Nuove opzioni terapeutiche nel carcinoma mammario metastatico nel 2023

Tumori tripli negativi e BRCA mutati

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SEZIONE REGIONE LAZIO

Gemelli

Disclosures

Scientific advisory board, meeting, congresses, consulence:

Lilly,
Novartis,
Roche,
Pfizer,
Astra Zeneca
Dompè
Exact Science
Pierre Fabre
Epihonpharma

…

Ci si Insinua fra :

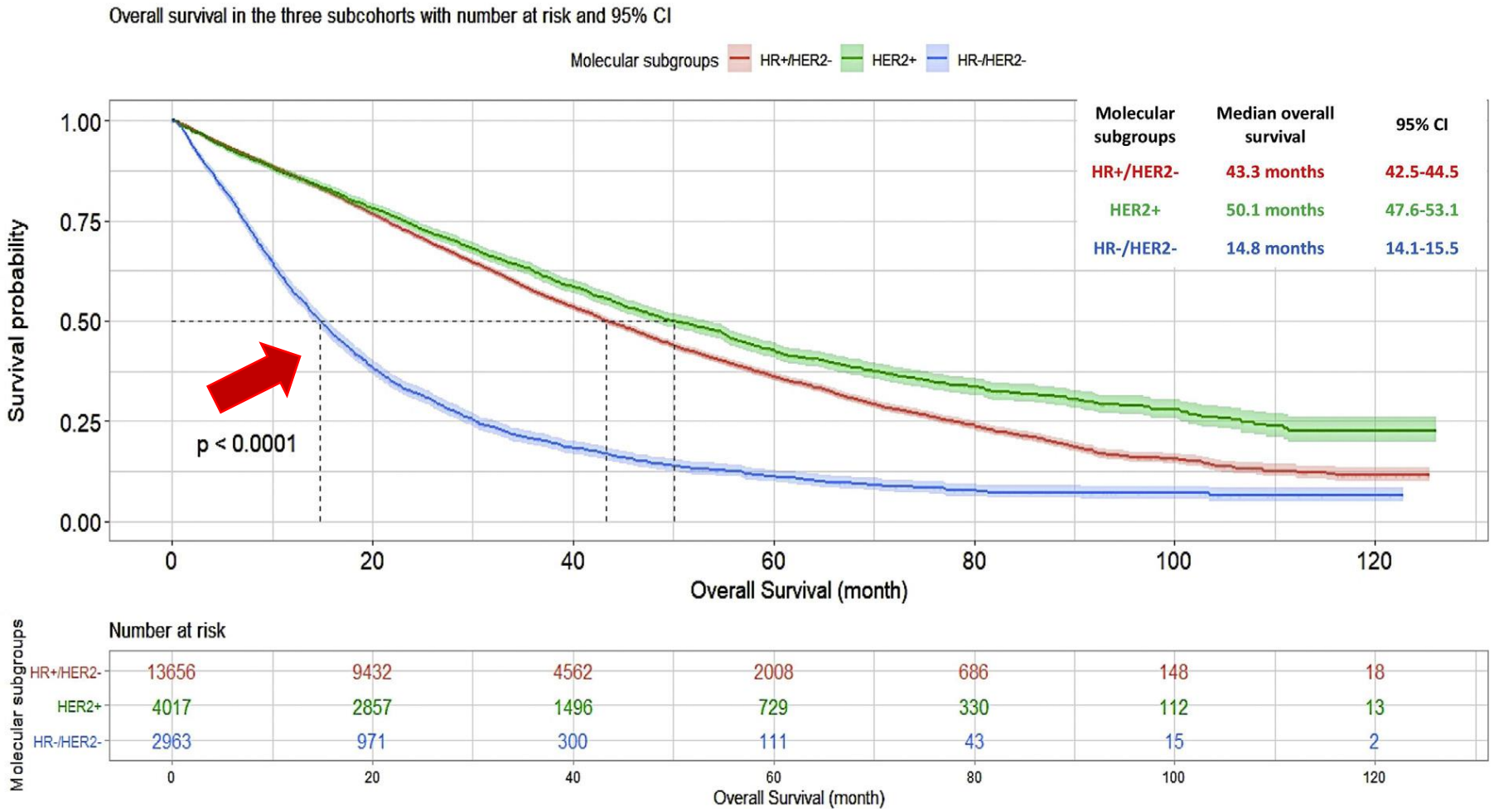
Immunoterapia, Chemioterapia and Antibody Drug Coniugate

&

Biomarcatori!!

TNBC Remains an Unmet Medical Need

ESME cohort (n=22,109 patients between 2008 and 2016)



Deluche E et al, Eur J Cancer 2020;129:60-70

Genoma

Tumor

Patient

TNBC Epidemiologia: Genomica e Fattori di Rischio

BRCA mutation

- 68% (range 42%-100%) *BRCA1* carriers develop TNBC compared to 24% in non-carriers and LN involvement more common in BRCA carriers[2,3]

Family history

- First-degree relative: 1.56 to 1.73-fold
- One affected relative: 1.72-fold
- Two affected relatives: 2.52-fold[4]

✓

Premenopausal state

- Mostly occurs in young, premenopausal women under 40 years of age[5]

Age

- TNBC has higher relative incidence in younger age groups (20-39 years old)[1,6]

Race

- Black women have about a 2-fold higher mortality incidence compared with NHW women, resulting in a disproportionately higher (>65%) risk of death[7]

Obesity

- 20% higher risk of developing TNBC[8]
- Premenopausal women with BMI ≥30 kg/m^2 have a 42% higher risk of developing TNBC compared with nonobese women[8]

Oral Contraceptives

- Use ≥1 year was associated with a 2.5-fold increase in risk of TNBC for women under the age of 45[9]

Nonmodifiable risk factors | **Modifiable risk factors**

Demographic features and risk factors for TNBC
Adapted from Zohora F and Rabbi M. *Int J Res Med Sci*. 2018[11]

Although early age at menarche, nulliparity and late age at first completed pregnancy are established risk factors for all subtypes of breast cancer, their specific association with TNBC is not consistent[10]

TNBC is associated with Black race, deprivation status, younger age at diagnosis, more advanced disease stage, higher grade, high mitotic indices, family history of breast cancer and *BRCA1* mutations[1]

BMI, body mass index; *BRCA*, breast cancer gene; NHW, non-Hispanic white; TNBC, triple-negative breast cancer.
1. Boyle P. *Ann Oncol*. 2012;23(suppl 6):vi7-12; 2. De Talhouet S, et al. *Sci Rep*. 2020;10(1):19248; 3. Peshkin BN, et al. *Breast Dis*. 2010;32(1-2):25-33; 4. Brewer HR, et al. *Breast Cancer Res Treat*. 2017;165(1):193-200; 5. Yin L, et al. *Breast Cancer Res*. 2020;22(1):61; 6. Kolečková M, et al. Oncol Lett. 2017;13(6):4201-4207; 7. Prakash O, et al. *Front Public Health*. 2020;8:576964; 8. Sun H, et al. *Mol Clin Oncol*. 2017;7(6):935-942; 9. Dolle JM, et al. *Cancer Epidemiol Biomarkers Prev*. 2009;18(4):1157-1166; 10. Ma H, et al. *Breast Cancer Res*. 2017;19(1):6; 11. Zohora F, Rabbi M. *Int J Res Med Sci*. 2018;6(8):2554-2561.

