free CT)

- **NCIC.CTG MA.5 trial:** N=476 pts GEPs There was NS difference in benefit between CEF and CMF in basal-like tumors (n=94; HR 1.1 for RFS and HR 1.3 for OS) suggesting that non-anthracycline regimens may be adequate in this subtype while HER2-E strongly predicted anthracycline sensitivity
- **PATTERN trial:** N=647 pts TNBC PCb vs CEF-T (2011-16), 54.2% pT1; 74.3% N0; 10.2% gBRCA1/2 mut and 18.5% HRR-related gene deleterious. PCb regimen is an effective alternative for pts with operable TNBC pts (5yr-DFS 86.5% vs 80.3% HR 0.65* and OS HR 0.71 (NS))

PlanB & SUCCESS trials (N=5924 pts from 2RCTs, 21.6% TNBC)



ABC trials (N=4242 pts from 3RCTs, 31% TNBC)



Cheang et al CCR 2012; Blum et al JCO 2017; Hurvitz et al npj Breast Cancer 2021; de Gregorio et al npj Breast Cancer 2022; Yu et al JAMA Oncol 2020

Early TNBC algorithm of treatment: neoadjuvant chemotherapy (NACT)

Early TNBC

pT1a pN0 → No CT?

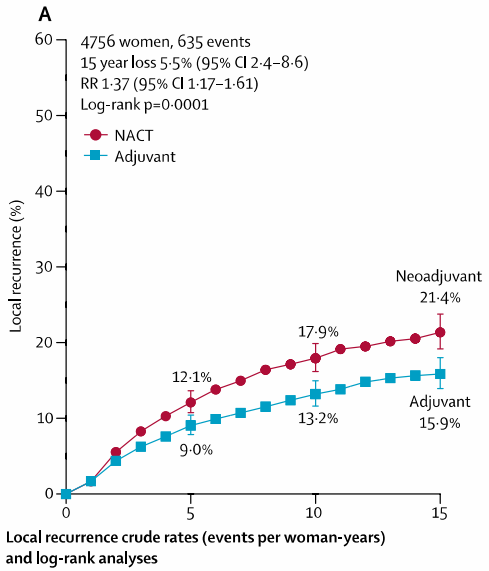
pT1b-c pN0 → Adjuvant CT

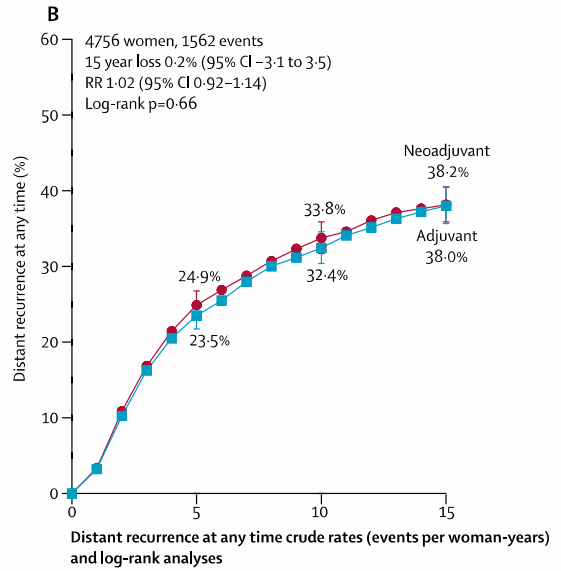
CT

≥T2 and/or ≥N1 → NACT

Sequential Regimens anthra/taxanes Including Platinums

- NACT equivalent to adjuvant CT in terms of survival (RR 1.00) and disease progression (RR 0.99) *[Meta-analysis N=3946 pts, 12 RCTs]*
- NACT equivalent to adjuvant CT and addition of NA taxanes to AC improves response (pCR 26 vs 13%* no impact on surival) *[NSABPB-18 & B-27 analysis]*
- Advantages of NACT in terms of ↓resection volumes and improved cosmetic outcomes after BCT not yet proven, well designed RCTs needed *[Systematic Rev, 26 studies] ≃42% TNBC conversion rate* [CALGB 40603]
- NACT as effective as adjuvant CT in ↓risk of distant recurrence (RR 1.02) and death from BC (RR 1.06) but NACT is associated with ↑local recurrence (RR 1.37*) partly by wider use of BCS after NACT→ Strategies to mitigate the ↑local recurrence after BCS should be considered (tumour localisation, detailed pathological assessment and appropriate RT) *[EBCTCG meta-analysis N= 5250 pts, 10 RCTs]*





Mauri et al JNCI 2005; Rastogi et al JCO 2008; Volders et al BCRT 2018; EBCTCG Lancet Oncol 2018

Early TNBC algorithm of treatment: neoadjuvant chemotherapy (NACT)

NACT (including platinum)

Study	Phase	Patients(N)	Design	pCR (%)	EFS/OS (HR)
GEICAM 2006/03	II	94	ECx4→T_{100}x4 vs T_{75}Cbx4	30% vs 30%	-
CALGB 40603	II	443	wP±Cbq3w→ddACx4±Beva	41% vs 54% (Δ13%*)	0.94 (NS); 5yr EFS 70.1 vs 70.4% 1.12 (NS) 5yr OS 75.6 vs 74.4%
GeparSixto/GBG66	II	315	wP+wNPLD±Beva±wCb	37% vs 53% (Δ16%*)	0.56 *; 3yr DFS 86.1 vs 75.8% 0.60 (NS); 3yr OS 91.9 vs 86%
ISPY-2	II	60	wP±Cb+Veliparib→ddACX4	26% vs 51%	-
GeparOcto/GBG84	III	403	wPMCb vs iddEPC	48.5% vs 51.7%	-
BrighTNess	III	634	wP±Cb±Veliparib→(dd)ACx4	31% vs 58% (Cb) vs 53% (CbV) (Δ26%*)	*0.63* & 0.57*; 4yr EFS 68.5 vs 78.2% & 68.5 vs 79.3%* *0.82 (NS) & 0.63 (NS); events 13.9 vs 12% & 13.9 vs 10%*

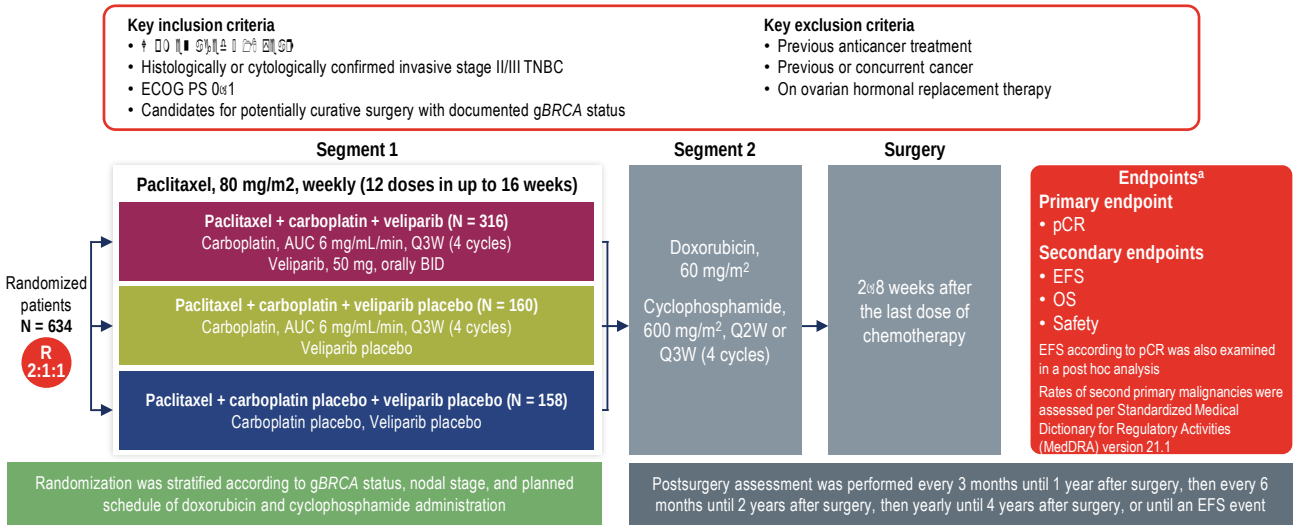
- Platinum-based NACT significantly increased pCR rate 37.0% to 52.1% (OR 1.96*) but NS difference in survival with higher risk of G3/4 hematological AEs ***[Meta-analysis, N=2109, 9 RCTs]***
- *EFS/OS update @2021 (6 RCTs and 5 RCTs respectively) EFS increase HR 0.70* and 18% (NS) reduction risk of death (HR 0.82)*

Alba et al BCRT 2012; Sikov et al JCO 2015 & JCO 2022; Von Minckwitz et al Lancet Oncol 2014 & Loibl et al Ann Oncol 2018; Loibl et al Lancet Oncol 2018; Rugo et al NEJM 2016 Schneeweiss et al EJC 2019; Chen et al PLoS ONE 2014; Petrelli et al BCRT 2014; Poggio et al Ann Oncol 2018 & 2021; Li et al P2-12-19 SABCS 2021

Early TNBC algorithm of treatment: neoadjuvant chemotherapy (NACT)

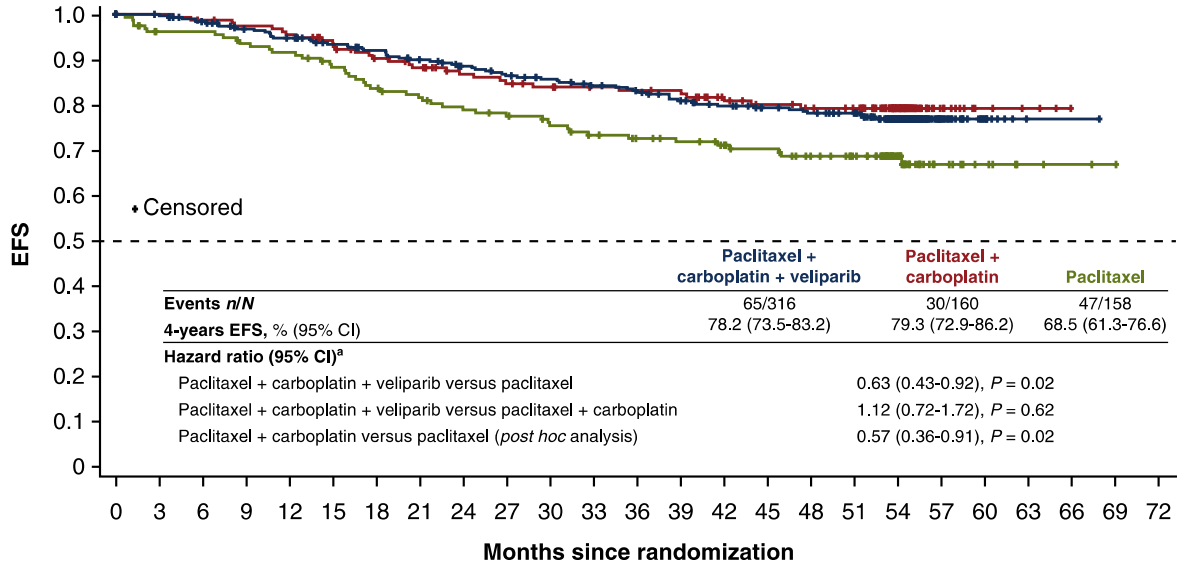
NACT (including platinum)

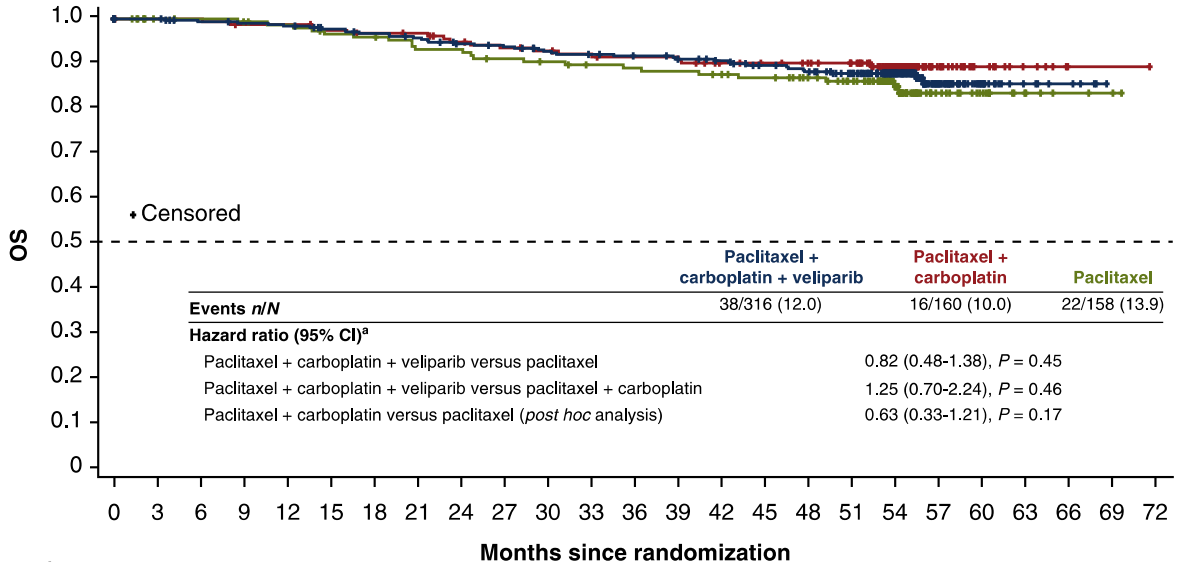
BrighTNess trial



gBRCAmut 14-16%; T2 68-74%; N0 57-59%

- Patients with pCR improved EFS vs without pCR (HR 0.26*) **regardless of BRCA mut status**
- Adding carbo improved pCR and translated into improved EFS while adding veliparib did not impact pCR, EFS or OS
- ↑hematologic AEs with Cb with/without veliparib did not compromise treatment delivery or impact of this treatment on the study's primary (pCR) or secondary (EFS/OS) endpoints
- The regimens had manageable safety profiles without increased risk of MDS, AML or other secondary malignancies



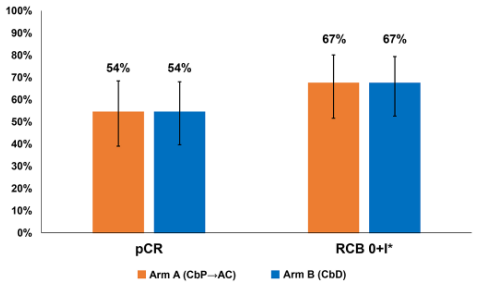


Loibl et al ESMO 2021 & Geyer et al Ann Oncol 2022

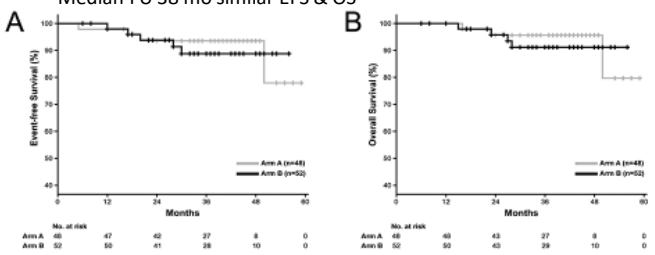
Early TNBC algorithm of treatment: neoadjuvant chemotherapy (NACT)

NACT (Anthra-free platinum based CT)

Study	Phase	Patients (N)	Design	pCR (%)	EFS/OS (HR)
NCT02303742 & NCT01560663	-	190	$Doce_{75}Cb$ q3w x6	55%	3yr RFS 79% 3yr OS 87%
NCT01276769	II	91	P+Cb q3w vs EP q3w x4-6	14.0% vs 38.6%	3yr RFS 61.6 % vs 81.2%* 3yr OS 83.2% vs 85.8% (NS)
WSG-ADAPT	II	336	wNabP+Gem vs wNabP+wCb	28.7% vs 45.9%	3yr EFS 78% vs 80% (NS)
TBCRC030	II	140 gBRCA1/2wt or UK	wPx12 vs CDDP q3wx4	11.9% vs 15.3%	-
NeoCART	II	93	$Doce_{75}Cb$ q3wx6 vs $EC_{90}x4 \rightarrow Doce_{100}x4$	61.4% 38.6% (non-inferiority/sup)	0.76; 3yr EFS 88.3 vs 90.8% (NS) 0.96; 3yr EFS 93.1vs 92.8% (NS)
NeoSTOP	II	100	wP±Cbq3wx4 →ddACX4 vs $Doce_{75}Cb$ q3wx6	54% vs 54%	-



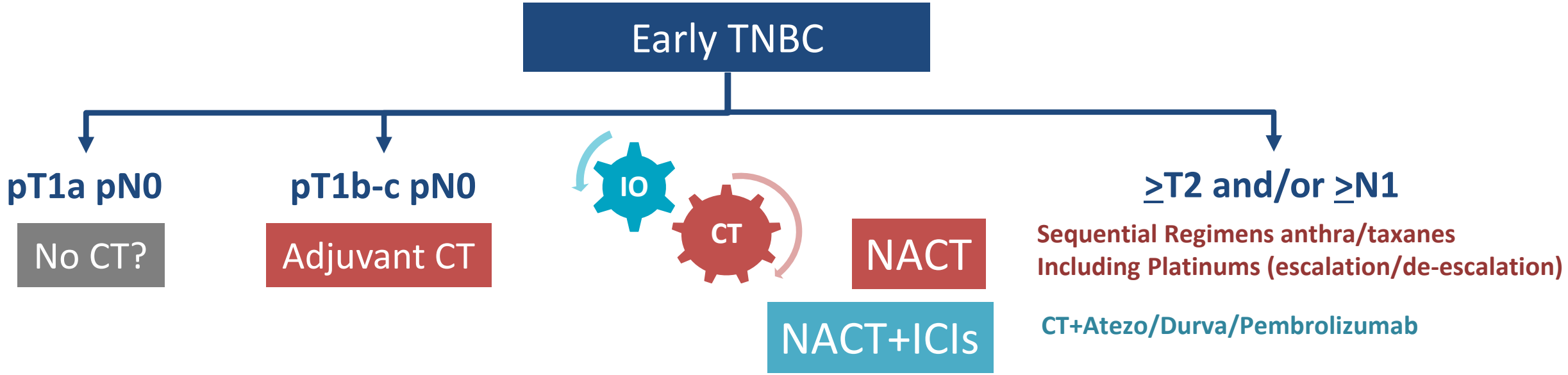
Median FU 38 mo similar EFS & OS



Adverse Events	Arm A (CbP→AC) *N* (%)	Arm B (CbD) *N* (%)	*P*
Anemia[a]	22 (46%)	2 (4%)	0.0001
Neutropenia	29 (60%)	4 (8%)	0.0001
Thrombocytopenia	8 (17%)	2 (4%)	0.05
Febrile neutropenia[b]	9 (19%)	0	<0.001
Hypokalemia	2 (4%)	1 (2%)	0.61
Hyponatremia	2 (4%)	1 (2%)	1
Nausea	1 (2%)	0	0.48
Constipation	1 (2%)	0	0.48
Diarrhea	1 (2%)	4 (8%)	0.36

Sharma et al CCR 2017 and 2018; Zhang et al Oncotarget 2016; Gluz et al JNCI 2018 & SABCS 2018; Mayer et al Ann Oncol 2020; Sharma et al CCR 2021; Zhang et al IJC2021

Early TNBC algorithm of treatment: neoadjuvant chemotherapy (NACT)



Early TNBC algorithm of treatment: neoadjuvant chemo/immunotherapy (NACT+IO)

NACT+ICIs

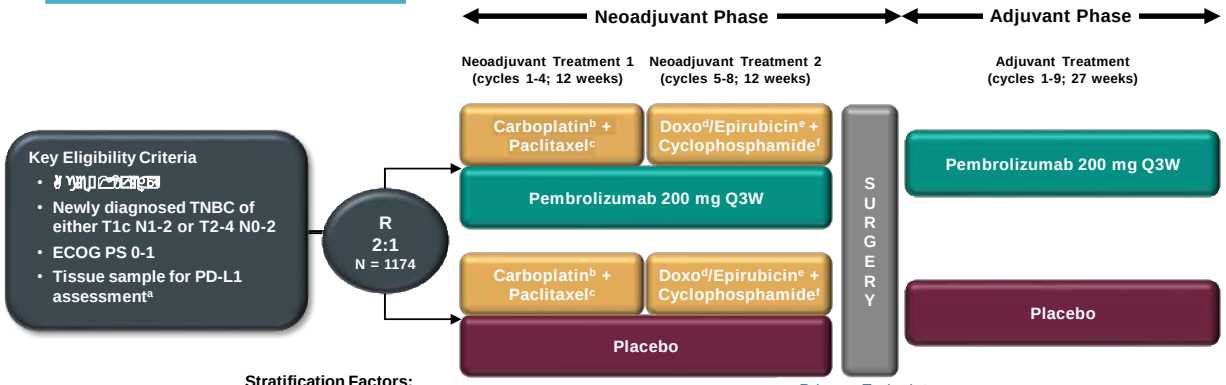
Study	Phase	Patients (N)	Design	pCR (%)	EFS/OS (HR)
ISPY-2	II	250 (29 TNBC_69/181)	(wP→ACx4)±Pembro No Adjuvant IO	**22% vs 60%** (graduated)	[EFS 0.6]
KEYNOTE 522	III	1174 PD-L1+ 83% T3-4 26%; N+ 51.5%	(wP+w/q3wCb→AC/ECx4)±Pembro Adjuvant Pembro (cape not allowed)	**51.2% vs 64.8% (Δ13.6*)** IA3 55.6% vs 63% (Δ7.5) 54.9% vs 68.9% PD-L1+ 39.3% vs 45.3% PD-L1-	**0.63* (3yr EFS 76.8% vs 84.5%, Δ7.7*)** 0.72 (NS) (3yr OS 86.9% vs 89.7%)
IMpassion 031	III	333 PD-L1+ 46.2% T3-4 28.2% N+ 38.4%	wNabPx12 →ddACx4±Atezo Adjuvant Atezo (cape if RD allowed)	**41.1% vs 57.6% (Δ16.5*)** **49.3% vs 68.8% (Δ19.5) PD-L1+**	0.76 (NS) (events 13.1% vs 10.3%) 0.69 (NS) (events 5.4% vs 4.2%)
NeoTRIPaPDL1	III	280 PD-L1+ 56% T3-4 43.5%; N+ 88%	wNabP+Cb (d1,8 q3w)x8±Atezo Adjuvant AC/EC/FECx4 no IO	40.8% vs 43.5% (Δ2.7) ITT [47.3% vs 52.0% (Δ4.64) PP] 48% vs 51.9% PD-L1+ 32.3% vs 32.2% PD-L1-	**Primary EFS (ITT)**
GeparDouze	III	1520	(wP+Cbq3w→ (dd)AC/ECx4)±Atezo Adjuvant Atezo	**Co-primary (pCR)**	**Co-primary (EFS)**
GeparNuevo	II	174 PD-L1+ 88% 35% stage <IIA T3-4 5.7%; N+ 31%	Durva→(wNabPx12→ddECx4)+Durva No Adjuvant IO (as per TPC)	**44.2% vs 53.4% (Δ9.2)** Window cohort 41.4% vs 61%	0.48* (3yr iDFS 77.2% vs 85.6%) 0.24* (3yr OS 83.5% vs 95.2%)

Nanda et al JAMA Oncol 2020; Schmid et al NEJM 2020 & ESMO 2021; Harbeck et al ESMO 2020; Mittendorf et al Lancet 2020; Gianni et al SABCS 2019; Bianchini et al ESMO 2020 & 2021; Loibl et al Ann Oncol 2019 & ASCO 2021

Early TNBC algorithm of treatment: neoadjuvant chemo/immunotherapy (NACT+IO)

NACT+ICIs

KN-522 trial



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

- Primary Endpoints
  - pCR (ypT0/Tis ypN0) assessed by local pathologist in ITT population[a]
  - Event-free survival (EFS) assessed by investigator in ITT population
- Secondary Endpoints
  - pCR as per alternative definitions (ypT0 ypN0 and ypT0/Tis)[a]
  - Overall survival (OS)
  - pCR[a], EFS and OS[b] in the PD-L1–positive population[c]
  - Safety in all treated patients

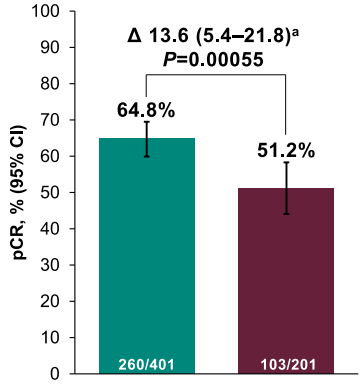
Characteristic, n (%)	All Subjects, N = 1174	
	Pembro + Chemo N = 784	Pbo + Chemo N = 390
Age, median (range), yrs	49 (22-80)	48 (24-79)
ECOG PS 1	106 (13.5)	49 (12.6)
PD-L1–positive[a]	656 (83.7)	317 (81.3)
Carboplatin schedule		
QW	449 (57.3)	223 (57.2)
Q3W	335 (42.7)	167 (42.8)
Tumor size		
T1/T2	580 (74.0)	290 (74.4)
T3/T4	204 (26.0)	100 (25.6)
Nodal involvement		
Positive	405 (51.7)	200 (51.3)
Negative	379 (48.3)	190 (48.7)

- Stage III ≃75% & stage II ≃ 25%
- Premen ≃ 56%

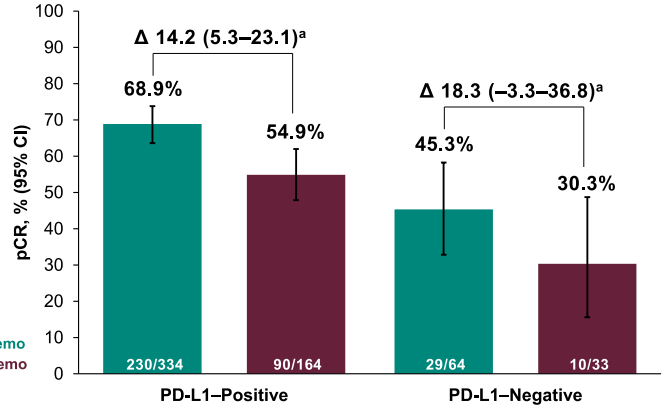
- Toxicity: irAEs (any grade) 43.6% overall vs 21.9% placebo & G≥3 14.9% vs 2.1% (infusion reactions >hypothyroidsm >hyperthyroidism >adrenal insufficiency) and 27.7 vs 14.1% led to discontinuation

IA1

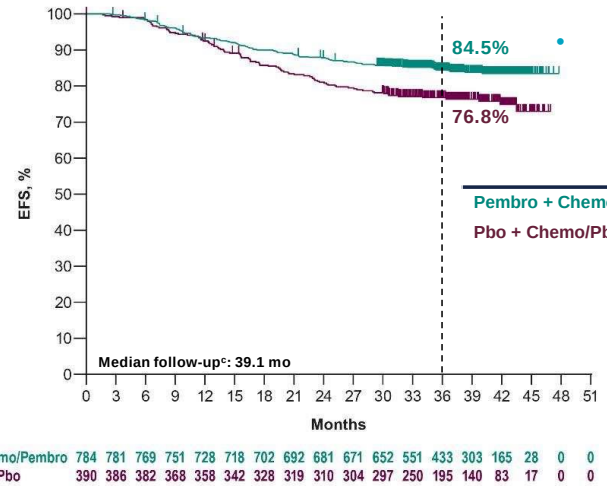
Primary Endpoint: ypT0/Tis ypN0



By PD-L1 Status[b]: ypT0/Tis ypN0



Statistically Significant and Clinically Meaningful EFS at IA4



- 36mo-OS 89.7% vs 86.9% , HR 0.72 immature

	Events	HR (95% CI)	*P*-value
Pembro + Chemo/Pembro	15.7%	0.63[a] (0.48-0.82)	0.00031[b]
Pbo + Chemo/Pbo	23.8%		

Event	All Subjects, N = 1174	
	Pembro + Chemo/Pembro N = 784	Pbo + Chemo/Pbo N = 390
Any EFS event	123 (15.7%)	93 (23.8%)
Progression of disease that precludes definitive surgery	14 (1.8%)	15 (3.8%)
Local recurrence[a]	28 (3.6%)	17 (4.4%)
Distant recurrence	60 (7.7%)	51 (13.1%)
Secondary primary malignancy[a]	6 (0.8%)	4 (1.0%)
Death	15 (1.9%)	6 (1.5%)

3yr DP or DRFS 80.7% vs 87.0%

HR 0.61 (95%CI 0.46-0.82)

Schmid et al NEJM 2020 & SABCS 2019 & ESMO VP7 2021 & NEJM 2022

Early TNBC algorithm of treatment: evaluation of response after NA treatment

Early TNBC

pT1a pN0 → No CT?

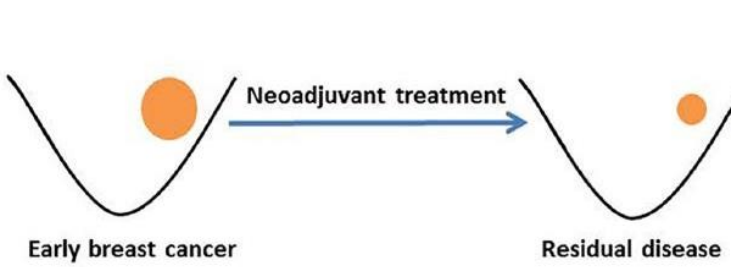
pT1b-c pN0 → Adjuvant CT

≥T2 and/or ≥N1 → NACT

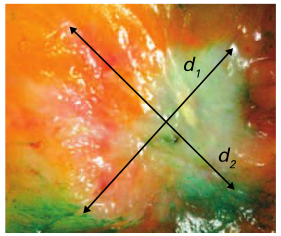
Sequential Regimens anthra/taxanes Including Platinums (escalation/de-escalation)

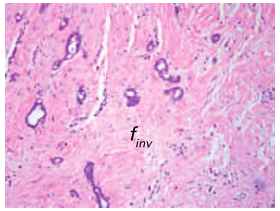
NACT+ICIs

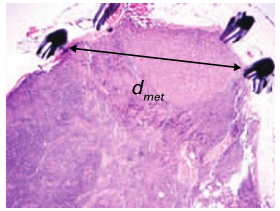
CT+Atezo/Durva/Pembrolizumab



- RCB score and class were independently prognostic in all subtypes of BC and generalisable to multiple practice settings

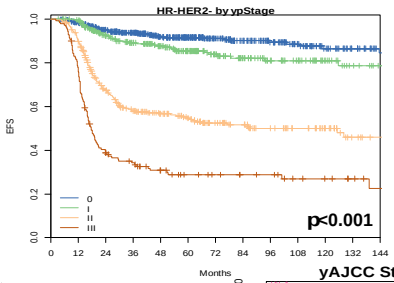




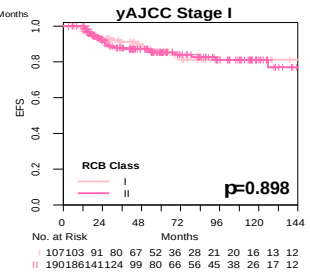


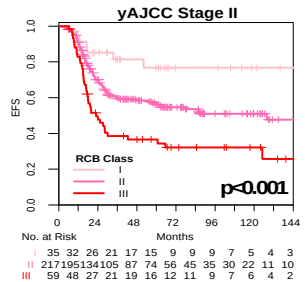
Variable	Hazard Ratio (95% CI)	P
Primary tumor bed dimensions ($\sqrt{d_1 d_2}$)	1.24 (1.04 to 1.48)	.02
Cellularity fraction of invasive cancer (f_{inv})	7.37 (2.16 to 25.1)	.001
Size of largest metastasis (d_{met})	1.17 (0.99 to 1.38)	.06
No. of positive lymph nodes	1.11 (1.04 to 1.19)	.002

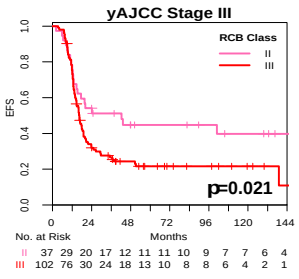
No pCR

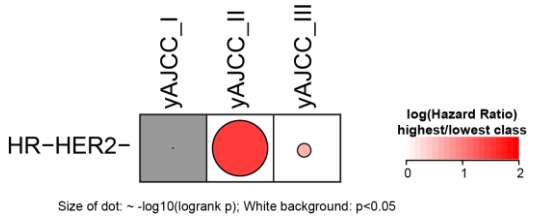


RCB differentiates outcomes for TNBC in yAJCC stage II and III









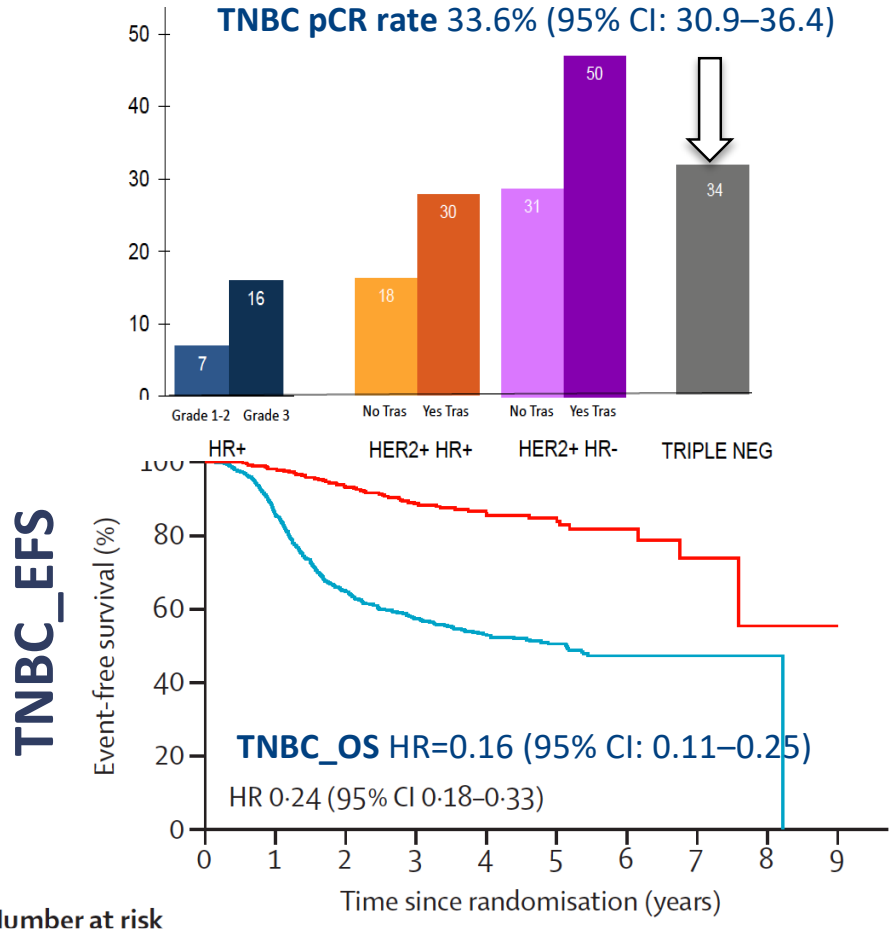
pCR

Kim et al Cancers 2021; Caparica et al Ther Adv Mol Oncol 2019; Balko et al Cancer Discov 2014; Yau et al Lancet Oncol 2022; Yau et al Cancer Res 2020; Symmans et al JCO 2007

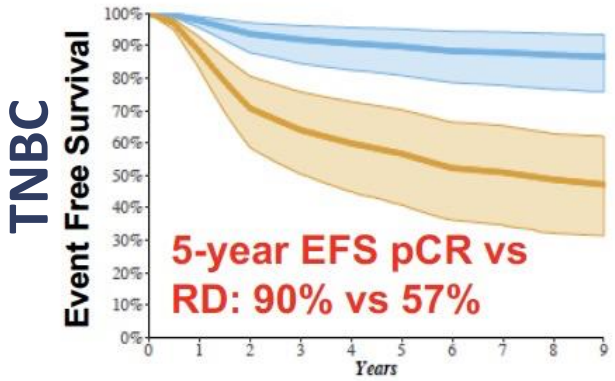
Early TNBC "risk-adapted" treatment strategies based on RD post-NACT

CTNeoBC pooled analysis (FDA)

- More aggressive subtypes >pCR (HER2+ and TNBC)
- Most favourable outcomes after pCR: HER2-/HR- tumours with trastuzumab and TNBC



Individual patient-level meta-analysis



- 52 studies (27,895 pts): 51.1% CTs, 42.8% retrospective studies; 6.1% single arm trials
- Median FU for recurrence: 48 mo
- Median FU for survival: 49.9 mo

- Pts who had pCR vs those with RD had better EFS (HR 0.31), for TNBC (HR 0.18, 95%CI 0.10-0.31)
- Pts who had pCR vs those with RD had better OS (HR 0.22)
- **86% 5-year EFS in pts with pCR →adjuvant CT vs 88% in pts with pCR without additional adjuvant CT**

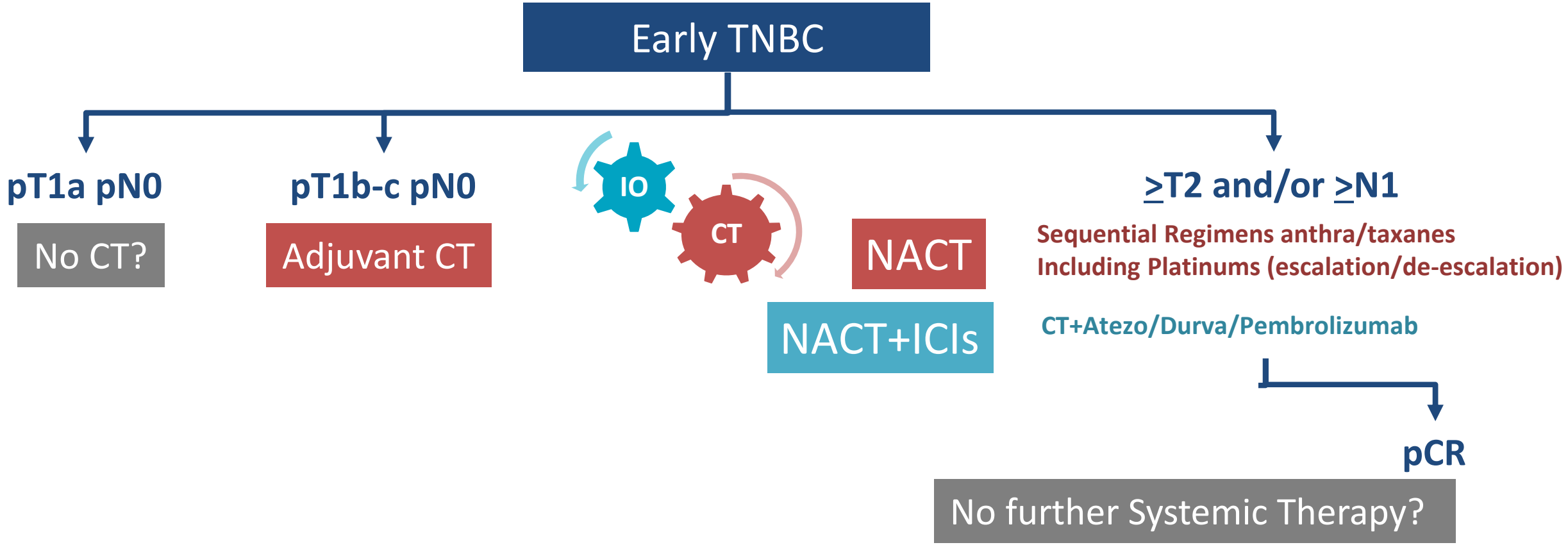
"Is pCR a surrogate for long-term survival?" yes at the individual patient level