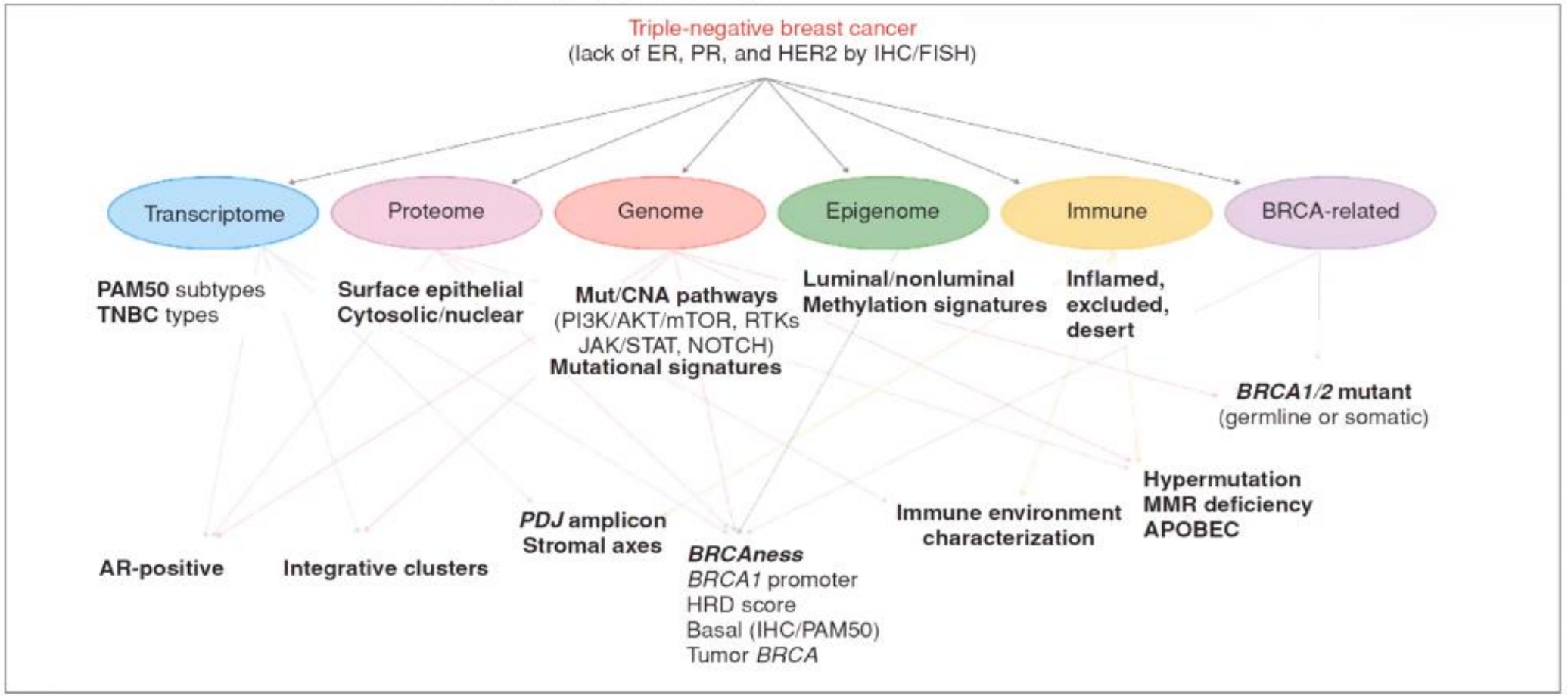
Come Guardare oggi un TN ?

Published OnlineFirst January 24, 2019; DOI: 10.1158/2159-8290.CD-18-1177

REVIEW

Insights into Molecular Classifications of Triple-Negative Breast Cancer: Improving Patient Selection for Treatment

Ana C. Garrido-Castro[1,2], Nancy U. Lin[1,2], and Kornelia Polyak[1,2]



Quakli Targets?

ER

PGR

HER2 (0; 1+-2+SISH/FISH NA)

PDL1

TROP2

IHC

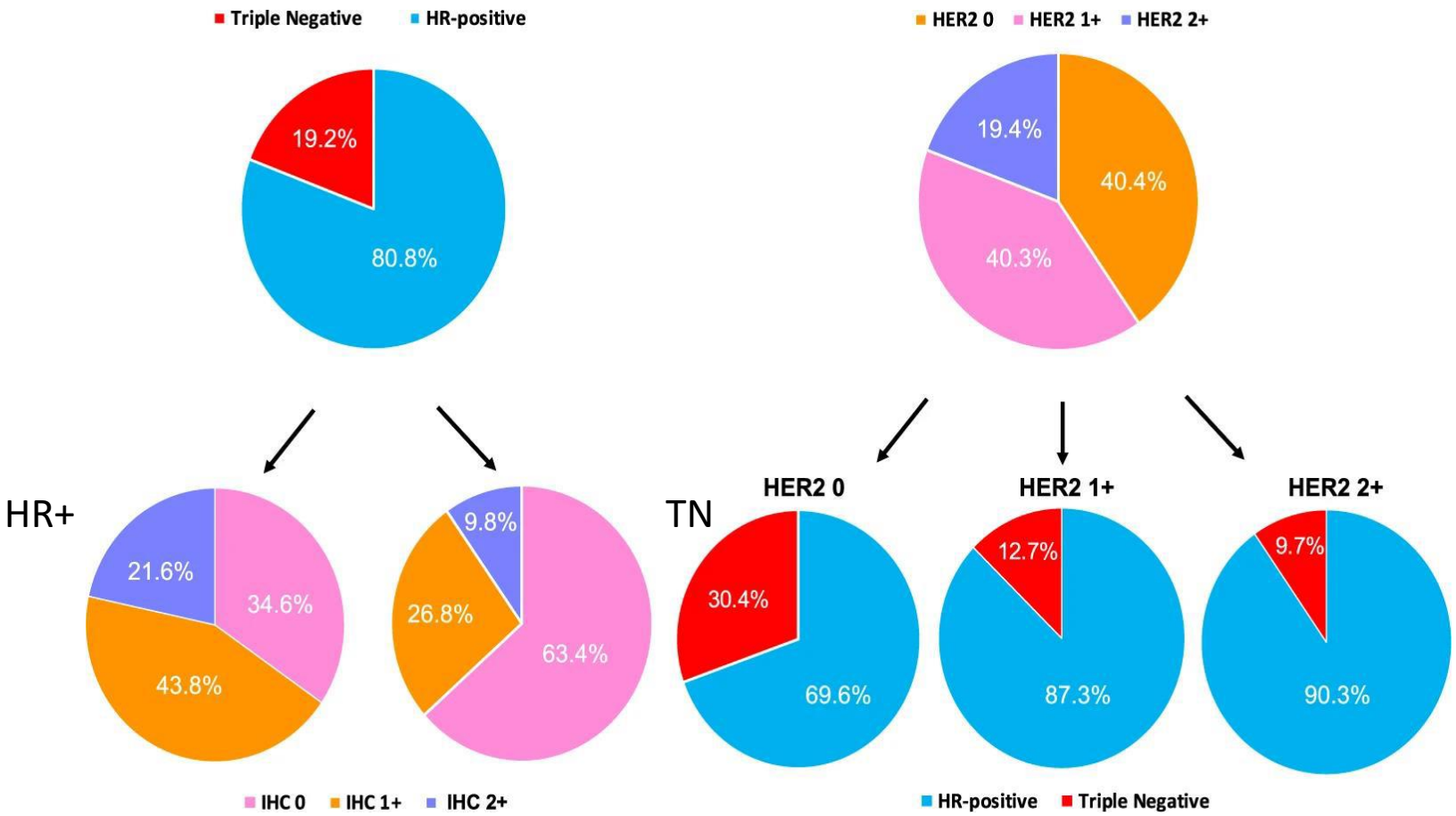
BRCA

GENOMIC

TILs

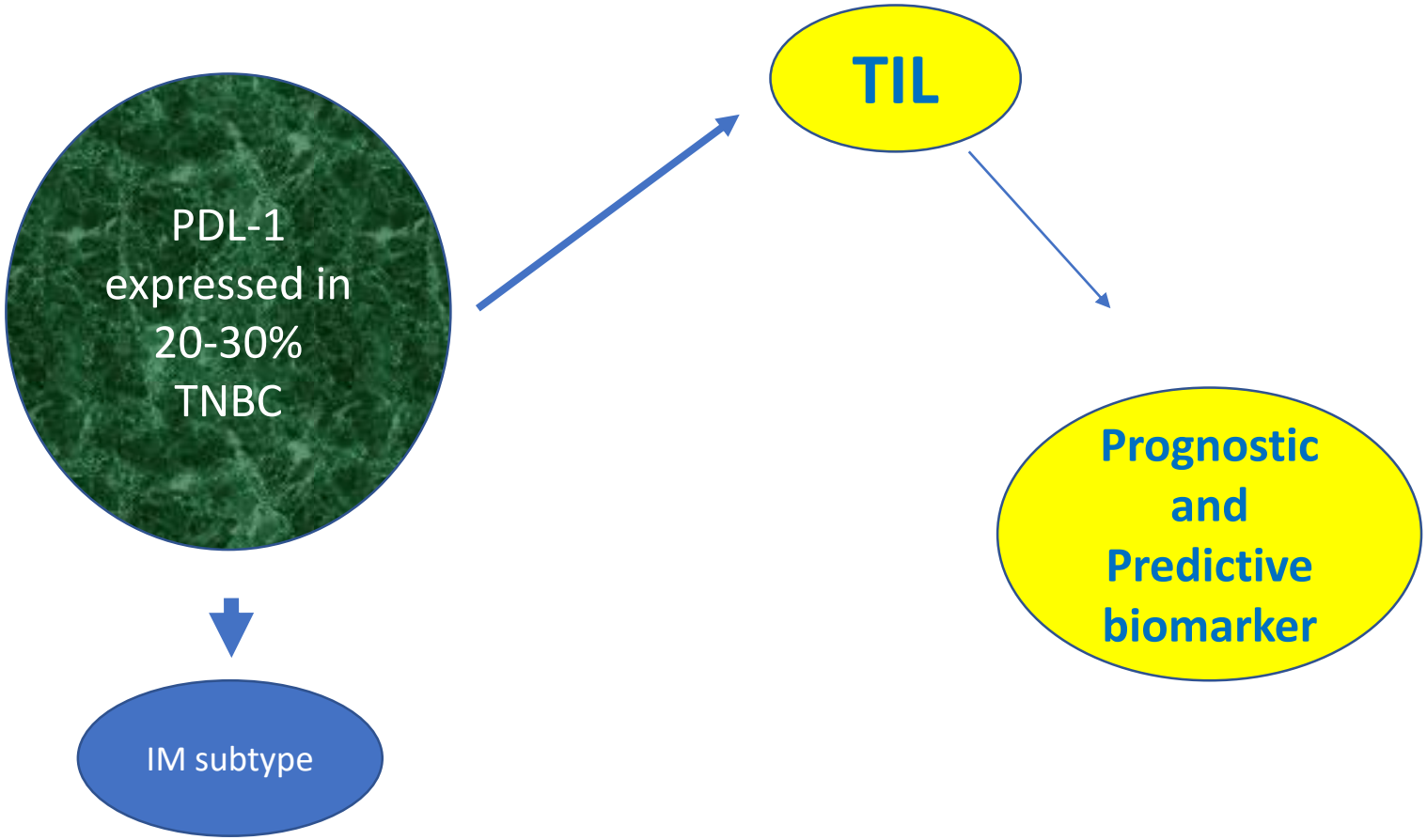
stroma-morphology

RE, HER2-low e la distribuzione negli HER2-



Schettini F, et al. NPJ Breast Cancer 2021

PDL-1, TIL & TNBC



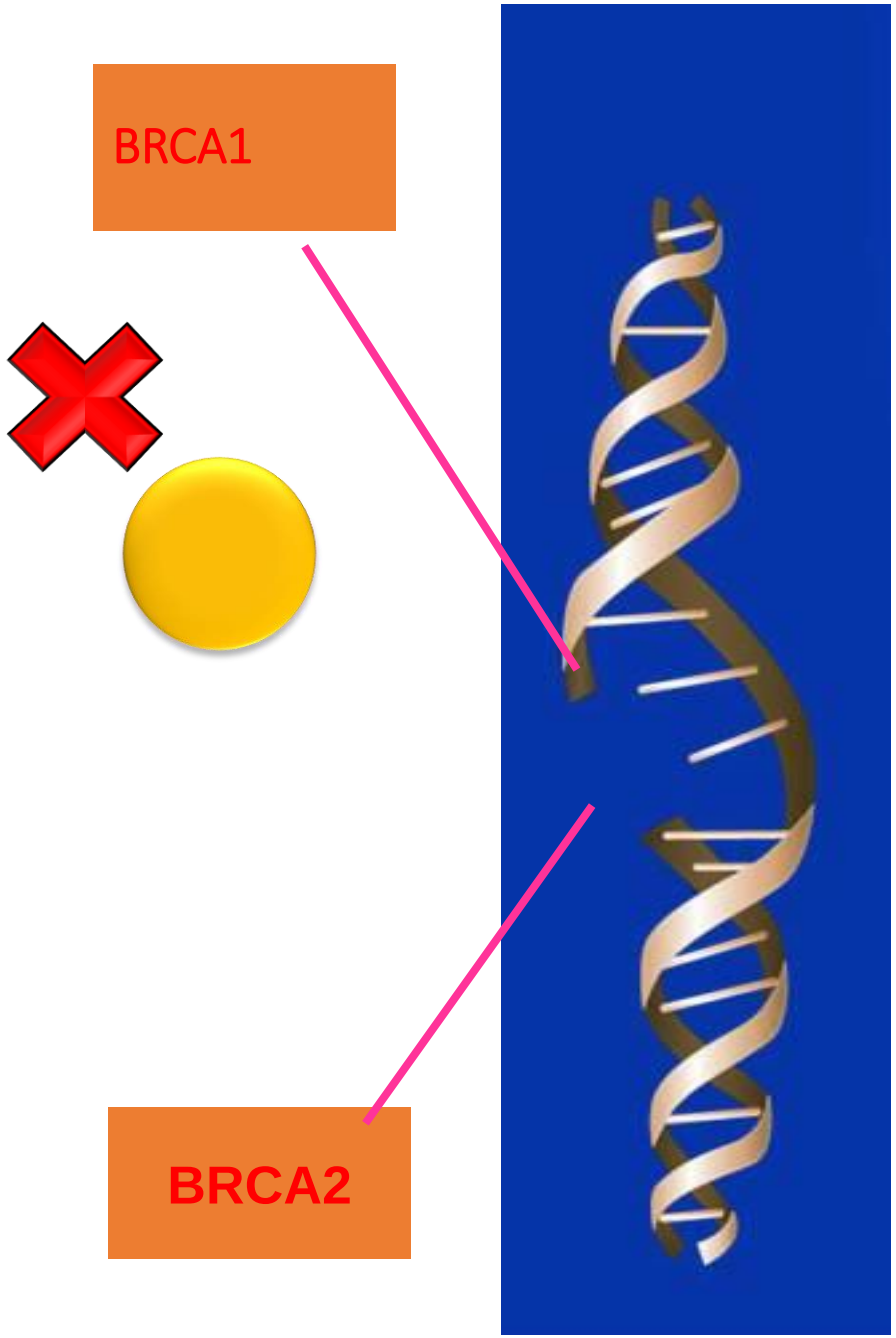
PERCHE' LA MUTAZIONE BRCA AUMENTA IL RISCHIO DI AMMALARE?

- **BRCA1 : Cromosoma 17q21**
- **BRCA2 : Cromosoma 13q12-13**

- **Responsabili dei meccanismi di riparazione del DNA**

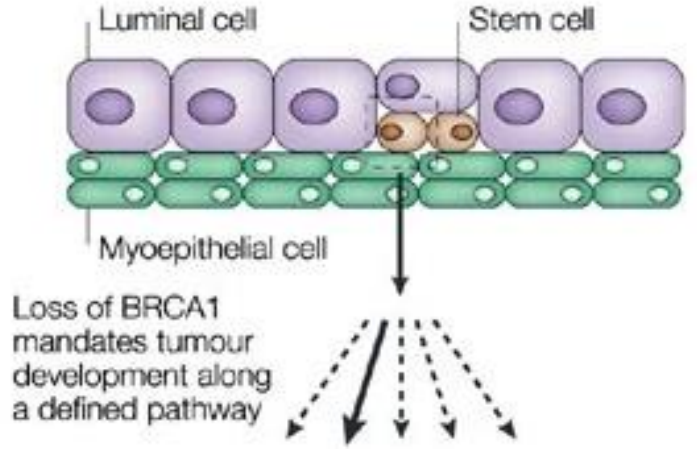
- **Geni onco- soppressori la cui mutazione è associata a maggior rischio di sviluppare cancro della mammella e dell'ovaio**

- **La mutazione di BRCA1 è responsabile di più della metà dei tumori ereditari della mammella**



Targeting BRCAness

- **Germline or somatic BRCA1/2mt in 20% of TNBC in TCGA**
- **BRCAness = similarities in sporadic BC to germline BRCA-associated**
- **Underlying molecular aberration = ineffective homologous recombination repair of DNA double strand breaks**
- **Implications for treatment (DNA crosslinking agents, PARP inhibitors)**
- **How to identify and is it actionable?**



***BRCA1* phenotype**
Basal
ER-negative
EGFR expression
Lymphocytic infiltration
c-MYC amplification
TP53 mutations
Loss of RAD51-focus formation
Extreme genomic instability
Sensitivity to DNA-crosslinking agents

Turner N et al, Nat Rev Cancer 2004

Come si Trasla nella pratica clinica?

Triple Negative……ER- PGR- HER2-

HER2
Classical and Actual Definition
HER0, 1+, 2+ FISH/SISH NA

……Looking for the Target !