"Is increased pCR rate a surrogate for improved survival in a trial arm?" depends on the absolute improvement in pCR rate, baseline prognosis of the trial population, interaction of pCR with prognostic variables, and efficacy of postNA treatment modalities

- *The majority of St Gallen Panel (60%) and audience (83%) believed that pCR was not the appropriate endpoint for defining standard neo/adjuvant systemic regimens favoring longer term endpoints (DFS or OS)*

Kim et al Cancers 2021; Caparica et al Ther Adv Mol Oncol 2019; Balko et al Cancer Discov 2014; Yau et al Lancet Oncol 2022; Yau et al Cancer Res Prowell & Pazdur NEJM 2012 and Cortazar P et al. Lancet 2014 (SABCS 2012) ; Spring et al CCR 2020; Symmans et al JCO 2007; Symmans et al JCO 2017; Yau et al Cancer Res 2020; Mittendorf et al JAMA Oncol 2016; Hatzis et la CCR 2015; Burstein et al Ann Oncol 2021; Esserman L CCR 2020; Liedtke et al JCO 2008; Von Minckwitz et al JCO 2012; Symmans et al JCO 2007

Early TNBC algorithm of treatment: post-NACT setting

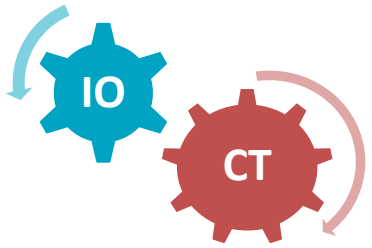


Early TNBC algorithm of treatment: adjuvant post-NACT+IO setting (no-RD)

Early TNBC

pT1a pN0 → No CT?

pT1b-c pN0 → Adjuvant CT



NACT

NACT+ICIs

≥T2 and/or ≥N1

Sequential Regimens anthra/taxanes Including Platinums (escalation/de-escalation)

CT+Atezo/Durva/Pembrolizumab

pCR

No further Systemic Therapy?

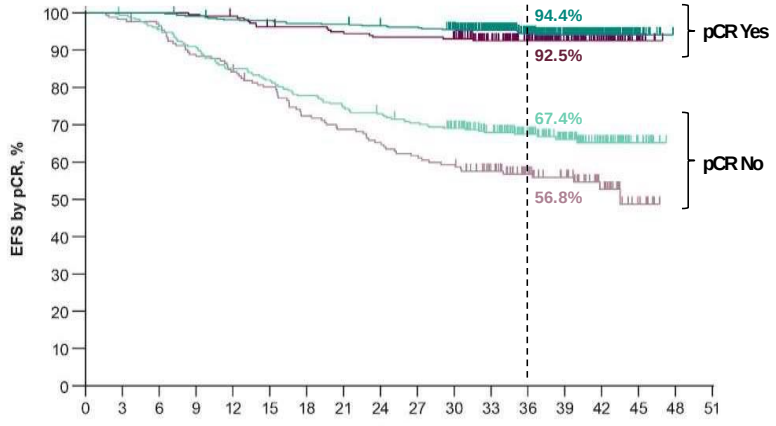
Adjuvant postNA ICIs — **Pembrolizumab?**

KN-522 trial

Adjuvant Pembrolizumab in pCR:

1. **KEYNOTE-522 established the benefit of 1 year of pembrolizumab as neoadjuvant/adjuvant therapy**
2. **The trial cannot answer how much the neoadjuvant or adjuvant phases contribute to overall outcome**
3. **The HR for EFS in pCR patients is 0.73 ('Pembro' versus 'No Pembro'), resulting in a 2%□ in 3a EFS rates (no formal statistics applied)**
4. **Additional trials required to define the contribution of adjuvant pembrolizumab to the overall benefit**

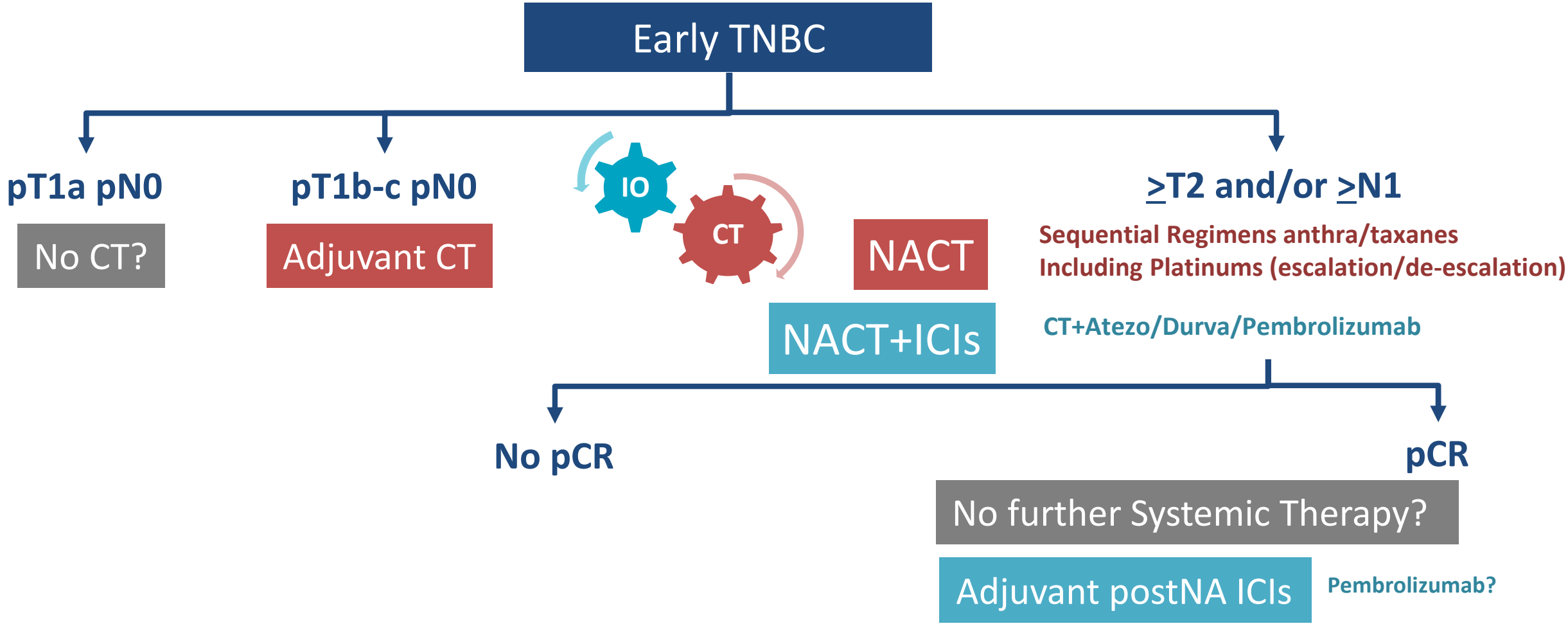
EFS by pCR (ypT0/Tis ypN0)



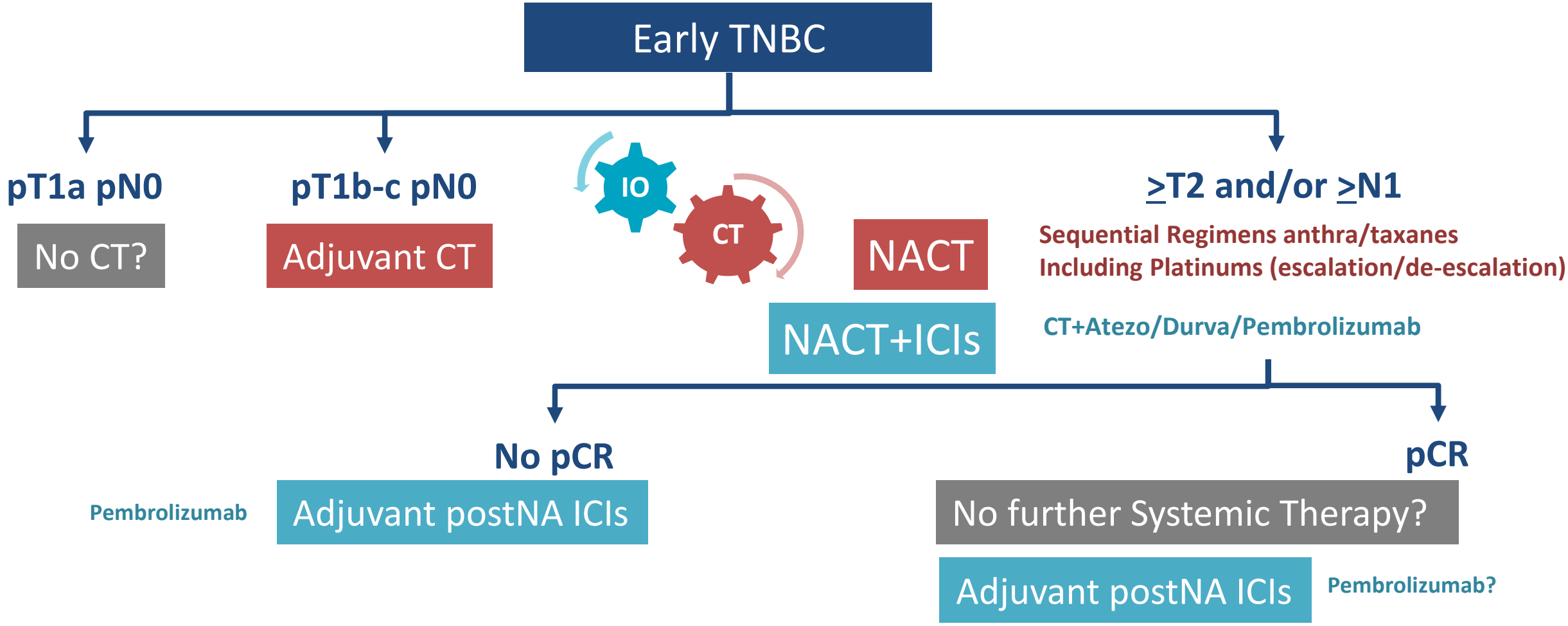
No. at Risk																	
Pembro + Chemo/Pembro Responder	494	494	494	489	483	482	478	477	472	470	460	387	307	220	122	18	0	0
Pbo + Chemo/Pbo Responder	217	217	217	216	214	207	206	203	200	200	197	165	130	87	56	9	0	0
Pembro + Chemo/Pembro Non-Responder	290	287	275	262	245	236	224	215	209	201	192	164	126	83	43	10	0	0
Pbo + Chemo/Pbo Non-Responder	173	169	165	152	144	135	122	116	110	104	100	85	65	53	27	8	0	0

Schmid et al NEJM 2020 & ESMO 2021; Harbeck et al ESMO 2020; Mittendorf et al Lancet 2020; Gianni et al SABCS 2019; Bianchini et al ESMO 2020 & 2021; Loibl et al Ann Oncol 2019 & ASCO 2021

Early TNBC algorithm of treatment: adjuvant post-NA setting



Early TNBC algorithm of treatment: adjuvant post-NACT+IO setting (RD)

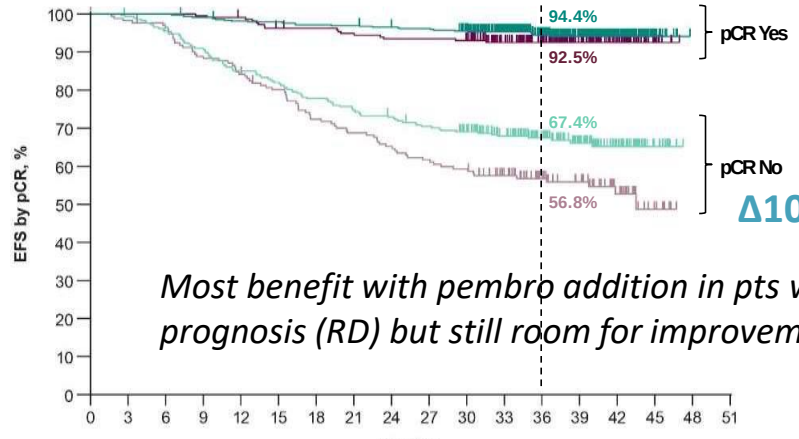


Early TNBC algorithm of treatment: adjuvant post-NACT+IO setting (RD)

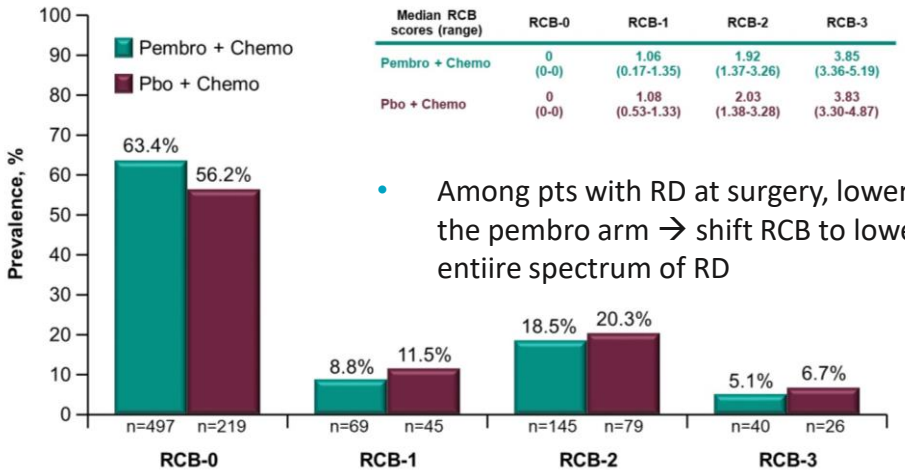
NACT+ICIs

KN-522 trial

EFS by pCR (ypT0/Tis ypN0)

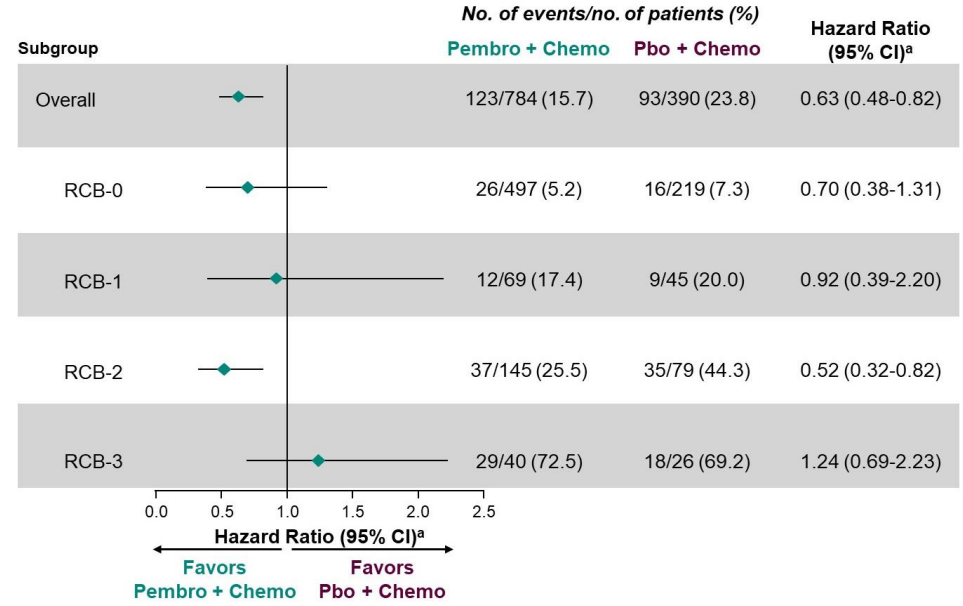


Most benefit with pembro addition in pts with worse prognosis (RD) but still room for improvement

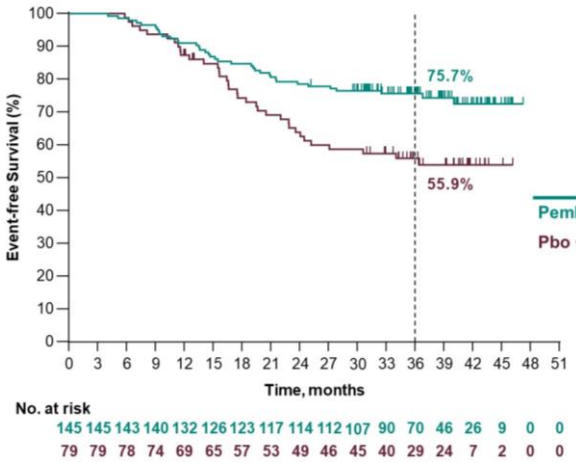


Median RCB scores (range)	RCB-0	RCB-1	RCB-2	RCB-3
Pembro + Chemo	0 (0-0)	1.06 (0.17-1.35)	1.92 (1.37-3.26)	3.85 (3.36-5.19)
Pbo + Chemo	0 (0-0)	1.08 (0.53-1.33)	2.03 (1.38-3.28)	3.83 (3.30-4.87)

- Among pts with RD at surgery, lower pts in each RCB category in the pembro arm → shift RCB to lower categories across the entiire spectrum of RD