PDL1

+ / -

BRCA

m / wt

Scenario 1

ER- / PGR-/ HER2 0/1+/2+ SISH NA

PDL-1 + BRCAm

Scenario 2

ER- / PGR-/ HER2 0/1+/2+ SISH NA

PDL-1- BRCAm

Scenario 3

ER- / PGR-/ HER2 0/1+/2+ SISH NA

PDL-1+ BRCAwt

Scenario 4

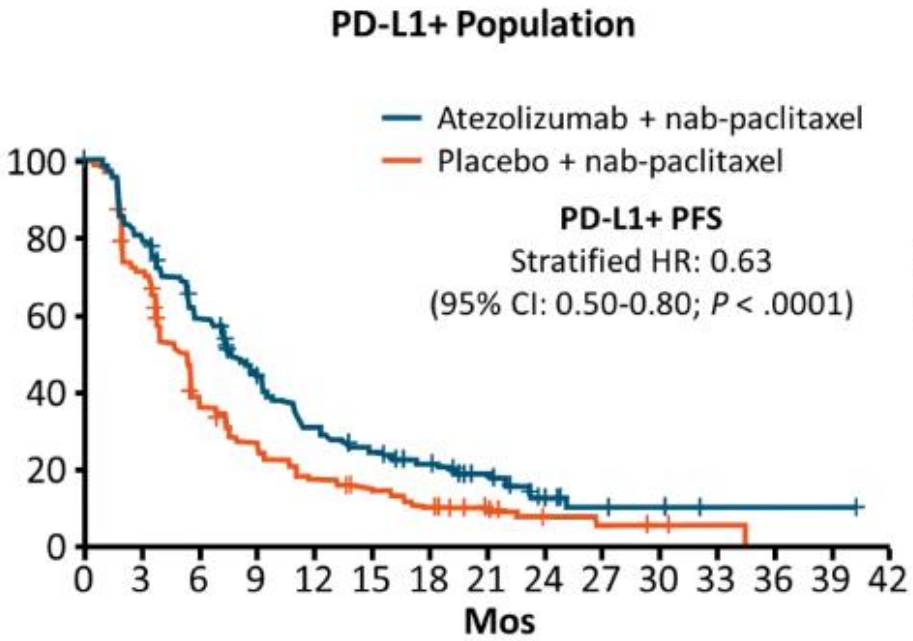
ER- / PGR-/ HER2 0/1+/2+ SISH NA

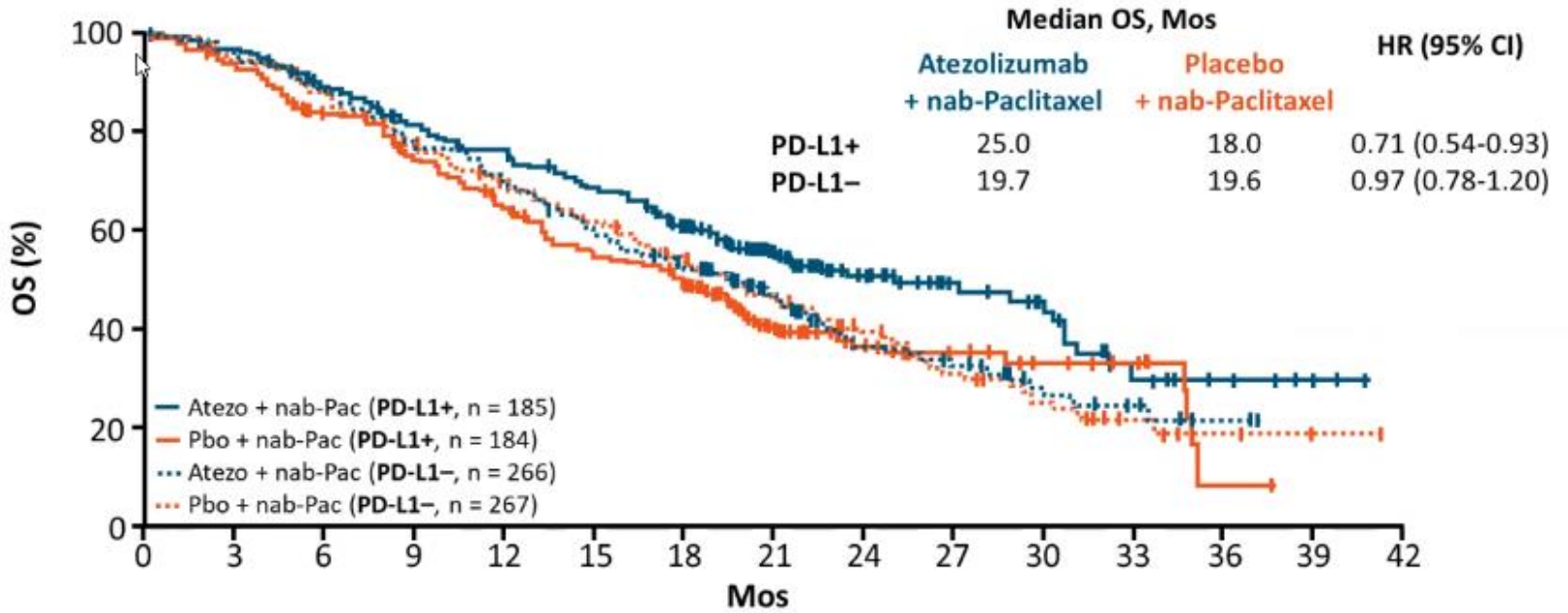
PDL-1- BRCAwt

Quale cambiamento?

IMpassion 130:
Improved PFS and OS in PD-L1+* mTNBC

1 st Line TN



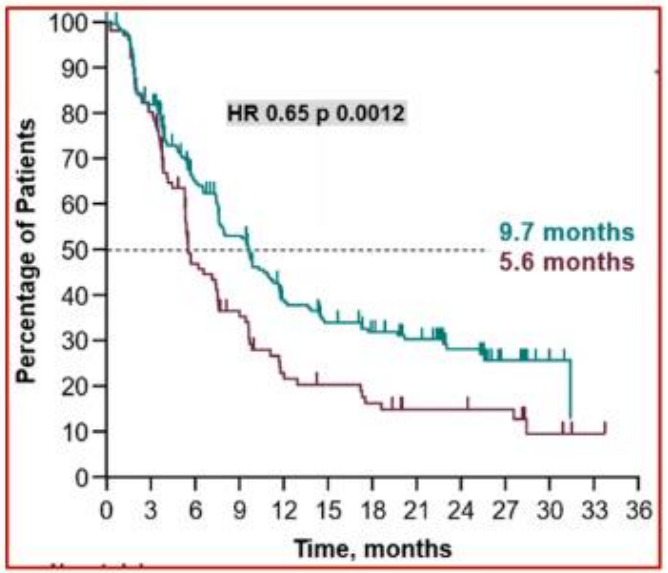


PD-L1+ defined as ≥ 1% IC positive using VENTANA SP142 assay.

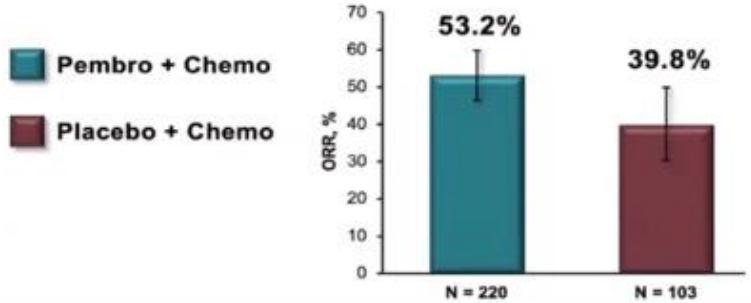
Schmid. NEJM 2018.; Emens. ESMO 2020.; Cortes J. Lancet 2021.

KEYNOTE 355:
Improved PFS and DoR in PD-L1+* mTNBC

PD-L1 CPS ≥10



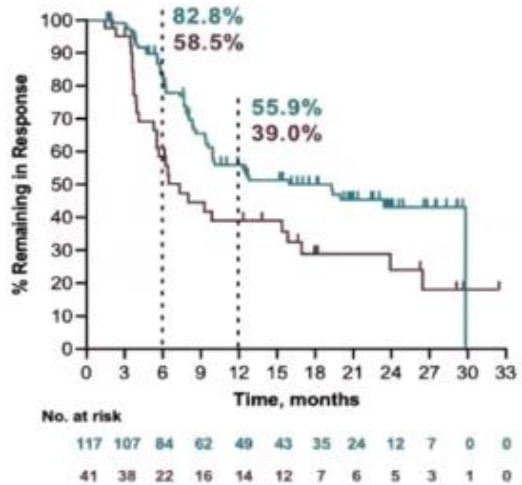
PD-L1 CPS ≥10



PD-L1 CPS ≥10	Pembro + Chemo (N = 220)	Placebo + Chemo (N = 103)
ORR, % (95% CI)	53.2 (46.4–59.9)	39.8 (30.3–49.9)
DCR,[a] % (95% CI)	65.0 (58.3–71.3)	54.4 (44.3–64.2)

PD-L1 CPS ≥10

Duration of response	Median, mo (range)
Pembro + Chemo	19.3 (1.6+ to 29.8)
Placebo + Chemo	7.3 (1.5 to 32.5+)



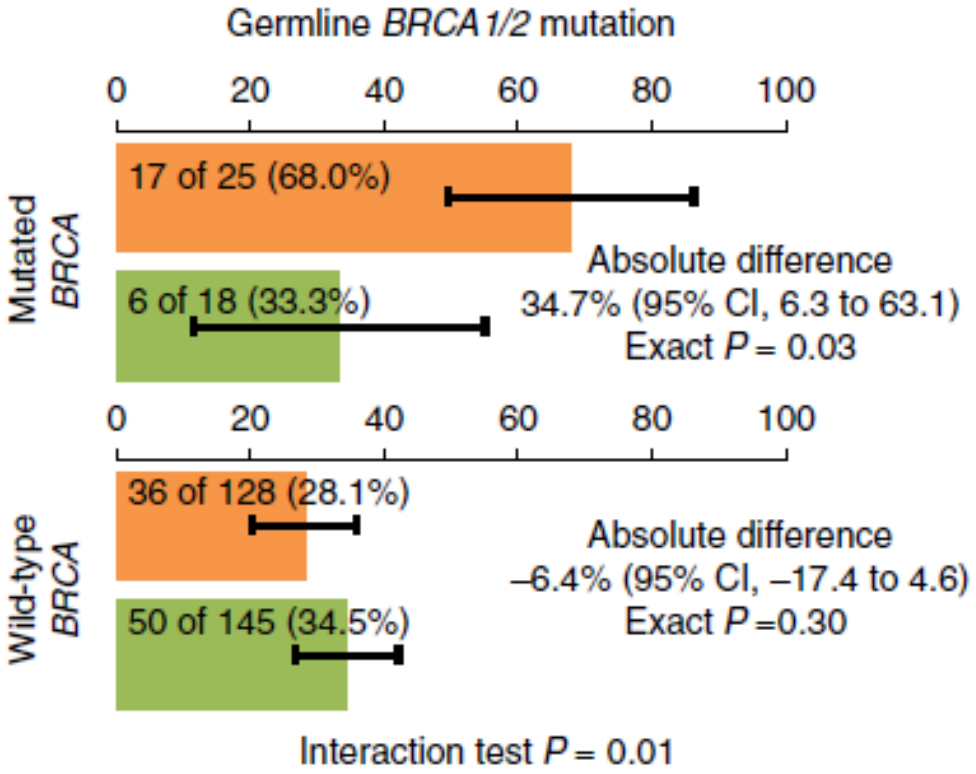
*PD-L1+ defined as CPS ≥ 10 using DAKO 22C3 assay.
Cortes J. Lancet 2021.

I LINEA CarboplatinO in TNBC

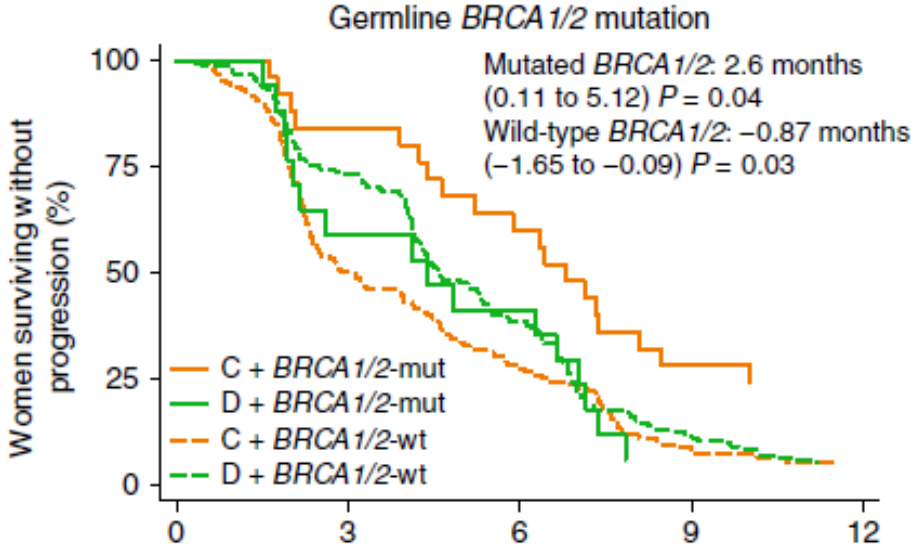
TNT TriaL

Results in patients with germline BRCA pathogenic variants

Objective Response Rate



Progression-Free Survival



n at risk (events)								
C + *BRCA1/2*-wt	128 (64)	64 (29)	35 (24)	11 (5)	6
C + *BRCA1/2*-mut	25 (4)	21 (6)	15 (8)	7 (1)	6
D + *BRCA1/2*-wt	145 (39)	106 (50)	56 (39)	17 (10)	7
D + *BRCA1/2*-mut	18 (7)	10 (3)	7 (7)	1 (0)	1

Tutt A et al, Nat Med 2018;24(5):628-37

COME LAVORA UN FARMACO PARP-INIBITORE

Mutazioni BRCA, fattori esterni , chemioterapici ecc. producono un danno in una delle due eliche del DNA

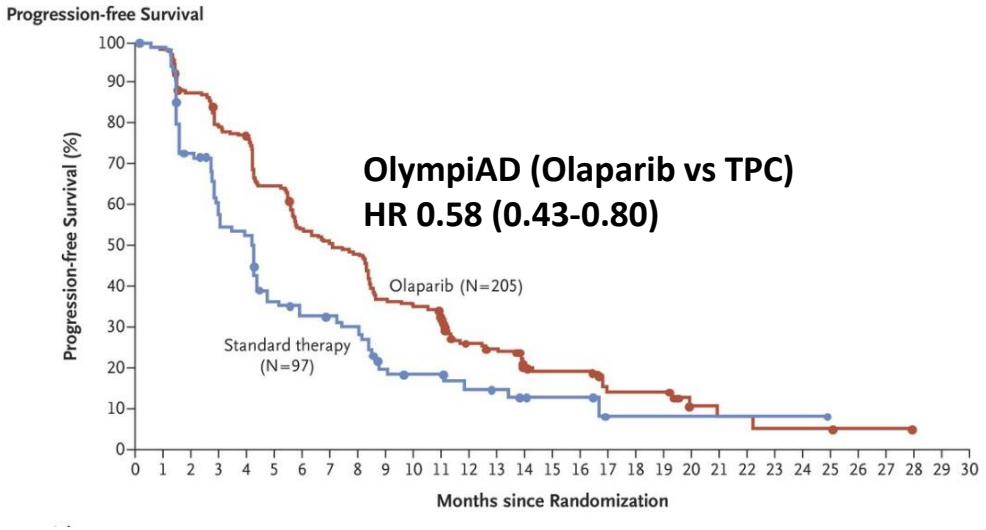
PARP ripara il danno alla singola elica di DNA

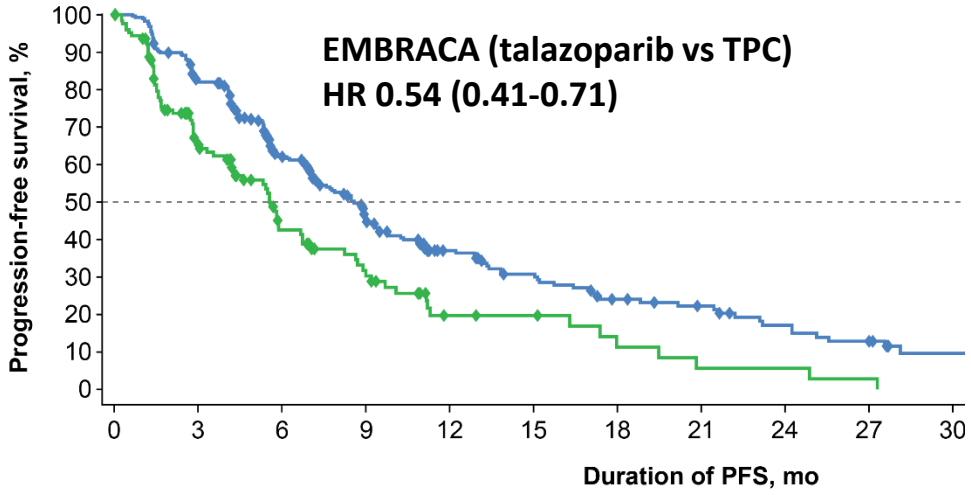
L'inibizione di PARP 1 impedisce l'azione di PARP e di altri enzimi che riparano il danno alla singola elica di DNA

Replicazione cellulare (fase S)

Dopo la replicazione l' accumulo di alterazione danneggia il DNA definitivamente

PARP Inhibition in Germline + Somatic BRCA1/2, Germline PALB2 Mutations





- PARPi better, more tolerable than 2nd line chemo
- Neither has an OS advantage
- Also active in germline PALB2, somatic BRCA1/2 mt

Used in 1st-2nd line therapy regardless of clinical subtype (enriched – 10% of TNBC)

Robson et al, NEJM 2017; Litton et al, NEJM 2018; Tung N et al, JCO 2021

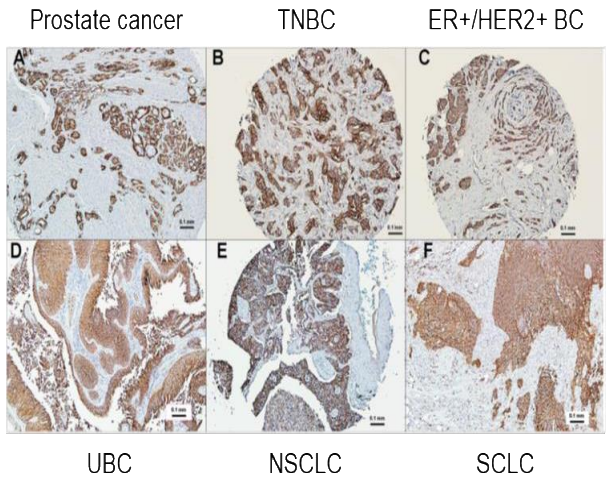
E TROP2?