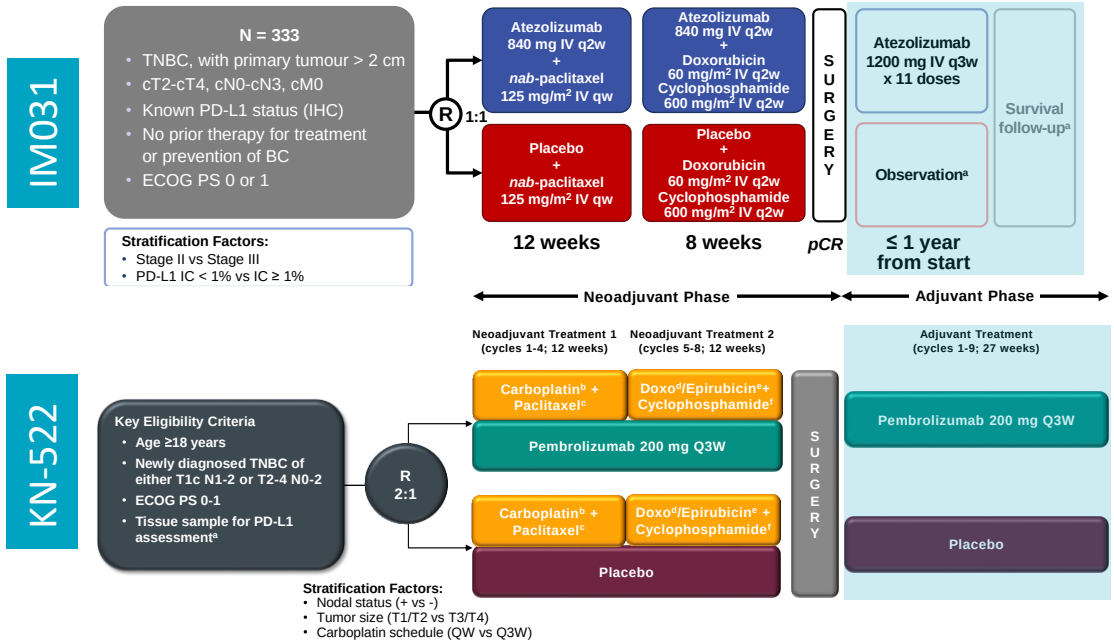
EFS in RCB-2

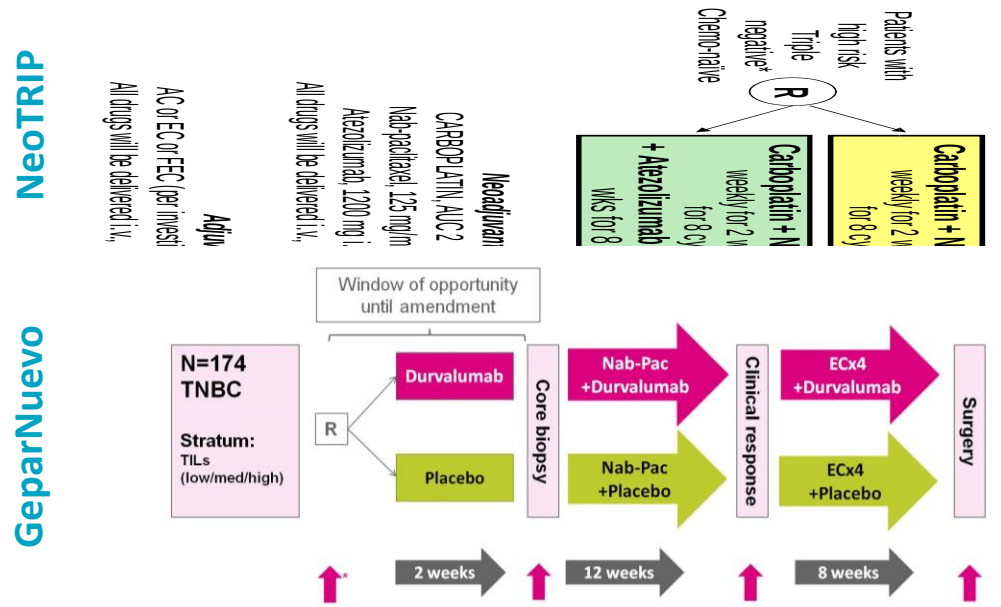


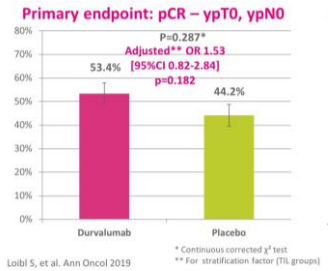
	n/N	Events	HR (95% CI)
Pembro + Chemo	37/145	25.5%	0.52a (0.32-0.82)
Pbo + Chemo	35/79	44.3%	

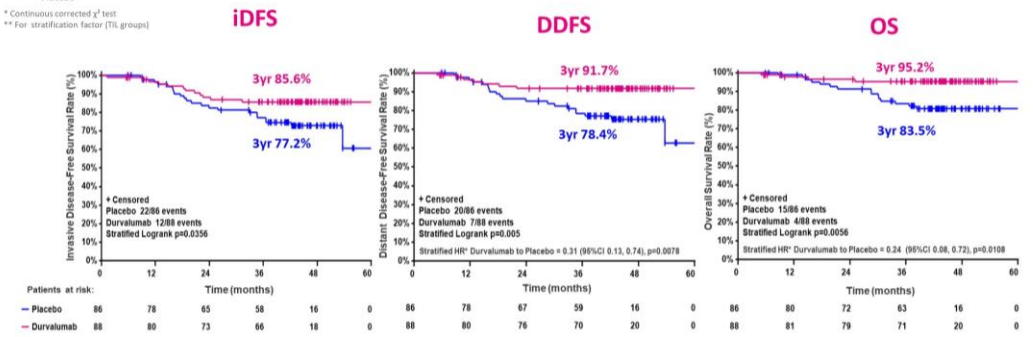
Schmid et al NEJM 2020 & SABCS 2019 & ESMO VP7 2021 & NEJM 2022; Puzstai et al ASCO 2022

Early TNBC algorithm of treatment: adjuvant post-NACT+IO





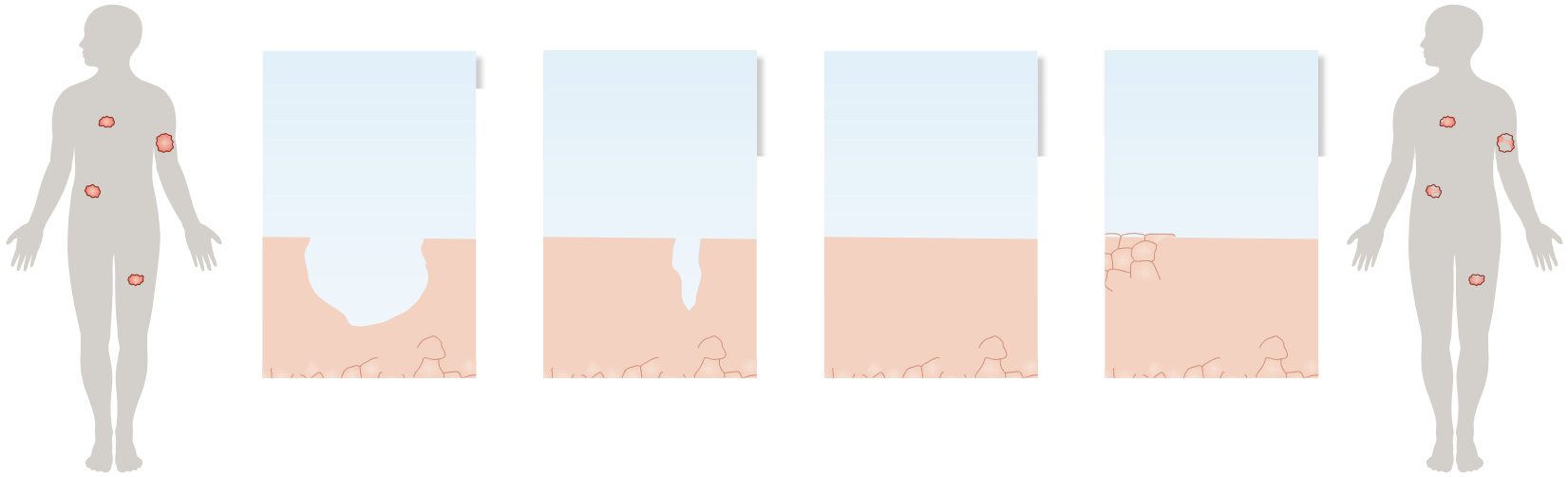




- What is the **best CT-backbone** to combine with IO? Any role for CT de-escalation with ICIs (potential QoL impact)?
- How to **integrate IO** with new approaches (i.e. PARP inh, ADCs in the ABC setting..)?
- Is pCR the **best surrogate of** survival benefit for CT+IO combinations?
- How to develop and validate useful **biomarkers** beyond clinical variables to predict response and advance in a "risk-adapted" strategy for patients with eTNBC? (i.e PD-L1, TILs, dynamic markers, spatial profiling?)

Schmid et al NEJM 2020 & SABCS 2019 & ESMO VP7 2021 & NEJM 2022; Puzstai et al ASCO 2022

Early TNBC algorithm of treatment: IO evolving landscape of trials



Adjuvant

- **Atezolizumab**
  - **Impassion 30 (n=2300)**
    - **Pac → AC/EC**
- Avelumab
  - A-Brave (n=335)
    - Adjuvant and post NAC high risk: avelumab alone
- **Pembrolizumab**
  - **SWOG S1418/NRG BR006 (n=1000)**
    - **Post NAC: Pembro vs Obs x 1 yr**

Neoadjuvant/adjuvant

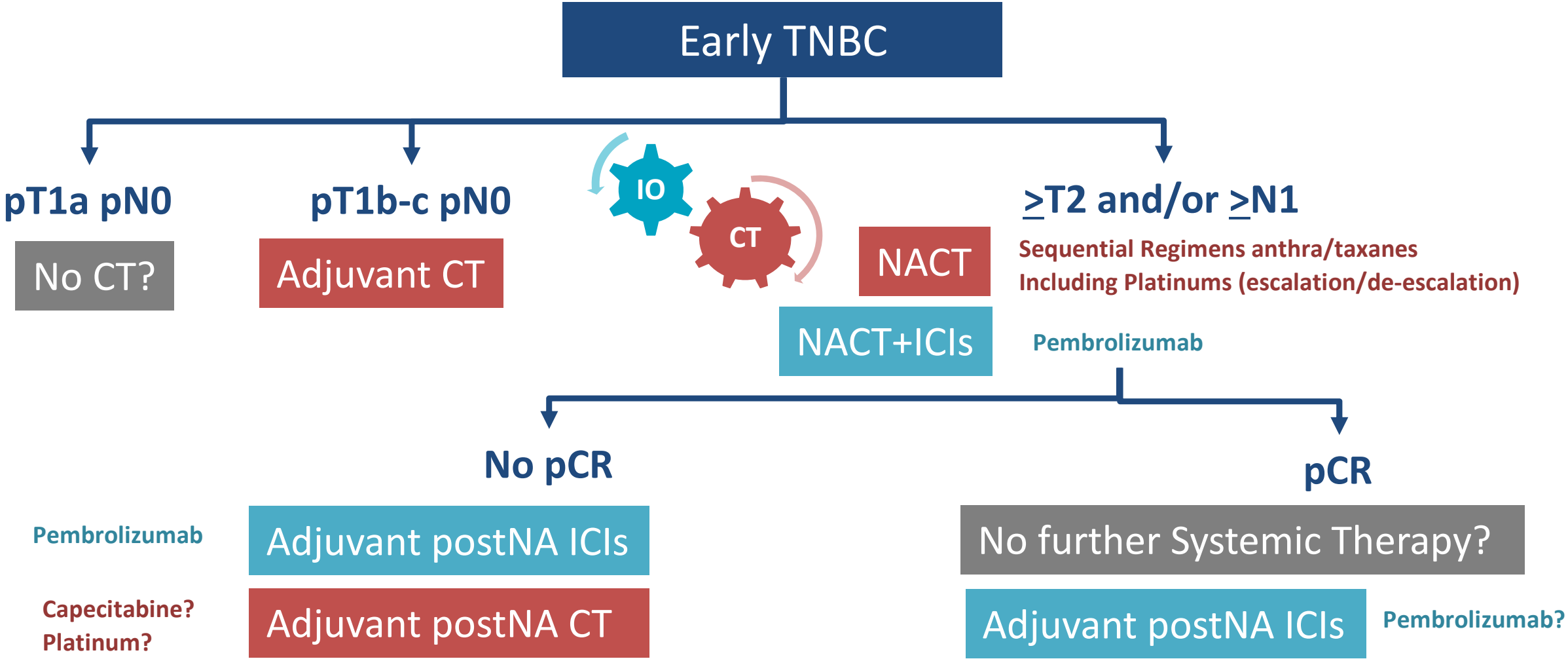
X no adjuvant IO

- **Atezolizumab**
  - **NSABP B59/GeparDouze (n=1520)**
    - **Pac/carbo→ AC/EC**
  - X EFS NeoTRIPaPDL1 (n=272)
  - EFS Impassion 031 (n=333)
- Pembrolizumab
  - NeoPACT (n=100)
  - X • Docetaxel/carbo/pembro x 6

- NA ph2 trial non-anthra backbone (N=115 2018-22)
- pCR 58% (N0 65% and N+ 46% & PD-L1+ 76% vs PD-L1- 39%)
- 2-yr EFS 89% ALL (98% pCR and 78% RD), median FU 24.4mo
- AEs: 26.9% G≥3 and 27% irAEs (4.3% G≥3) and 12% discontinution rate

Versulis et al Nat Med 2020; Rugo et al SACBS 2021 GS1 discusión; Marme et al ESMO Breast 2022 ; Sharma et al ASCO 2022

Early TNBC algorithm of treatment: adjuvant post-NACT+IO setting (RD)

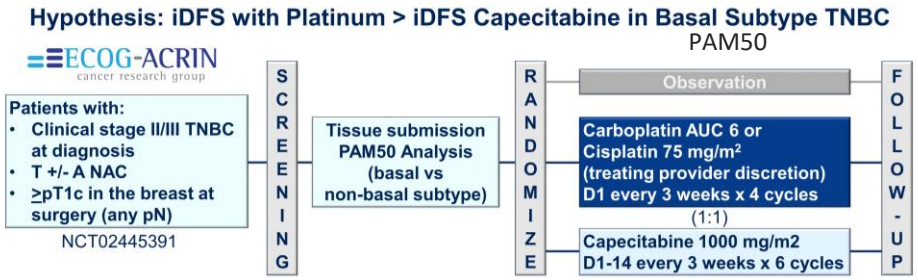


Early TNBC algorithm of treatment: adjuvant post-NACT setting (RD)

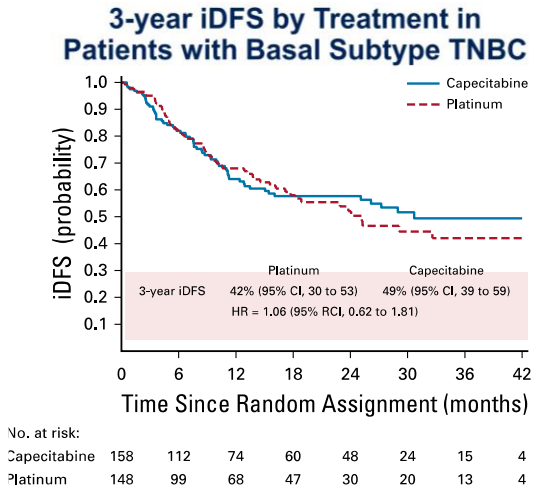
Adjuvant post-NA Capecitabine

Study	Phase	Patients (N)	Design	EFS/OS (HR)
GEICAM/2003-11 **CIBOMA/2004-01**	III	876 (80% adjuvant CT)	Extended Cape after (neo)adjuvant vs Observation	**0.82; 5yr DFS 76.8 vs 79.6% (NS)** 0.92; 5yr OS 85.9 vs 86.2% (NS) *Non-basal subgroup trends in DFS/OS benefit
SYSUCC-001	III	434 (93% adjuvant CT)	Metronomic Cape x12m vs Obs.	0.63; 5yr DFS 73 vs 83%* 0.74; 5yr OS 81 vs 86% (NS)
CREATE-X	III	910 (32% TNBC)	Cape x6-8 vs Observation	**0.70 (0.58 TNBC); 5yr DFS 56.1 vs 69.8%*** 0.59 (0.52 TNBC); 5yr OS 70.3 vs 78.8%*

Adjuvant post-NA Platinum [ECOG-ACRIN 1131 trial]



N= 410/775 pts (22% non basal)



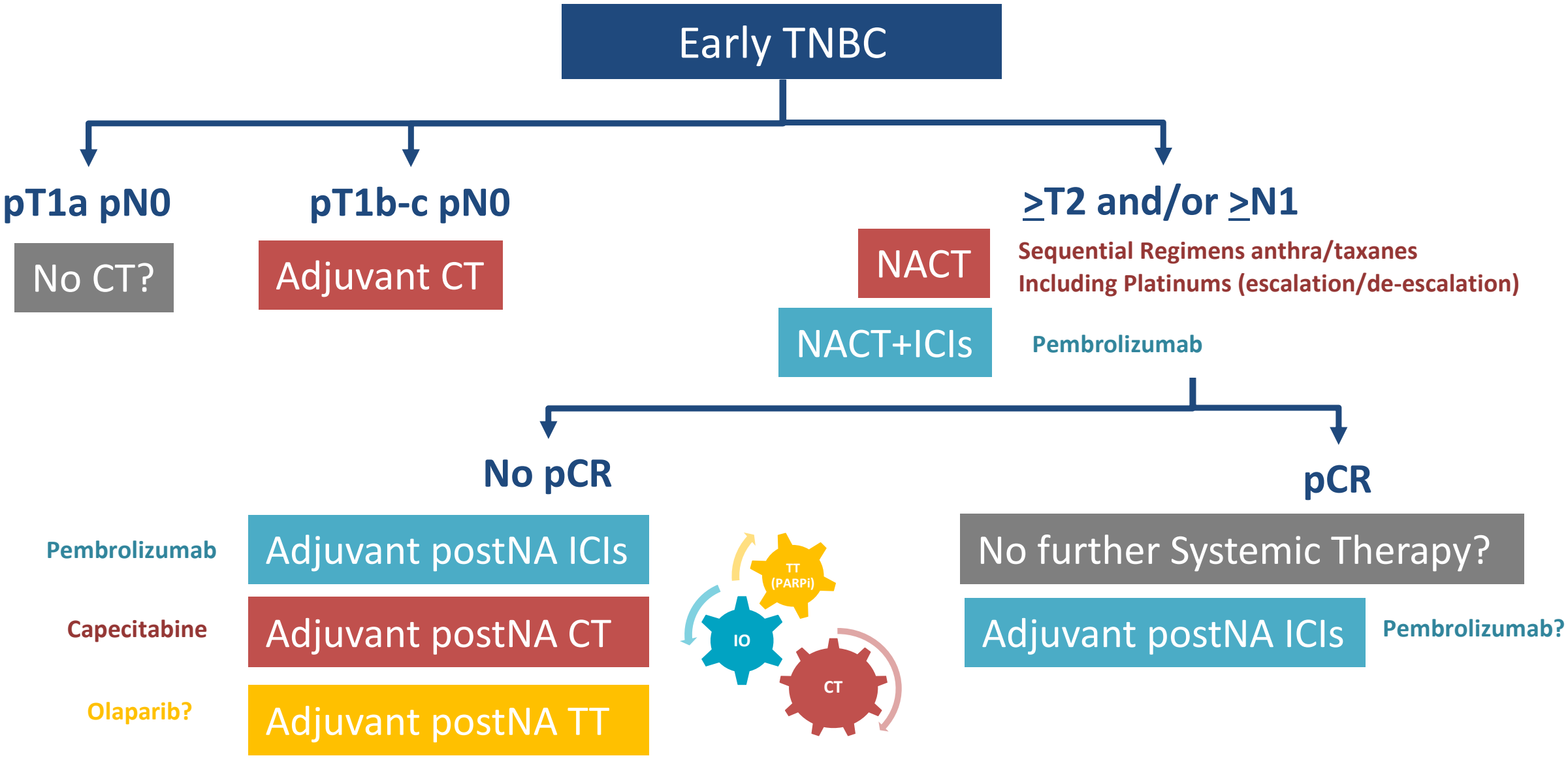
- 85% NA anthras, 61% mastectomy, 60% cT2, 47% cN0, 52% ypN+
- 5IA STOP recommendation for futility (03.2021) median FU 20 mo

- 3-yr RFS 46% vs 49%, HR 0.99 (basal)
- 3-yr OS 58% vs 66%, HR 1.13 (basal)
- Grade 3/4 toxicities more common with platinum agents
- Platinums unlikely to be non-inferior or superior to CAPE in iDFS regardless intrinsic subtype (78% basal) reinforcing role of CAPE

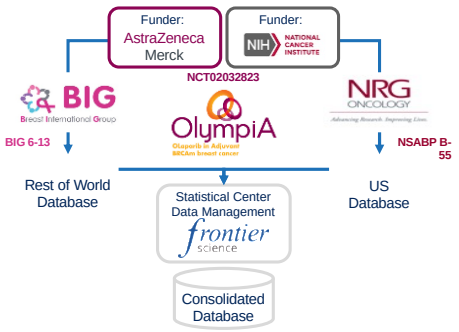
Pts with basal subtype TNBC had higher-than-expected observed risk of recurrence vs previously reported in other treatment-escalation trials

Masuda et al NEJM 2017; Li et al JCO 2020; Lluch et al JCO 2020; Wang et al ASCO 2020; Van Mackelenberg et al SABCS 2019; Mayer et al ASCO 2021 & JCO 2021

Early TNBC algorithm of treatment: TT in the adjuvant post-NACT setting (RD)



Early TNBC algorithm of treatment: PARP inh in early TNBC disease (gBRCA1/2 mut)



- 15.8% TNBC gBRCAm no family history (BRCA1 14.7% & BRCA2 1.1%) mut prevalence 32.9% 20-29 yrs vs 6.9% in 60-69 yrs [GC-HBOC]
- **TNBC** is the predominant subtype in individuals with a germline **BRCA1 mut** (60-80% of tumors in women carrying BRCA1 mut have TN phenotype)

- Local genetic testing or on-study central screening (Myriad Genetics Inc.)
- Germline pathogenic or likely pathogenic *BRCA1/2* mutation
- HER2–negative (hormone receptor–positive or TNBC)
- Stage II-III Breast Cancer or lack of PathCR to NACT

Neoadjuvant Group
- *TNBC:* non-pCR
- *Hormone receptor–positive:* non-pCR and CPS+EG score ≥ 3

≥ 6 cycles Neoadjuvant Chemotherapy → Surgery → +/- Radiotherapy

Adjuvant Group
- *TNBC:* ≥ pT2 or ≥ pN1
- *Hormone receptor–positive:* ≥ 4 positive lymph nodes

Surgery → ≥ 6 cycles Adjuvant Chemotherapy → +/- Radiotherapy

1:1 Randomization N=1836

Olaparib 300 mg twice daily for 1 year

Placebo twice daily for 1 year

Primary End Point
- Invasive disease-free survival (IDFS) by STEEP system[1]

Secondary End Points
- Distant disease-free survival[1] (DDFS)
- Overall survival[1] (OS)
- BRCA1/2 associated cancers
- Symptom / Health related QoL
- Safety

Stratification Factors
- Hormone receptor–positive vs. TNBC
- Neoadjuvant vs. adjuvant
- Prior platinum-based chemotherapy (yes vs. no)

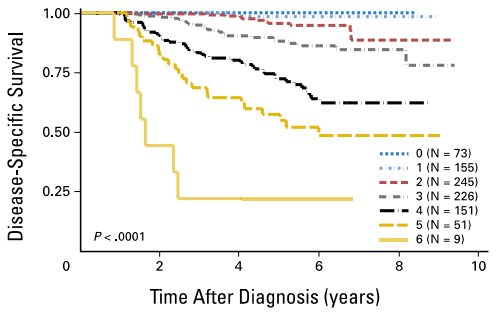
Concurrent Adjuvant Therapy
- Endocrine therapy
- Bisphosphonates
- No 2nd Adjuvant Chemotherapy

Hormone receptor +ve defined as ER and/or PgR positive (IHC staining ≥ 1%)
Triple Negative defined as ER and PgR negative (IHC staining < 1%)
[1]Hudis CA. J Clin Oncol 2007

Characteristic	Olaparib (N=921)	Placebo (N=915)
Median age (interquartile range) — yr	42 (36–49)	43 (36–50)
Germline *BRCA* mutation — no. (%)†		
BRCA1	657 (71.3)	670 (73.2)
BRCA2	261 (28.3)	239 (26.1)
BRCA1 and *BRCA2*	2 (0.2)	5 (0.5)
Missing data	1 (0.1)	1 (0.1)
Previous adjuvant or neoadjuvant chemotherapy — no. (%)		
Adjuvant	461 (50.1)	455 (49.7)
Neoadjuvant	460 (49.9)	460 (50.3)
Regimen with both anthracycline and taxane	871 (94.6)	849 (92.8)
Anthracycline regimen, without taxane	7 (0.8)	13 (1.4)
Taxane regimen, without anthracycline	43 (4.7)	52 (5.7)
Regimen not reported	0	1 (0.1)
<6 Cycles of neoadjuvant or adjuvant chemotherapy	7 (0.8)	15 (1.6)
Platinum-based neoadjuvant or adjuvant therapy		
No	674 (73.2)	676 (73.9)
Yes	247 (26.8)	239 (26.1)
Concurrent hormone therapy (hormone-receptor–positive patients only) — no./total no. (%)	146/168 (86.9)	142/157 (90.4)
Hormone-receptor status — no. (%)‡		
Hormone-receptor positive and HER2 negative§	168 (18.2)	157 (17.2)
Triple-negative breast cancer¶	751 (81.5)	758 (82.8)
Menopausal status (women only) — no./total no. (%)		
Premenopausal	572/919 (62.2)	553/911 (60.7)
Postmenopausal	347/919 (37.8)	358/911 (39.3)
Surgery for primary breast cancer — no. (%)		
Mastectomy	698 (75.8)	673 (73.6)
Conservative surgery only	223 (24.2)	240 (26.2)
Missing data	0	2 (0.2)

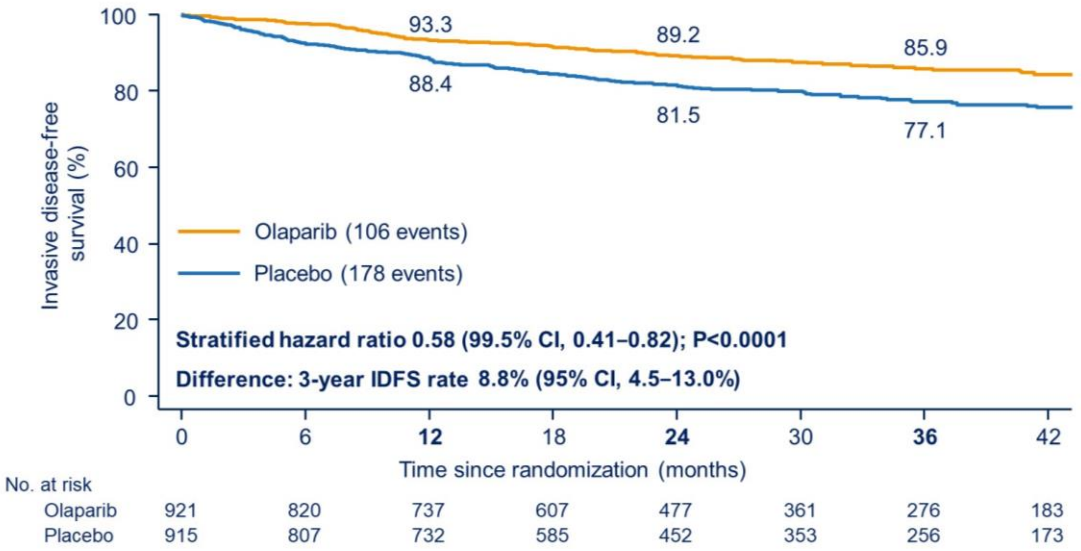
***CPS+EG score**

Stage	Score
Clinical stage	
I	0
IIA	0
IIB	1
IIIA	1
IIIB	2
IIIC	2
Pathologic stage	
0	0
I	0
IIA	1
IIB	1
IIIA	1
IIIB	1
IIIC	2
Tumor marker	
ER negative	1
Nuclear grade 3	1

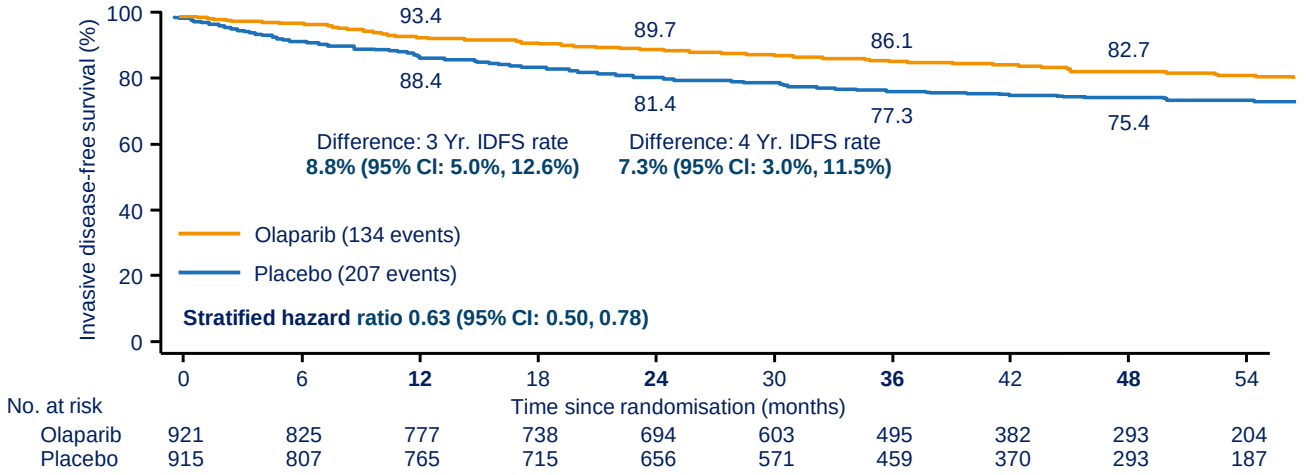


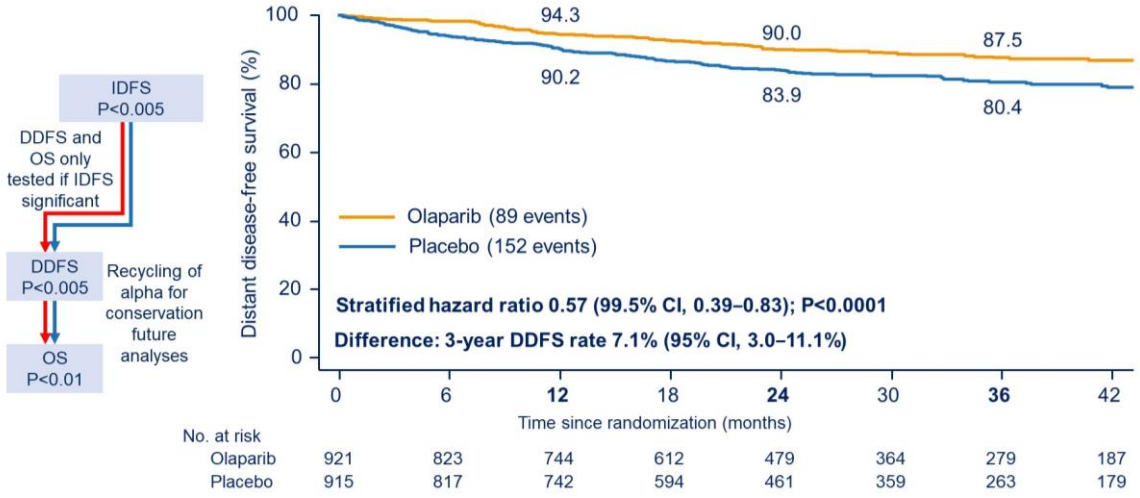
Brown et al Cancer Discov 2017; Pilié et al NRCO 2018; Dorling et al NEJM 2021; Hu et al NEJM 2021; Engel et al BMC Cancer 2018; Tutt et al NEJM 2021 & ASCO 2021; Jeruss et al JCO 2008

Early TNBC algorithm of treatment: PARP inh in early TNBC disease (gBRCA1/2 mut)

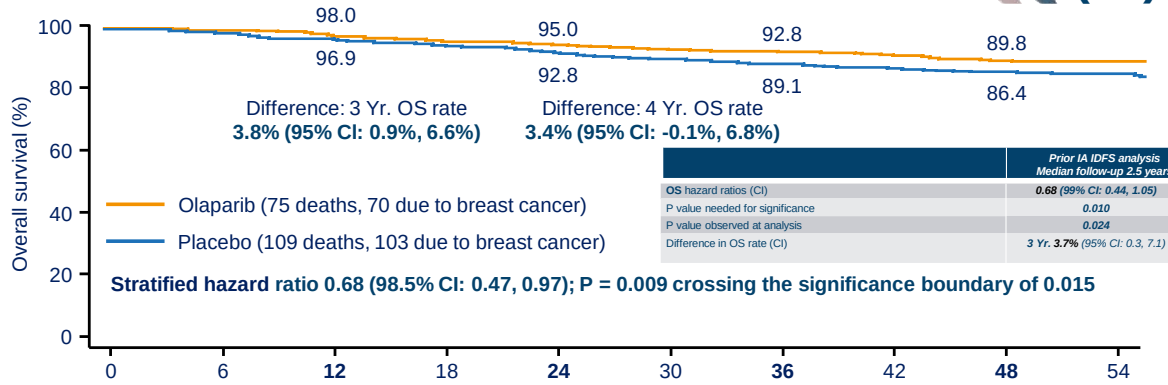


ANALYSIS OF IDFS (ITT) AT OS IA2





SECOND OVERALL SURVIVAL INTERIM ANALYSIS - OS IA2 (ITT)



	Prior IA IDFS analysis Median follow-up 2.5 years
OS hazard ratios (CI)	0.68 (99% CI: 0.44, 1.05)
P value needed for significance	0.010
P value observed at analysis	0.024
Difference in OS rate (CI)	3 Yr. 3.7% (95% CI: 0.3, 7.1)

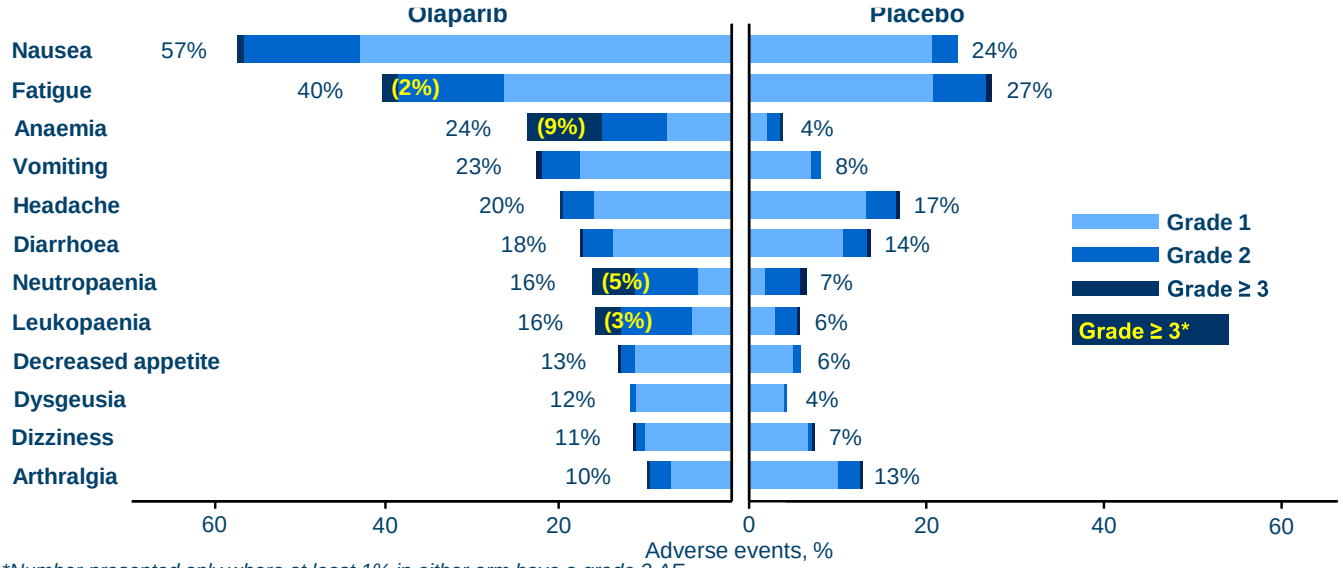
98.5% confidence intervals are shown for the hazard ratio because P < 0.015 is required for statistical significance

Tutt et al NEJM 2021 & ASCO 2021 & ESMO VP_3.2022

Early TNBC algorithm of treatment: PARP inh in early TNBC disease (gBRCA1/2 mut)

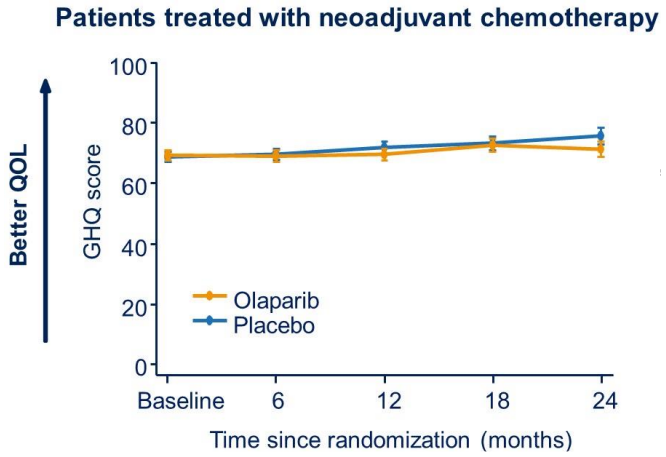
	Olaparib (N = 911)	Placebo (N = 904)
Any adverse event	**836 (91.8%)**	**758 (83.8%)**
Serious adverse event (SAE)	79 (8.7%)	**78 (8.6%)**
Adverse event of special interest*	**31 (3.4%)**	**51 (5.6%)**
MDS/AML	2 (0.2%)	3 (0.3%)
Pneumonitis	9 (1.0%)	**12 (1.3%)**
New primary malignancy	**21 (2.3%)**	**36 (4.0%)**
Grade ≥ 3 adverse event	**223 (24.5%)**	102 (11.3%)
Grade 4 adverse event	17 (1.9%)	4 (0.4%)
Adverse event leading to permanent discontinuation of treatment†	**98 (10.8%)**	**42 (4.6%)**
Adverse event leading to death‡	1 (0.1%)	2 (0.2%)

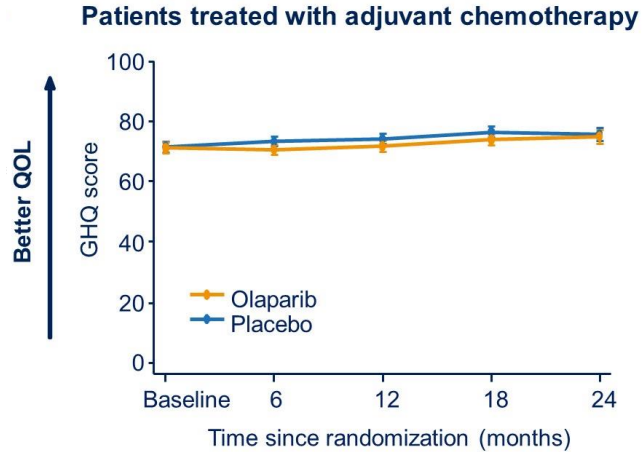
There have been no additional adverse events leading to death reported since IA IDFS