TROP2 as a Therapeutic Target for Breast Cancer

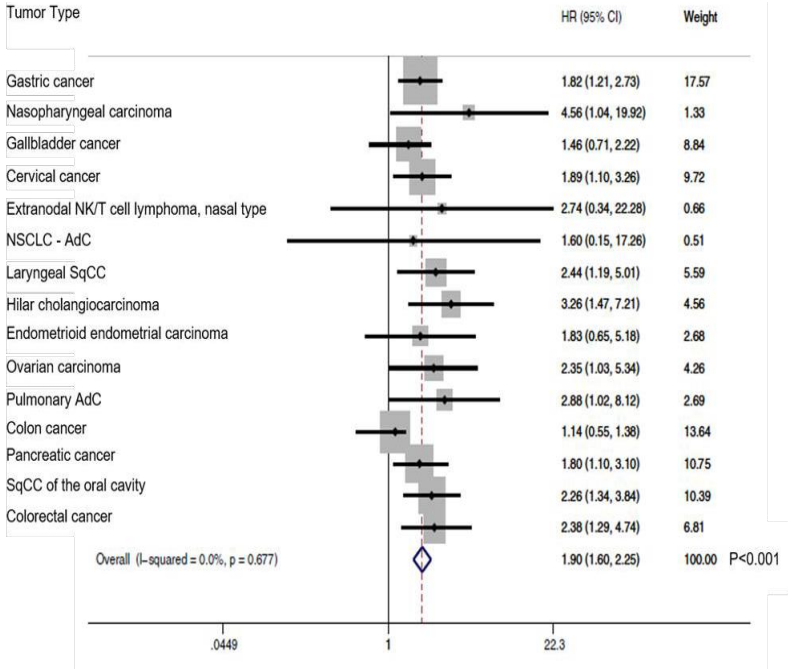
TROP2 is upregulated in many solid tumors

In a meta-analysis, TROP2 overexpression was significantly associated with poor overall and disease-free survival across multiple tumor types

TROP2 staining of solid tumors by IHC



Correlation between TROP2 expression and OS



Goldenberg DM, et al. *Oncotarget*. 2018;9(48):28989-29006. Zeng P, et al. *Sci Rep*. 2016;6:33658.

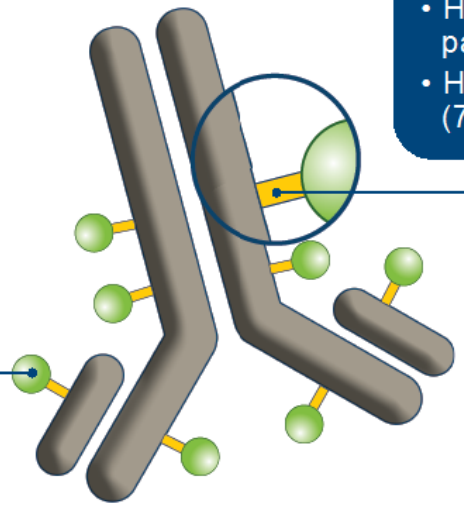
From Promising to standard of care in TNBC

Epithelial Antigens: Sacituzumab Govitecan

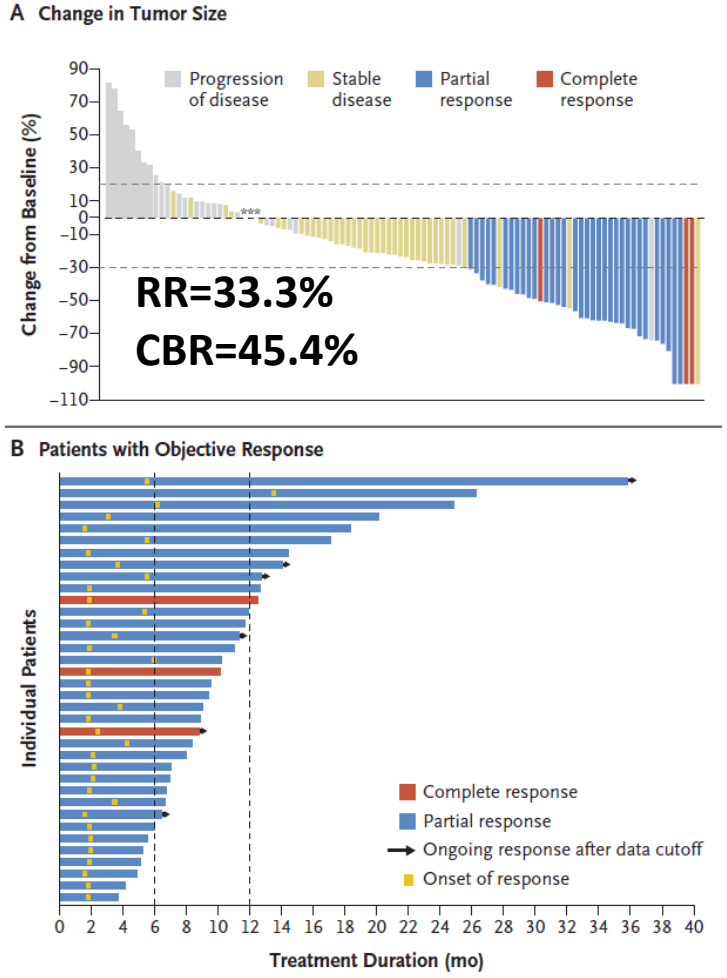
Humanized anti-Trop-2 antibody
- Targets Trop-2, an epithelial antigen expressed on many solid cancers, including mTNBC

Linker for SN-38
- Hydrolysable linker for payload release
- High drug-to-antibody ratio (7.5:1)

SN-38 payload
- SN-38 more potent than parent compound, irinotecan
- ADC delivers up to 136-fold more SN-38 than irinotecan *in vivo*