*Number presented only where at least 1% in either arm have a grade 3 AE

OlympiA: EORTC QLQ-C30 Global Health QoL Score

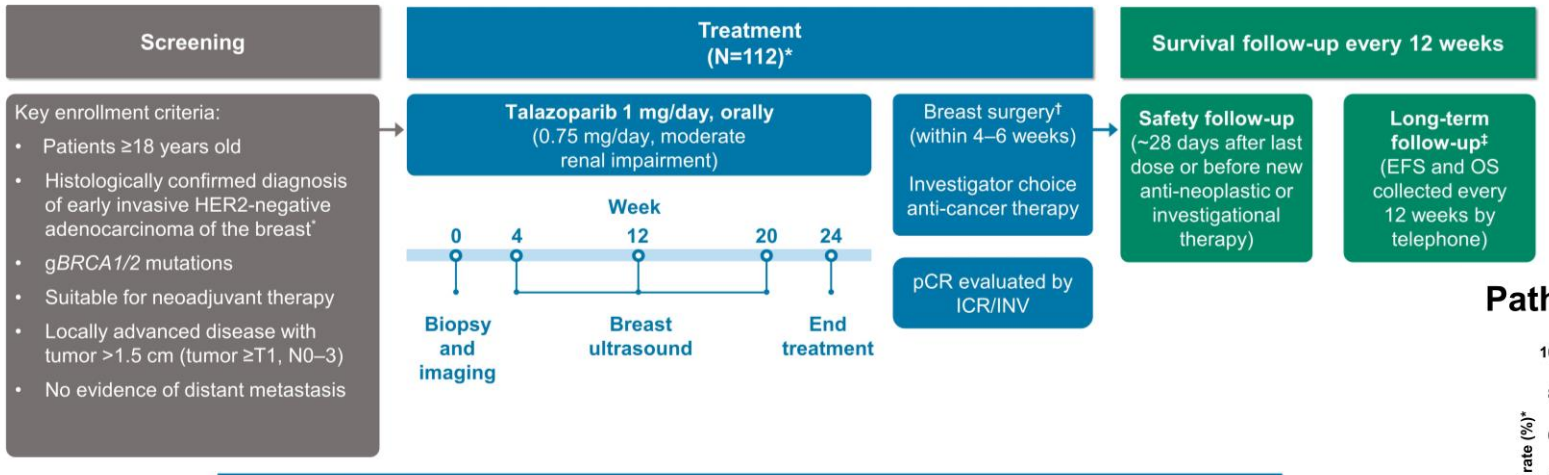




Early TNBC algorithm of treatment: PARP inh potential for NA de-escalation

[NEOTALA trial]

NEOTALA is a non-randomized, open-label, multi-center, single-arm, Phase 2 trial (NCT03499353)



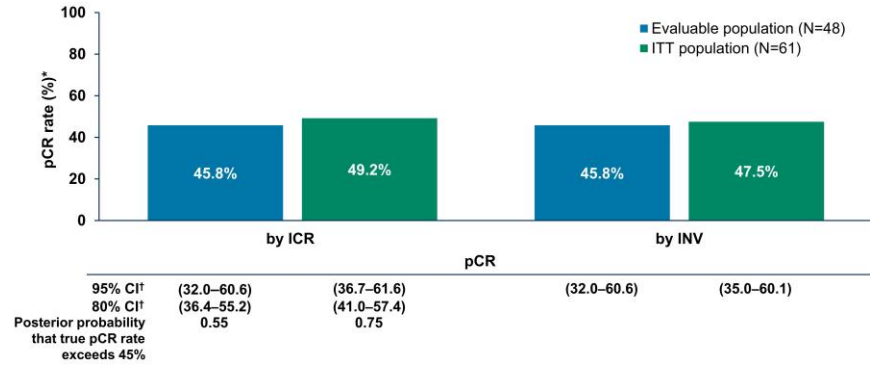
Primary and key secondary endpoints

Primary endpoint
- pCR* by ICR in the evaluable population

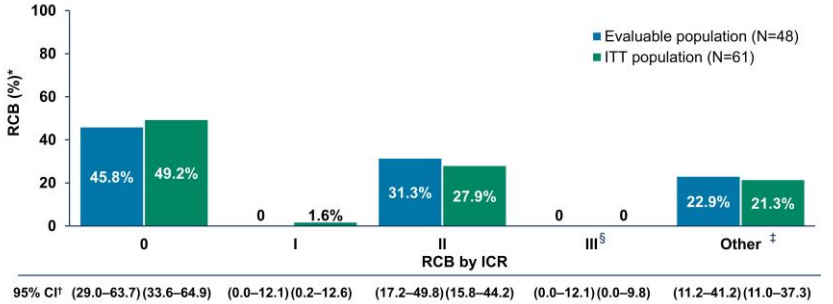
Secondary endpoints
- pCR by ICR in the ITT population
- pCR by INV in the ITT and evaluable populations
- RCB by ICR in the ITT and evaluable populations
- To evaluate the safety and tolerability of talazoparib
- EFS (estimated at 3 years†)
- OS (estimated at 3 years†)

Patient baseline characteristics	Talazoparib (N=61)
Age (years), n (%)	
18–44	37 (60.7)
45–64	18 (29.5)
≥65	6 (9.8)
Median	42
Mean	44.6
Gender, n (%)	
Female	61 (100.0)
Menopausal status	
Premenopausal	36 (59.0)
Postmenopausal	25 (41.0)
Race, n (%)	
White	47 (77.0)
Black or African American	7 (11.5)
Asian	3 (4.9)
Not reported	4 (6.6)
Breast cancer	
Duration since onset (weeks)	
Mean (min, max)	4.54 (0.4, 21.1)
Adenocarcinoma	60 (98.4)
Squamous carcinoma with spindle cell	1 (1.6)
TNBC	61 (100.0)
*BRCA1**	48 (78.7)
*BRCA2**	13 (21.3)
Staging	
Stage I	20 (32.8)
Stage II	27 (44.3)
Stage III	14 (22.9)

Pathologic Complete Response



Residual Cancer Burden

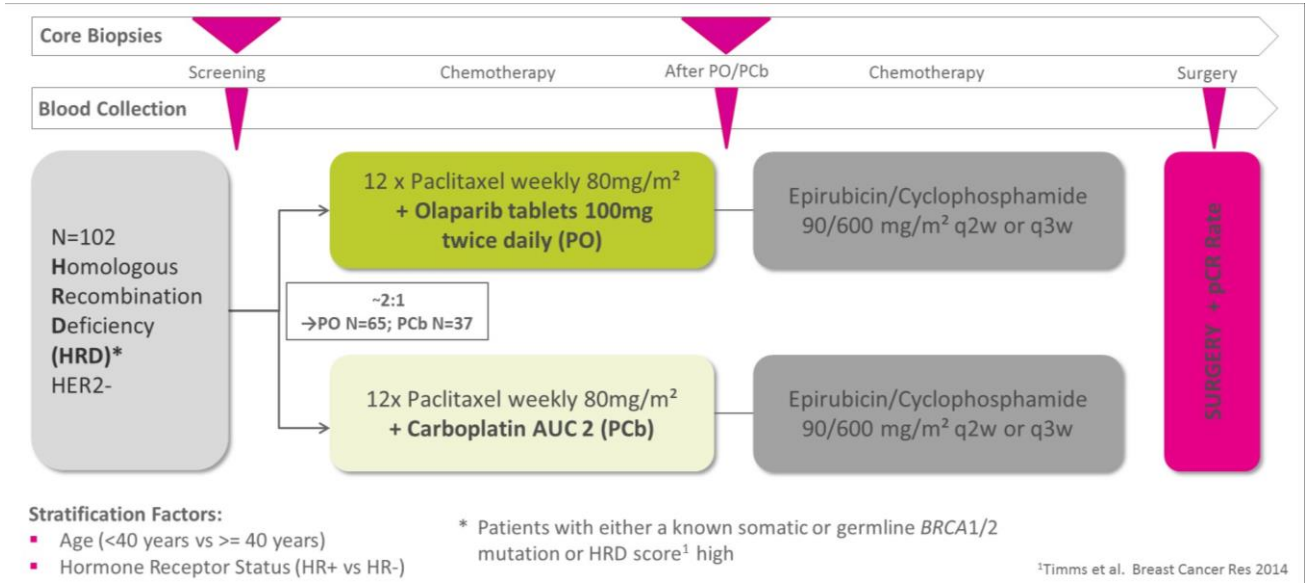


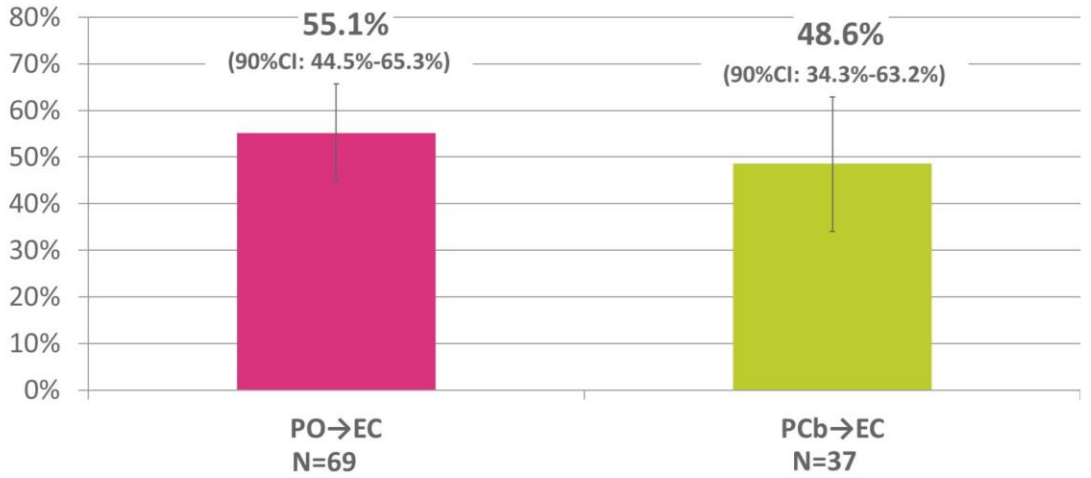
- 90.2% received TALAZO for > 20wks
- 18% pts experienced all-casualty TEAEs (G3 anemia the most common 14.8%, no deaths)
- pCR rates comparable to those with Anthra/taxane CT regimens

Litton et al ASCO 2021

Early TNBC algorithm of treatment: PARP inh potential for NA de-escalation

[GeparOla trial]

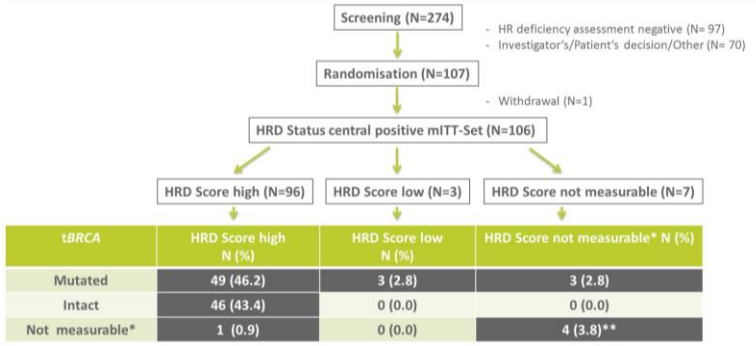




*Sample size was calculated to exclude the pCR rate lower boundary of ≤55% in PwO→EC arm (primary endpoint focused on OLA) and trial could not exclude a pCR rate ≤55%

Primary Objective and Endpoint:

- To assess the pathological complete response (ypT0/is ypN0) rate of neoadjuvant treatment of olaparib and paclitaxel followed by epirubicin and cyclophosphamide (PO→EC) in patients with early BC and HR deficient tumors (defined as either t*BRCA1/2* mutation and/or HRD score high and/or known g*BRCA* mutation).

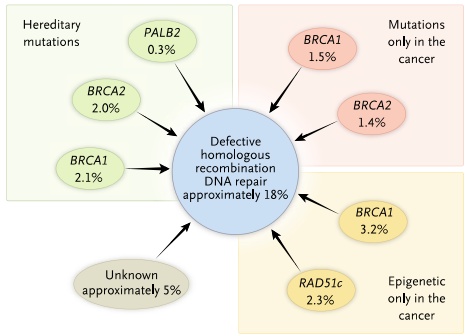


tBRCA	HRD Score high N (%)	HRD Score low N (%)	HRD Score not measurable* N (%)
Mutated	49 (46.2)	3 (2.8)	3 (2.8)
Intact	46 (43.4)	0 (0.0)	0 (0.0)
Not measurable*	1 (0.9)	0 (0.0)	4 (3.8)**

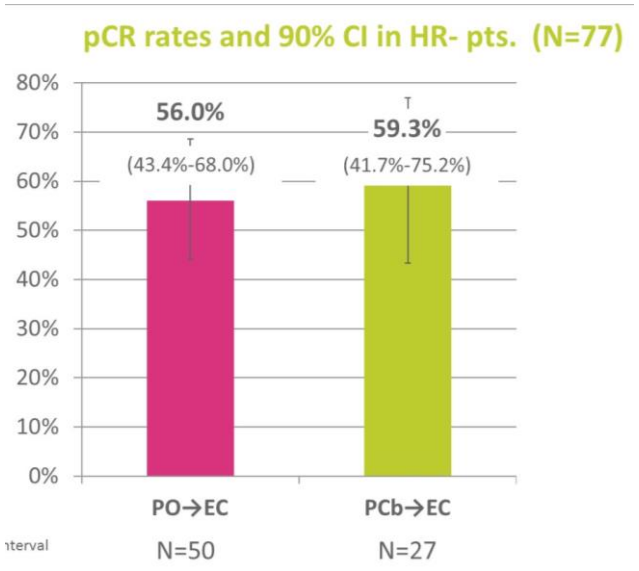
HRD= high HRD score and/or g/tBRCA1/2mut

■ Eligible patients
* Insufficient quality or quantity of DNA
** Eligibility criteria: g*BRCA* local positive

Paths to Defective HR DNA Repair



- **Subgroup analyses are hypothesis generating and need further confirmation:**
  - patients wit HR+ tumors (pCR rate PO 52.6% vs. PCb 20.0%)
  - patients <40 years (pCR rate PO 76.2% vs. PCb 45.5%)
  - HRD score high, *BRCA1/2* wildype patients (pCR rate PO 51.7% vs. PCb 37.5%)



Fasching et al ASCO 2019 & Ann Oncol 2021; Turner N NEJM 2017

Early TNBC algorithm of treatment: TT for gBRCA1/2mut patients with high-risk TNBC

Early TNBC

pT1a pN0

No CT?

pT1b-c pN0

Adjuvant CT

[≥pT2 and/or ≥pN1]

Adjuvant CT

Olaparib (gBRCAmut)

Adjuvant TT

≥T2 and/or ≥N1

NACT

Sequential Regimens anthra/taxanes Including Platinums (escalation/de-escalation)

NACT+ICIs

Pembrolizumab

No pCR

Pembrolizumab

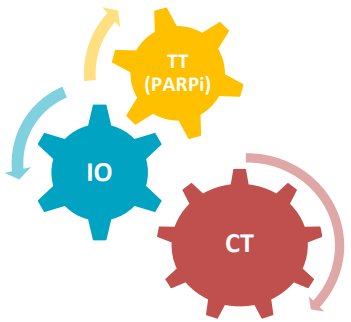
Adjuvant postNA ICIs

Capecitabine

Adjuvant postNA CT

Olaparib (gBRCAmut)

Adjuvant postNA TT



pCR

No further Systemic Therapy?

Adjuvant postNA ICIs

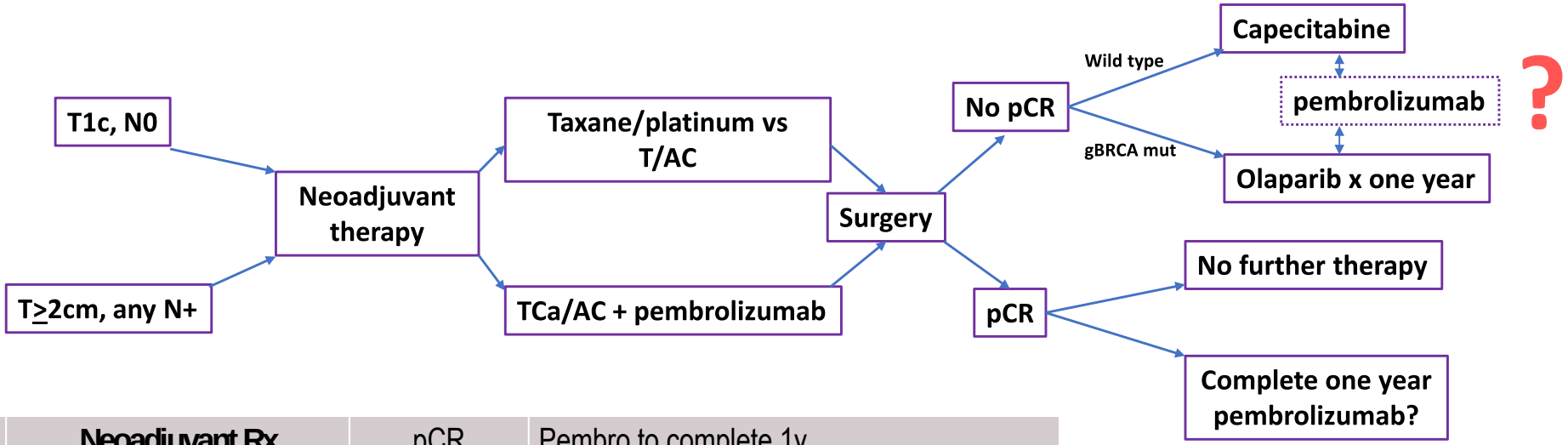
Pembrolizumab?