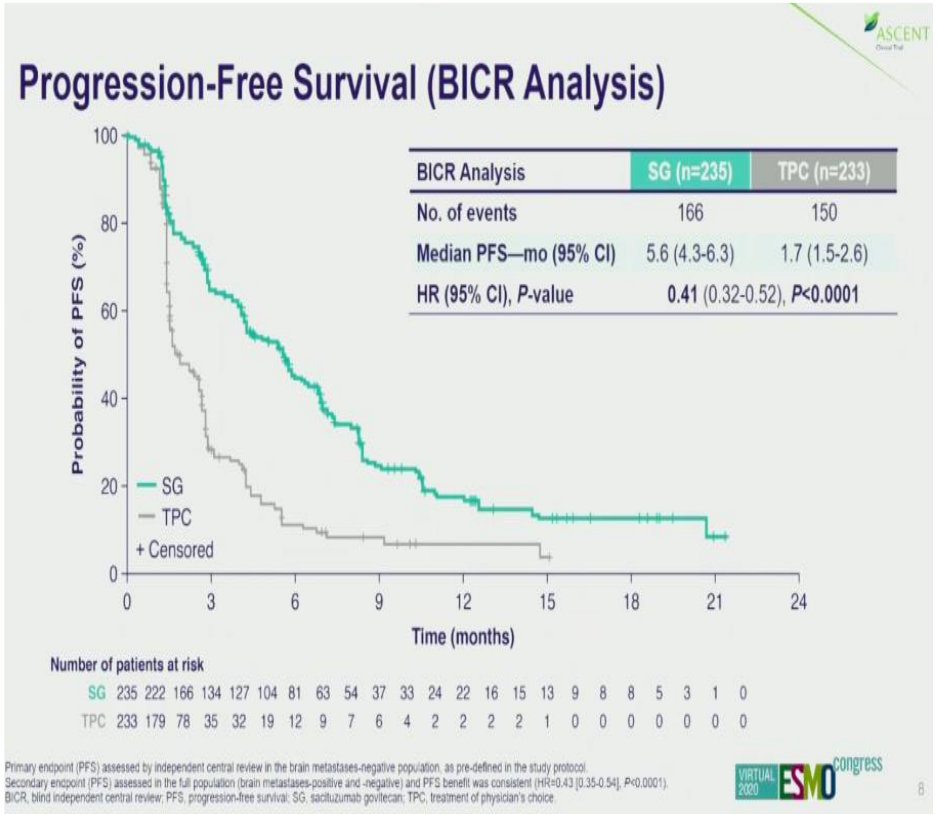


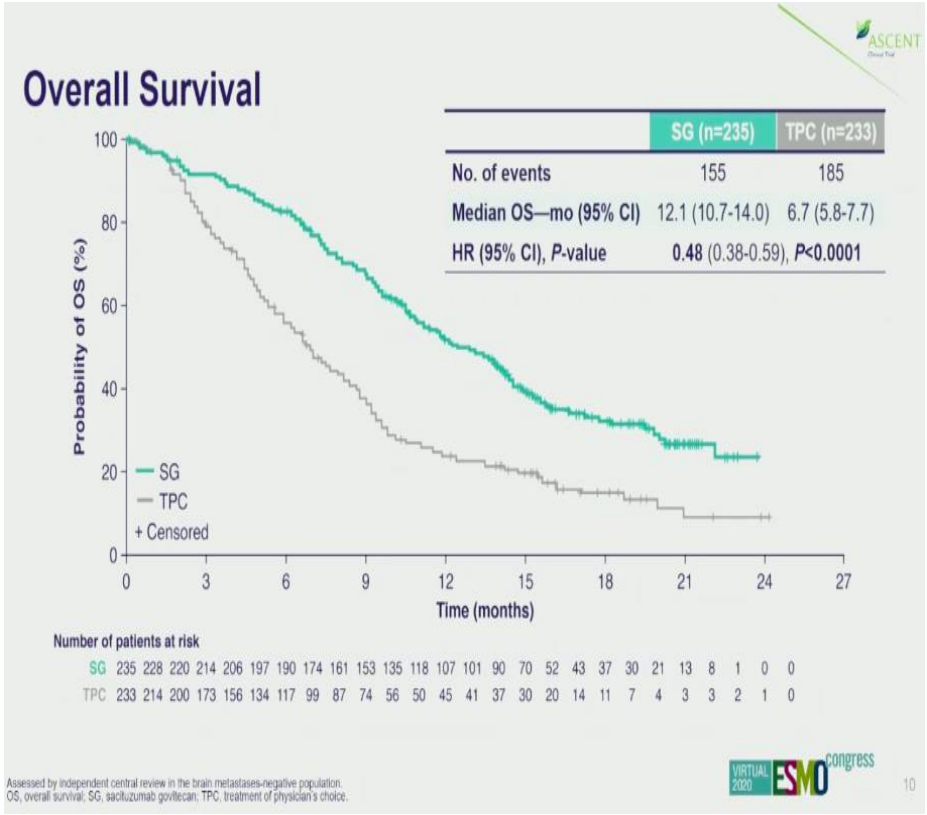
Granted accelerated approval by FDA !



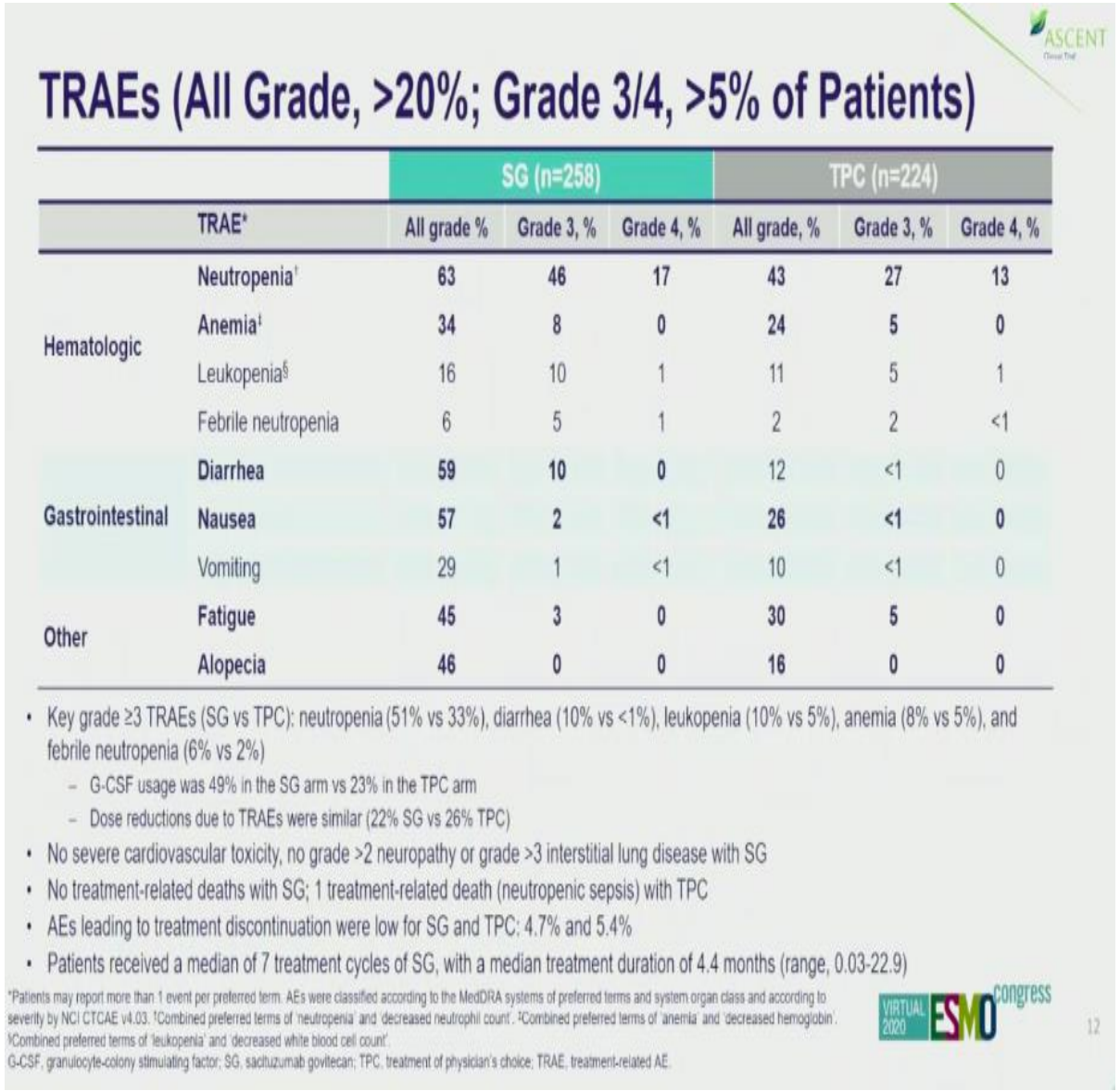
Bardia A et al, J Clin Oncol 2017;35(19):2141-8. Bardia A et al, N Engl J Med 2019;380(8):741-51

Sacituzumab Govitecan in Metastatic TNBC





Sacituzumab Govitecan in Metastatic TNBC



OlympiA: Trial schema

- 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

Neoadjuvant Chemotherapy (≥ 6 cycles) → **Surgery** → **+/- Radiotherapy**

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

Surgery → **Adjuvant Chemotherapy** (≥ 6 cycles) → **+/- 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

Patients Characteristics

OlympiA: Patient characteristics

	Olaparib (N = 921)	Placebo (N = 915)
Age, years, median (interquartile range)	**42** (36–49)	**43** (36–50)
BRCA gene affected in germline		
BRCA1	657 (**71.3%**)	670 (**73.2%**)
BRCA2	261 (**28.3%**)	239 (**26.1%**)
BRCA1 and *BRCA2*	2 (0.2%)	5 (0.5%)
BRCA testing available		
Local and central BRCA result*	550 (**59.7%**)	540 (**59.0%**)
Local testing only	130 (14.1%)	141 (15.4%)
Central Myriad testing only	240 (26.0%)	234 (25.6%)
No local or central Myriad testing available	1 (0.1%)	0 (0.0%)
Primary breast cancer surgery		
Mastectomy	698 (**75.8%**)	673 (**73.6%**)
Conservative surgery only	223 (24.2%)	240 (26.2%)
Missing	0 (0.0%)	2 (0.2%)

*Local/Central discordant results: Olaparib 12 (2.2%), Placebo 10 (1.9%), Total 22 (2.0%)