Early TNBC algorithm of treatment evolution: heading a new algorithm @2022

T1a/b, N0 → Surgery → +/- chemotherapy → taxane/carboplatin vs docetaxel/cyclophosphamide

ESMO

Stage I cT1N0	**Surgery**	pT1aN0	No systemic therapy
		pT1b-c,N0	TC x 4-6 (optional in T1bN0)



ESMO

Stage II-III cT2-3N0 cT0-2N1 cT3N1 cT4N(any) cT(any)N2-3	**Neoadjuvant Rx** Chemo + ICI	pCR	Pembro to complete 1y
		Residual disease	Pembro to complete 1y AND MAY Consider capecitabine Or Olaparib if germline +*
Surgery first Stage II-III	Neoadjuvant recommended!	Stage II-III	Chemo + ICI

Rugo H SABCS 2021; Tung et al JCO 2021; Burstein et al Ann Oncol 2021; Carey et al ESMO Breast 2022

Challenges ahead in eTNBC

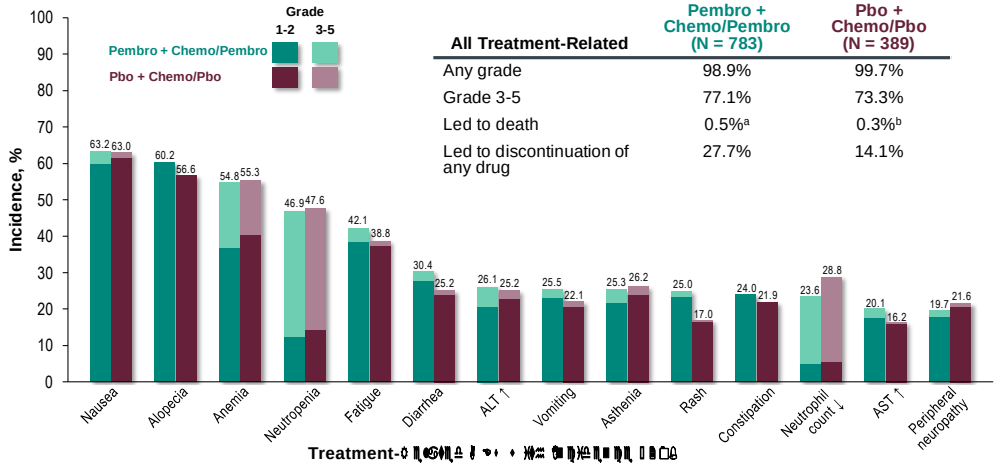
Managing toxicity in eTNBC patients beyond CT adverse events

CT

Capecitabine
Anthracyclines
Taxanes
Platinums

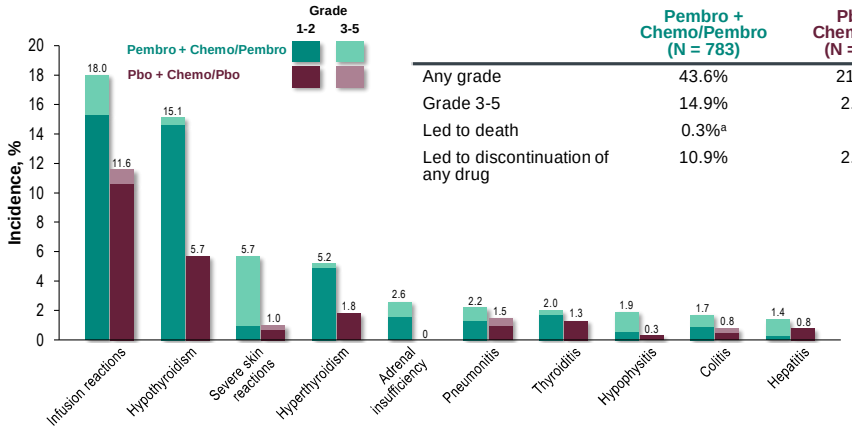
ICIs

Treatment-Related AEs in Combined Phases



All Treatment-Related	Pembro + Chemo/Pembro (N = 783)	Pbo + Chemo/Pbo (N = 389)
Any grade	98.9%	99.7%
Grade 3-5	77.1%	73.3%
Led to death	0.5%[a]	0.3%[b]
Led to discontinuation of any drug	27.7%	14.1%

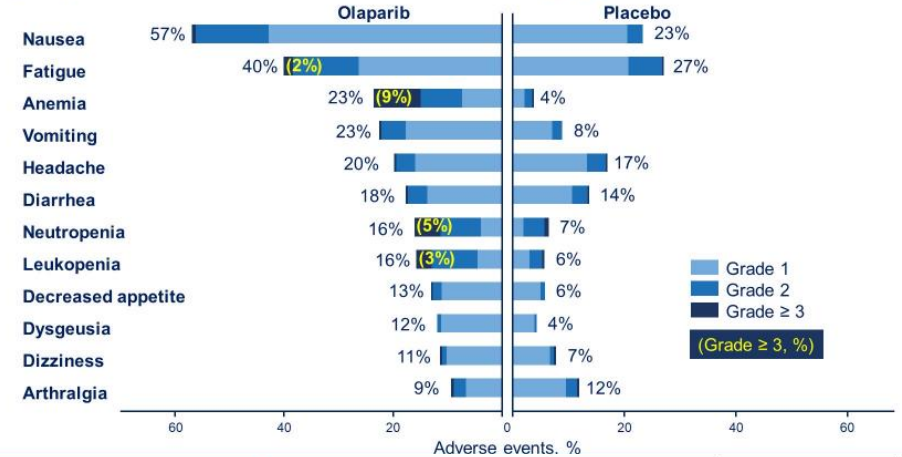
Immune-Mediated AEs and Infusion Reactions in Combined Phases



	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%

TT (PARPi)

OlympiA: Adverse events of any grade ≥ 10%



	Olaparib (N = 911)	Placebo (N = 904)
Any adverse event	835 (91.7%)	753 (83.3%)
Serious adverse event (SAE)	**79 (8.7%)**	**76 (8.4%)**
Adverse event of special interest	**30 (3.3%)**	**46 (5.1%)**
MDS/AML	**2 (0.2%)**	**3 (0.3%)**
Pneumonitis	9 (1.0%)	11 (1.2%)
New primary malignancy	**20 (2.2%)**	**32 (3.5%)**
Grade ≥ 3 adverse event	221 (24.3%)	102 (11.3%)
Grade 4 adverse event	**17 (1.9%)**	**4 (0.4%)**
Adverse event leading to permanent discontinuation of treatment*	**90 (9.9%)**	**38 (4.2%)**
Adverse event leading to death†	1 (0.1%)	2 (0.2%)

Checkpoint inhibitors, fertility, pregnancy, and sexual life: a systematic review

ESMO OPEN CANCER HORIZONS

Schmidt et al EESMO 2021; Tutt et al ASCO 2021; Garutti et al ESMO Open 2021

PARP inhibitor in early TNBC: impact on Genetic Counselling

TESTING CRITERIA FOR HIGH-PENETRANCE BREAST CANCER SUSCEPTIBILITY GENES
(Specifically *BRCA1, BRCA2, CDH1, PALB2, PTEN,* and *TP53*. See GENE-A)[a,d,e,f]

NCCN Guidelines Version 2.2022
Hereditary Cancer Testing Criteria

Testing is clinically indicated in the following scenarios:

- See General Testing Criteria on CRIT-1.
- Personal history of breast cancer with specific features:
  - By Age at Diagnosis and Family History
    - ◊ ≤45 y
    - ◊ 46–50 y with ANY:
      - Unknown or limited family history[g]
      - Multiple primary breast cancers (synchronous or metachronous)
      - ≥1 close blood relative[h] with breast, ovarian, pancreatic, or prostate cancer at any age
    - ◊ ≥51 y
      - ≥1 close blood relative[h] with ANY:
        - breast cancer at age ≤50 y or male breast cancer at any age
        - ovarian cancer any age
        - pancreatic cancer any age
        - metastatic,[i] intraductal/cribriform histology, or high- or very-high risk group (see NCCN Guidelines for Prostate Cancer) prostate cancer any age
      - ≥3 total diagnoses of breast cancer in patient and/or close blood relatives
      - ≥2 close blood relatives[h] with either breast or prostate cancer (any grade) at any age
  - ◊ Any Age
    - To aid in systemic treatment decisions using PARP inhibitors for breast cancer in the metastatic setting[j,k] (See NCCN Guidelines for Breast Cancer)
    - To aid in adjuvant treatment decisions with olaparib for high-risk,[l] HER-2 negative breast cancer[j]
    - Triple-negative breast cancer
    - Lobular breast cancer with personal or family history of diffuse gastric cancer. See NCCN Guidelines for Gastric Cancer
    - Male breast cancer
    - ≥1 close blood relative[g] with male breast cancer
  - By Ancestry
    - ◊ Ashkenazi Jewish ancestry
- Family history of cancer only
  - An affected individual (not meeting testing criteria listed above) or unaffected individual with a first- or second-degree blood relative meeting any of the criteria listed above (except unaffected individuals whose relatives meet criteria only for systemic therapy decision-making).[m]
    - ◊ If the affected relative has pancreatic cancer or prostate cancer only first-degree relatives should be offered testing unless indicated based on additional family history.
  - An affected or unaffected individual who otherwise does not meet the criteria above but has a probability >5% of a *BRCA1/2* pathogenic variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, CanRisk)[n]

Criteria met → See GENE-1

If testing criteria not met, consider testing for other hereditary syndromes → If criteria for other hereditary syndromes not met, then cancer screening as per NCCN Screening Guidelines

Continued on CRIT-3

Footnotes on CRIT-2A

NCCN recommendations have been developed to be inclusive of individuals of all sexual and gender identities to the greatest extent possible. On this page, the terms males and females refer to sex assigned at birth.

SEOM Sociedad Española de Oncología Médica

Regardless of family history:

Women with synchronous or metachronous breast and ovarian cancer

Breast cancer ≤ 40 years

Bilateral breast cancer (the first diagnosed ≤ 50 years)

Triple-negative breast cancer ≤ 60 years

High-grade epithelial non-mucinous ovarian cancer (or fallopian tube or primary peritoneal cancer)

Ancestry with founder mutations

BRCA somatic mutation detected in any tumor type with a allele frequency > 30% (if it is known)

Metastatic HER2-negative breast cancer patients eligible to consider PARP inhibitor therapy

2 or more first degree relatives with any combination of the following high-risk features:

Bilateral breast cancer + another breast cancer < 60 years

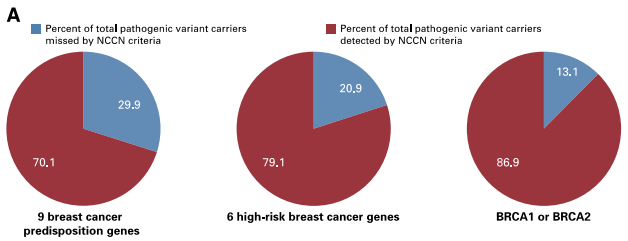
Breast cancer < 50 years and prostate or pancreatic cancer < 60 years

Male breast cancer

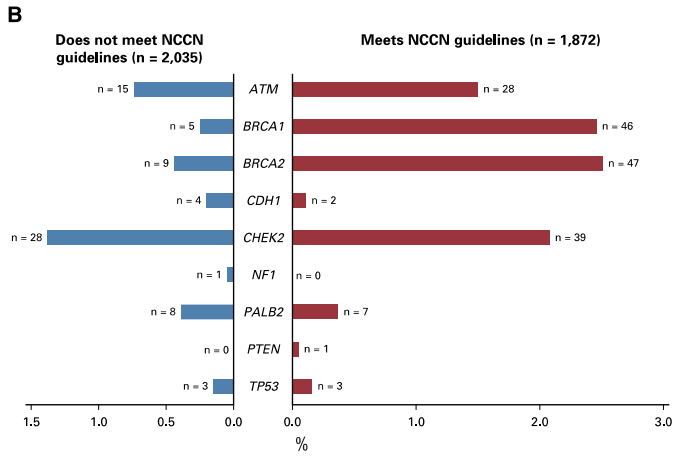
Breast and ovarian cancer

Two cases of breast cancer diagnosed before age 50 years

3 or more direct relatives with breast cancer (at least one premenopausal) and/or ovarian cancer and/or, pancreatic cancer or high Gleason (≥ 7) prostate cancer



- 48% of women with BC meet NCCN
- Sensitivity of NCCN for BRCA1/2 ~87%
- PPV/NPV of NCCN are 5.0% and 99.3%
- Testing all women doubles the number tested
- > 60 and not meeting NCCN has NPV of 99.7%
- > 50 and not meeting NCCN has NPV of 99.6%



- Universal testing for the most actionable genes (*BRCA1/2 +/- PALB2*) will be very low yield in women over 60 who do not meet NCCN guidelines
- Most testing (in U.S.) is done with multigene panels, and universal panel testing will identify non-*BRCA* PV in women who do not meet NCCN guidelines
- Most non-*BRCA* PV do not have clear treatment implications. Implications for family are complicated by incomplete understanding of risks
- If expanded multigene testing becomes the norm, it will be critical for there to be specialist genetic follow-up (i.e. cancer genetic counseling) to guide those who are found to carry PV (or VUS)

Robson M ESMO_VP3-2022; & ASCO 2022 Yadav et al JCO 2020; NCCN v2.2022 & González-Santiago et al Clin Trans Oncol 2020

Navigating the early TNBC algorithm of treatment: work in progress

Early TNBC

pT1a pN0

No CT?

pT1b-c pN0

Adjuvant CT

[≥pT2 and/or ≥pN1]

Adjuvant CT

Olaparib (gBRCAmut)

Adjuvant TT

≥T2 and/or ≥N1

NACT

Sequential Regimens anthra/taxanes Including Platinums (escalation/de-escalation)

NACT+ICIs

Pembrolizumab

No pCR

Pembrolizumab

Adjuvant postNA ICIs

Capecitabine

Adjuvant postNA CT

Olaparib (gBRCAmut)

Adjuvant postNA TT

Clinical Trials?

pCR

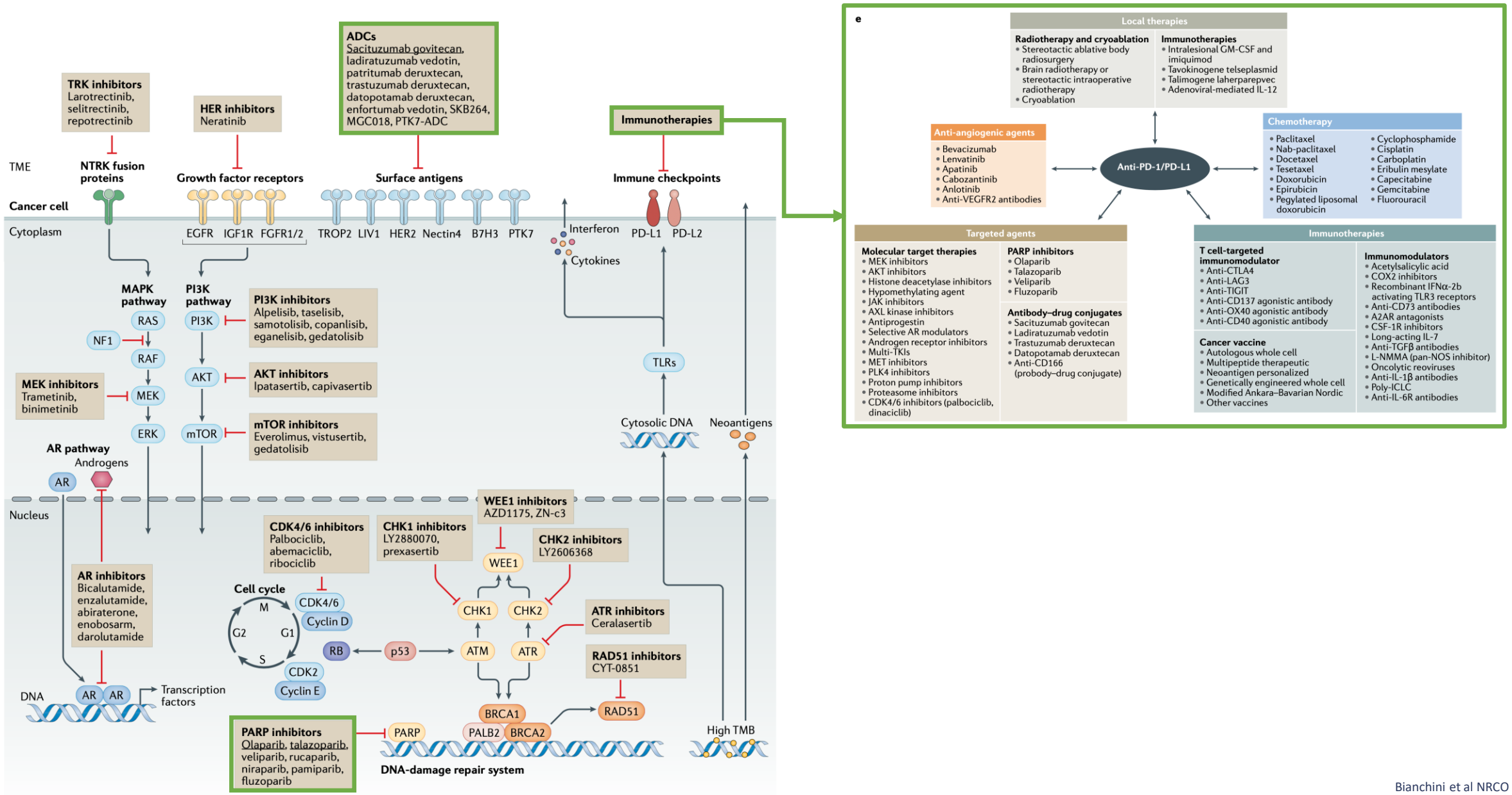
No further Systemic Therapy?

Adjuvant postNA ICIs

Pembrolizumab?

Clinical Trials?

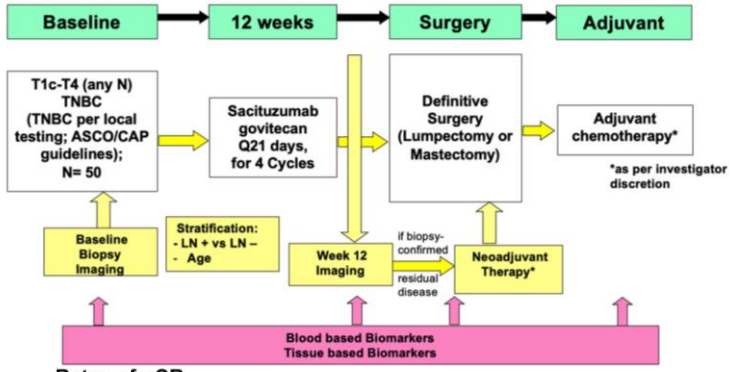
TNBC ecosystem: targeting vulnerabilities in TNBC

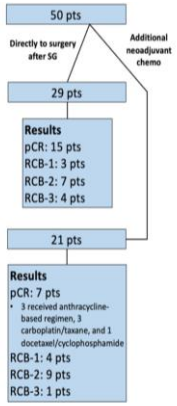


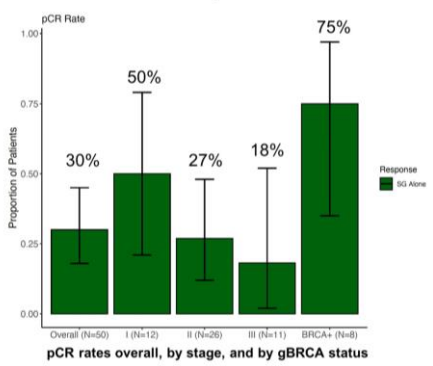
Bianchini et al NRCO 2021

Ongoing research based on ADCs in the early TNBC setting

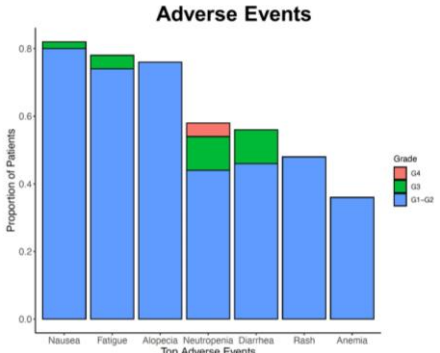
Neo STAR trial — NA setting (de-escalation)



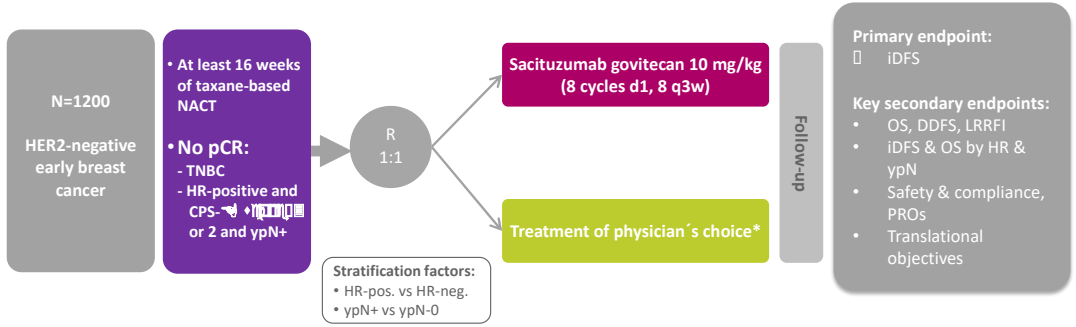




- 6% of pts required dose-reduction.
- No pts discontinued SG therapy due to disease progression or AEs. One discontinued due to minimal response per investigator discretion.



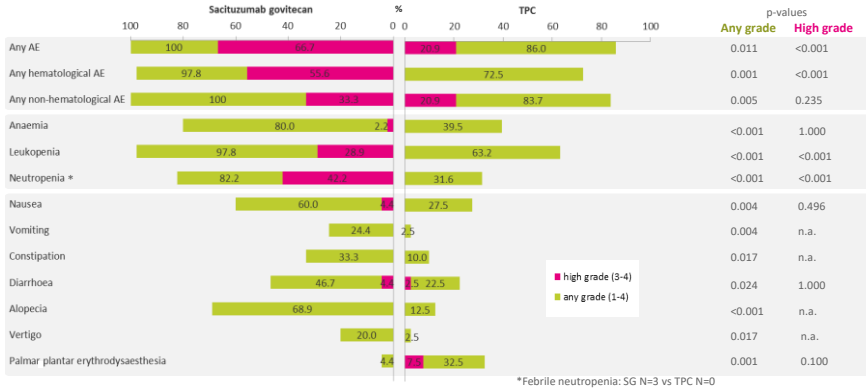
SASCIA trial — Adjuvant post-NA setting (escalation)



* **Capecitabine** (Cape, 2000 mg/m²/d, days 1-14, q21d for up to 8 cycles) or **platinum-based** chemotherapy (8 cycles) or **observation**.
Background therapy: in patients with HR-positive breast cancer, **endocrine-based therapy** will be administered according to local guidelines.

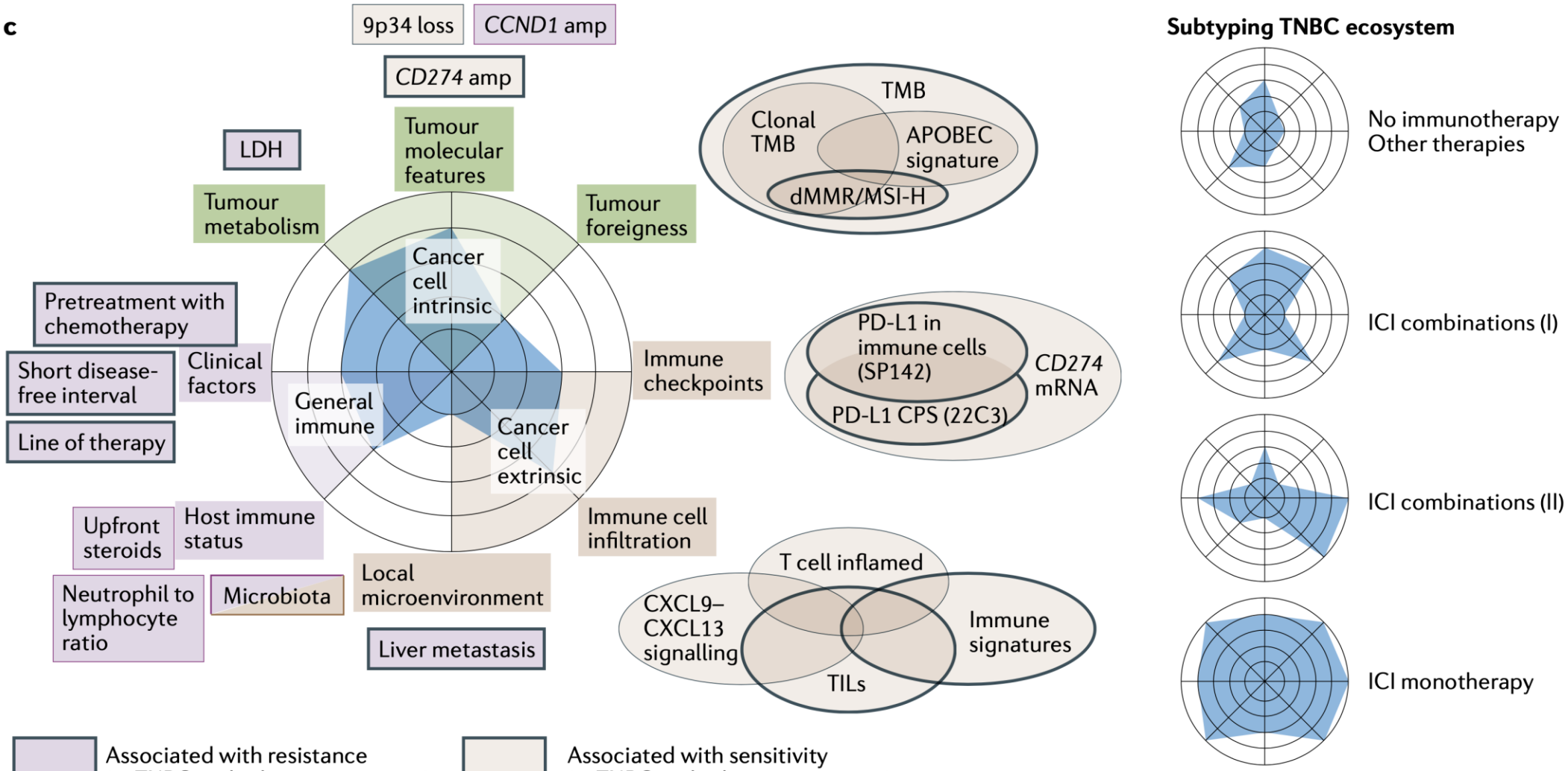
Clinical parameters	Category	SG N=45 N(%)	TPC N=43 N(%)
Age	Median (range)	46.0 (24.0-71.0)	51.0 (32.0-74.0)
BMI	Median (range)	25.8 (20.0-42.6)	23.8 (18.2-35.4)
ECOG	ECOG 0	41 (91.1)	33 (76.7)
	ECOG 1	4 (8.9)	10 (23.3)
ypN	ypN0	22 (48.9)	24 (55.8)
	ypN+	23 (51.1)	19 (44.2)
Grading	G2	7 (15.6)	8 (18.6)
	G3	38 (84.4)	35 (81.4)
ER/PgR (central)*	both negative (TNBC)	30 (66.7)	29 (67.4)
	at least one positive	15 (33.3)	14 (32.6)
CPS-EG (HR+ pts only)	CPS-[illegible]	10 (66.6)	9 (64.3)
	CPS-EG score 2, ypN+	5 (33.3)	5 (35.7)

- Patients in the SG arm more haematologic and non-haem toxicities
- More dose delays were observed in the SG vs TPC (Cape) arm
- Dose reductions occured equally in both arms, mostly due to haematologic toxicities in the SG and non-haematologic toxicities in the TPC (Cape) arm



Spring et al ASCO 2022; Marme et al ESMO Breast 2022

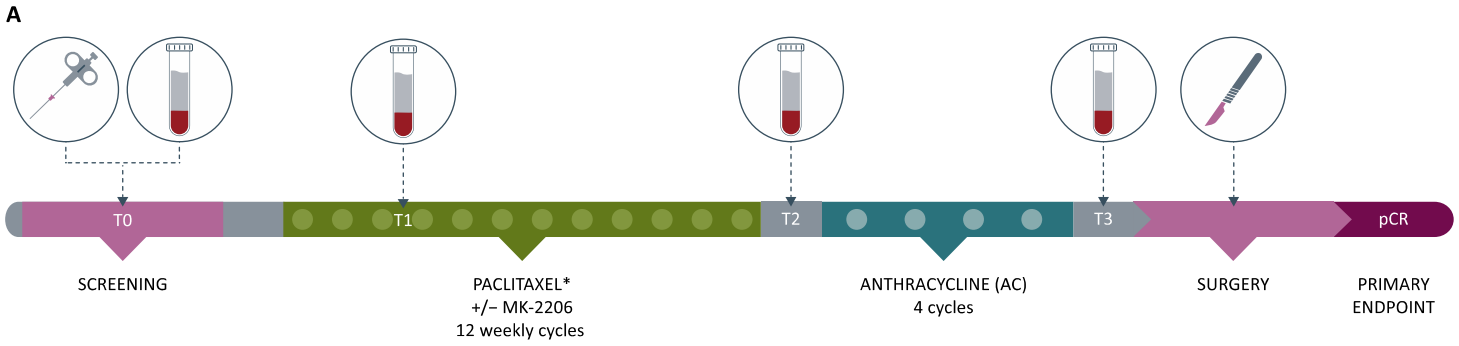
Ongoing research based on IO in need of biomarkers



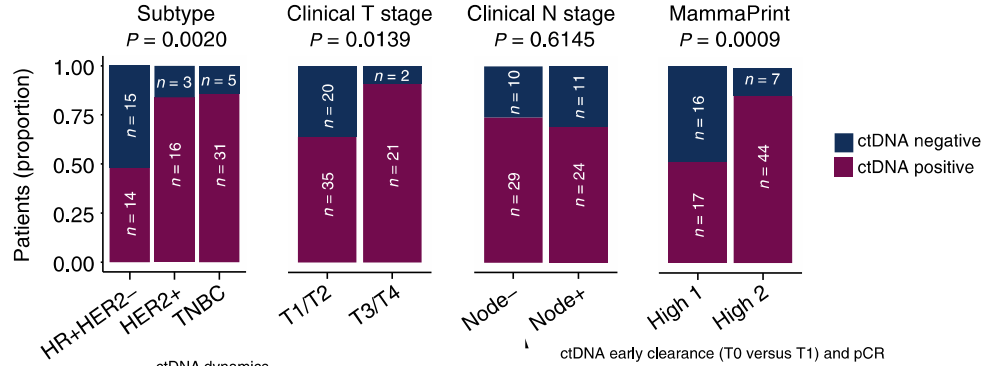
Bianchini et al Nat Rev Clini Oncol 2021

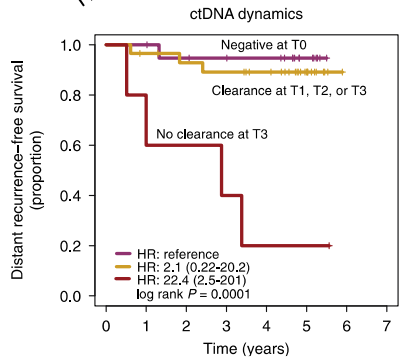
Ongoing research on biomarkers to guide “risk-adapted” strategies: MRD (liquid BIO)

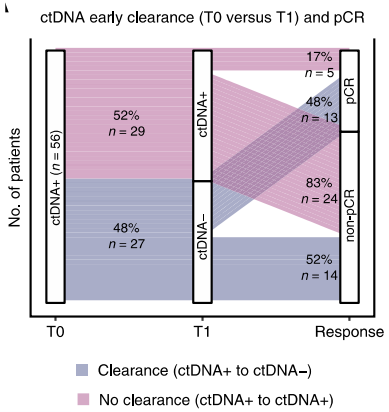
[I-SPY2 trial, N=84 high-risk eTNBC pts]

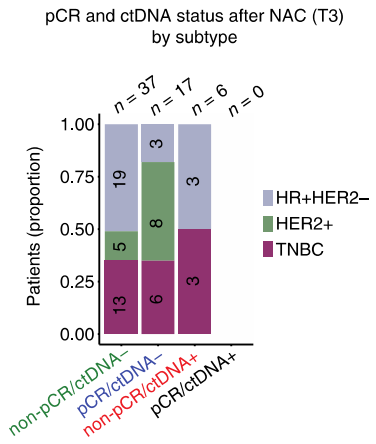


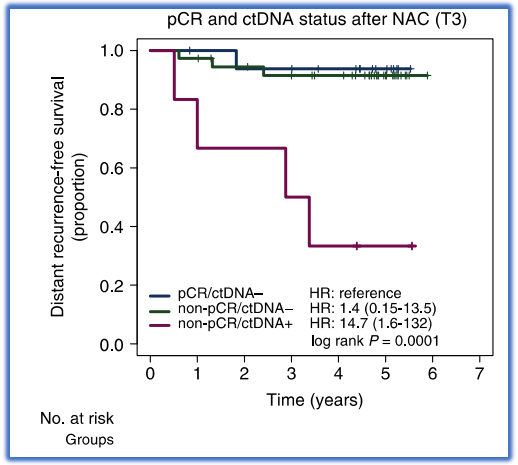
- Lack of ctDNA clearance predictor of poor response and metastatic recurrence vs clearance associated with improved survival even in pts who did not achieve pCR
- Personalized monitoring of ctDNA during NAC of high-risk eBC may aid in real-time assessment of treatment response and fine-tune pCR as a surrogate endpoint of survival (tool to escalate/de-escalate treatment?)





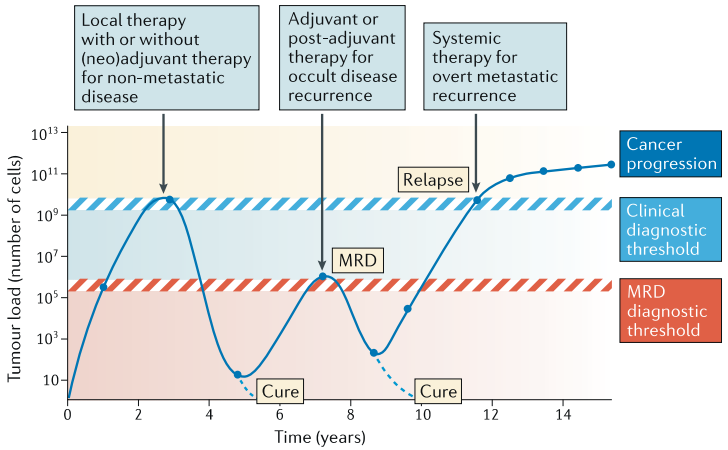






Magbanua et al Ann Oncol 2021

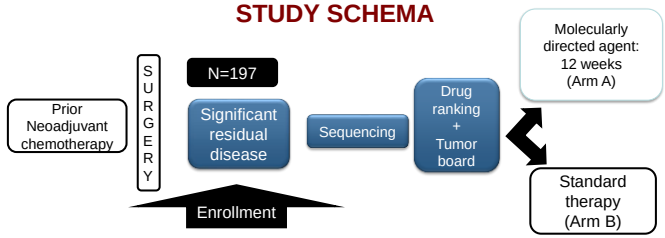
Ongoing research on biomarkers to guide “risk-adapted” strategies: MRD (liquid BIO)

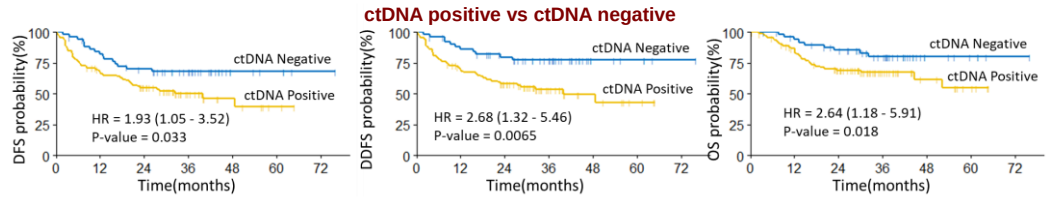


- ✓ **PERSEVERE trial:** ctDNA to guide therapy and add targeted agents to a standard backbone
- ✓ **ZEST trial:** Random. ph III evaluating eficacy and safety of niraparib in pts with HER2-BRCA-mut or TNBC with detectable ctDNA after definitive therapy

How to furher stratify the risk without pCR?

BRE12-158: post-NA random. ph II trial of personalized therapy vs TPC for pts with RD (TNBC)

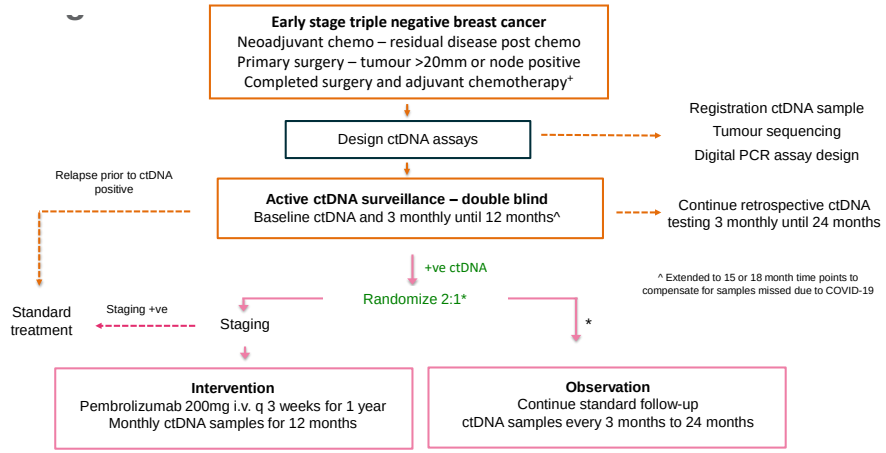




- ctDNA status remained a significant predictor of outcome with some pts demonstrating clearance with postNA therapy

ctDNA-guided adjuvant escalation trials?

cTRAK TN trial: utilising ctDNA mutation tracking to detect MRD and trigger intervention in pts with moderate/high risk early stage TNBC



- Proportion ctDNA positive @12mo 27.3% (7 pts relapsed without prior ctDNA detection)
  - High-risk 56.7% ctDNA + @12mo
  - Moderate risk 11.8% ctDNA+ @12mo
- 39.8% NACT only 28.6% adj only and 25.5% NACT & AdjCAPE
- 71.9% overt metastatic disease on staging @time of ctDNA detection
- 21.4% pts recurrence-free with ctDNA clearance after 6mo (OBS)
- No pts exhibited sustained ctDNA clearance 6mo after Pembro (5/9 pts treated)

We need to test ctDNA early, sensitive ctDNA assays (multiple variants), more frequent testing 0-6 mo (consider during postNA treatment) and reconsider highest-risk pts

Pantel et al NRCO 2019; Schneider et al JCO 2021 & PD9-10; Turner et al GS3-06 SABCS 2021; Pascual et al Ann Oncol 2022

Take Home Messages

- Efforts have beed done to optimize CT backbone for early TNBC: the combination of **anthracyclines and taxanes** is the preferred regimen, the inclusion of **platinums** in NACT regimens has been proposed while still controversial (pCR and EFS benefit vs toxicity balance), and the use of **capecitabine** in patients with RD after NACT is currently a standard of care
- The use of NA treatment allows for individualizarion of therapy according to treatment effect

- In patients with high-risk TNBC **NACT** (carbo/paclitaxel → AC/EC) **+ IO** (pembrolizumab) has demosntrated benefit in terms of pCR and EFS independently of PD-L1 status opening many questions regarding the optimization of the CT backbone, the integration with new drugs, the optimal duration of treatment, or the management of new toxicity profiles

- **PARP inhibitor** (olaparib) has to be considered in the adjuvant setting for 1 year in those patients with germline BRCA1/2 mutations and high-risk TNBC (if ≥pT2 or ≥pN1 disease after adjuvant CT, or if RD after preoperative CT). This new targeted approach is redefining the heredofamilial cancer unit protocols in the clinical practice, opens up new de-escalation oportunities in the early TNBC setting, and more importantly raises the interest on targeted therapies focused on DDR deficits

- We eagerly need to identify and validate **biomarkers** that led us to transform the general treatment algorithm into an individualized risk-based strategy for every patient diagnosed with early TNBC. **TILs**, GEPs, HRD markers, **RCB** measurement and characterization by multi-omics; multidimensional biomarkers of the TNBC dynamic ecosystem and detection of MRD through liquid biopsy are some of the potential candidates to meet this challenge

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