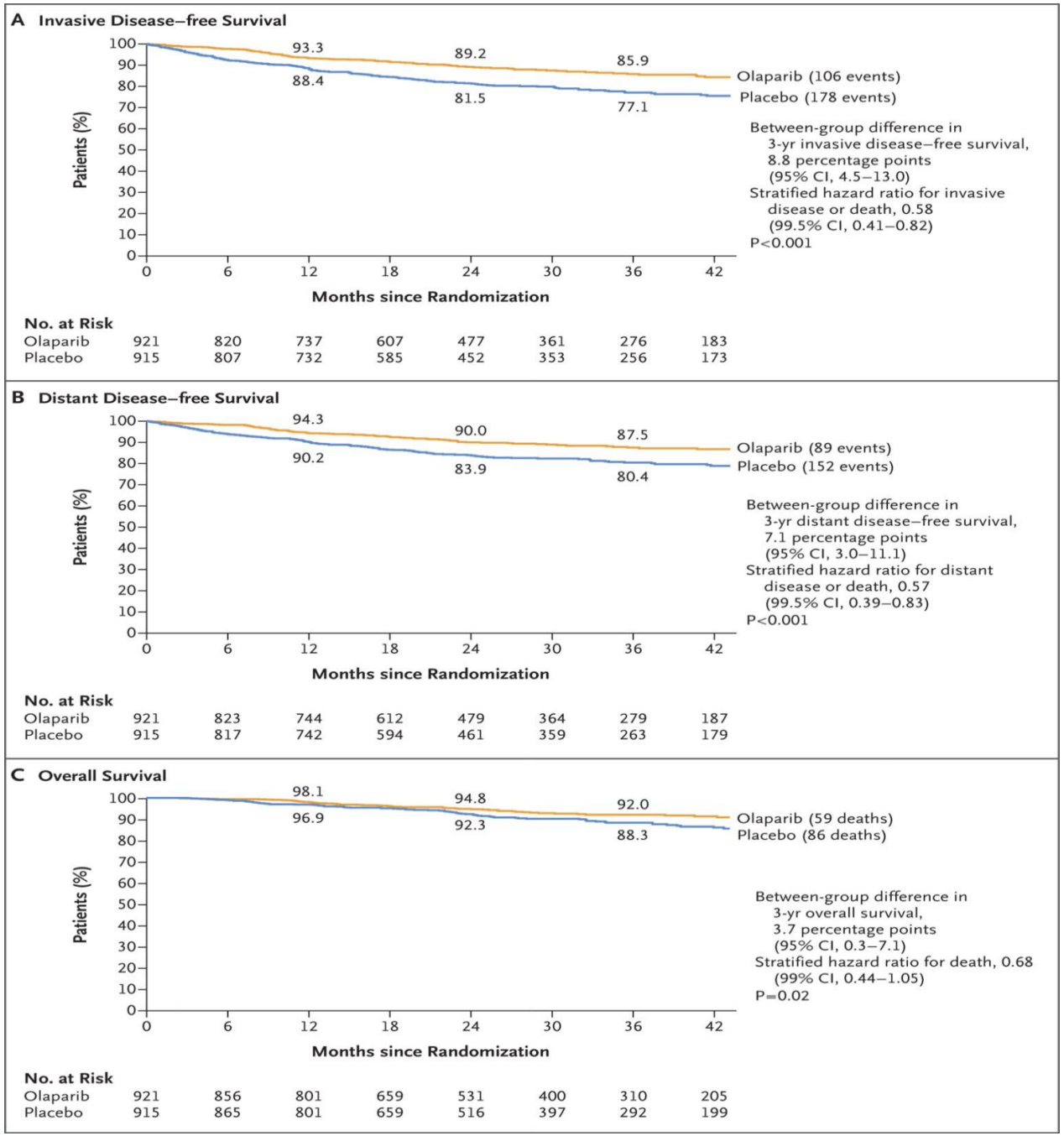
Prese

OlympiA: Patient characteristics

	Olaparib (N = 921)	Placebo (N = 915)
Hormone receptor status*		
Hormone receptor ≥ 1% / HER2-†	168 (**18.2%**)	157 (**17.2%**)
Triple Negative Breast Cancer‡	751 (**81.5%**)	758 (**82.8%**)
Menopausal status (female only)		
Premenopausal	572/919 (62.2%)	553/911 (60.7%)
Postmenopausal	347/919 (37.8%)	358/911 (39.3%)
Prior chemotherapy		
Adjuvant (ACT)	461 (**50.1%**)	455 (**49.7%**)
Neoadjuvant (NACT)	460 (**49.9%**)	460 (**50.3%**)
Anthracycline and taxane regimen	871 (**94.6%**)	849 (**92.8%**)
Neo(adjuvant) platinum-based therapy	247 (**26.8%**)	239 (**26.1%**)
Concurrent endocrine therapy (HR–positive only)	146/168 (86.9%)	142/157 (90.4%)

*Defined by local test results
†Following a protocol amended in 2015, the first patient with hormone receptor–positive disease was enrolled in December 2015
‡Two patients are excluded from the summary of the triple–negative breast cancer subset because they do not have confirmed HER2–negative status

NG



OlympiA: Type of first IDFS event

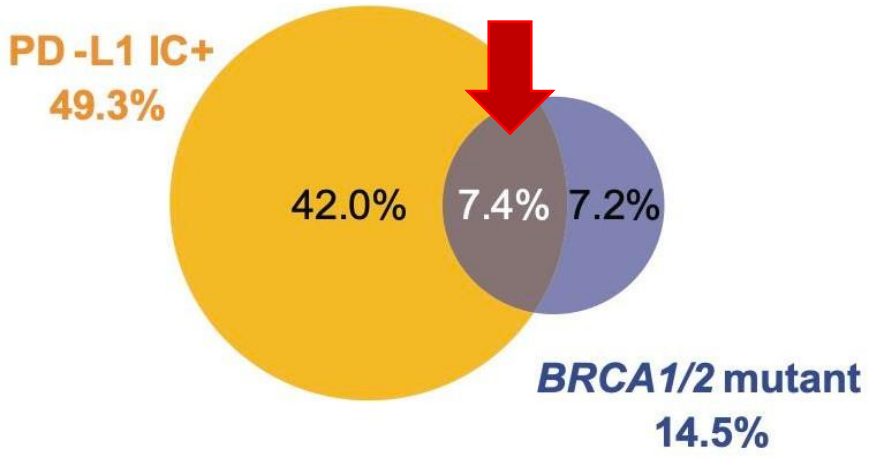
	Olaparib (N = 921)	Placebo (N = 915)
Number of patients with a first IDFS event	106 (11.5%)	178 (19.5%)
Distant recurrence	72 (7.8%)	120 (13.1%)
Distant CNS Recurrence	22 (2.4%)	36 (3.9%)
Distant excluding CNS Recurrence	50 (5.4%)	84 (9.2%)
Regional (Ipsilateral) Recurrence	6 (0.7%)	14 (1.5%)
Local (Ipsilateral) Recurrence	7 (0.8%)	11 (1.2%)
Contralateral invasive breast cancer	8 (0.9%)	12 (1.3%)
Second primary non-breast malignancies	11 (1.2%)	21 (2.3%)
Ovarian	1 (0.1%)	4 (0.4%)
Peritoneal	0 (0.0%)	0 (0.0%)
Fallopian tube	1 (0.1%)	4 (0.4%)
Other	9 (1.0%)	13 (1.4%)
Deaths without a prior IDFS event*	2 (0.2%)	0 (0.0%)

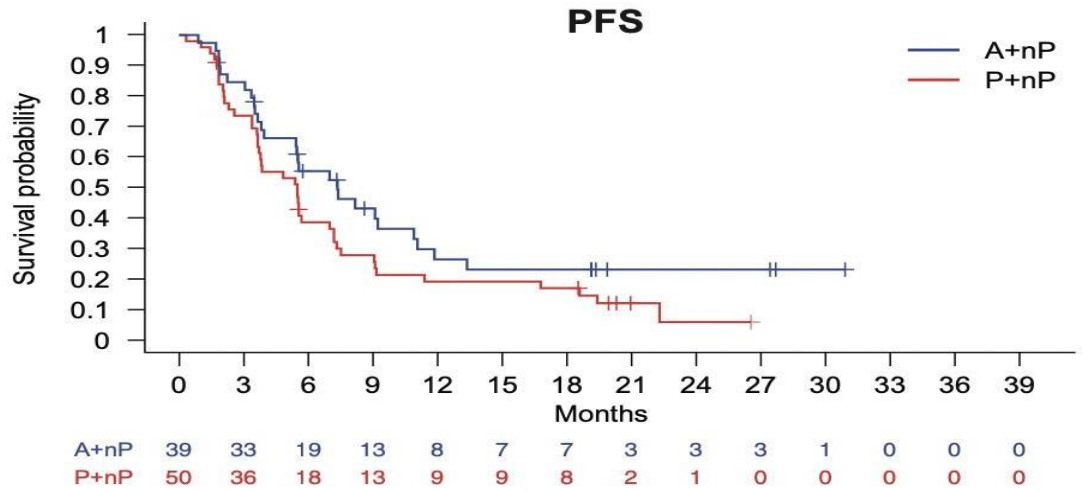
Tutt et al, NEJM 2021

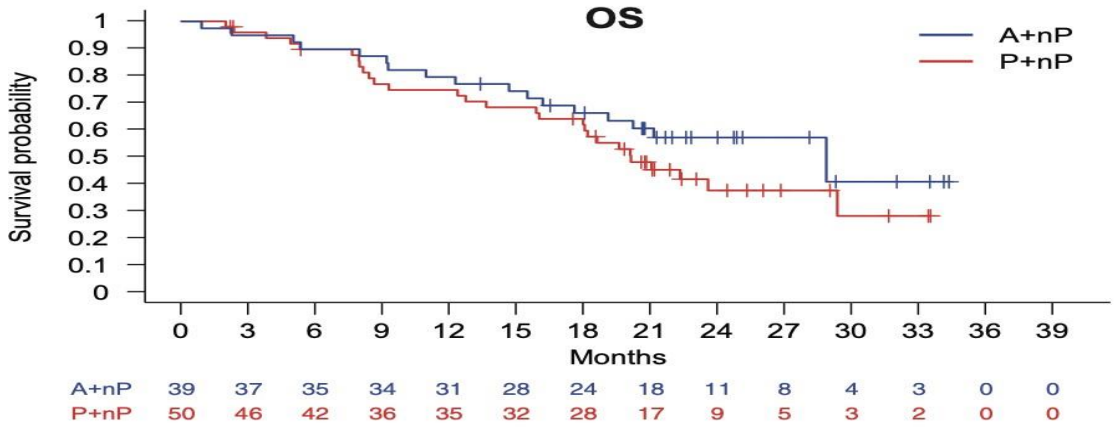
Cosa fare?

(alla luce dei nuovi biomarcatori)

Quando si incontrano 2 biomarcatori in contemporanea





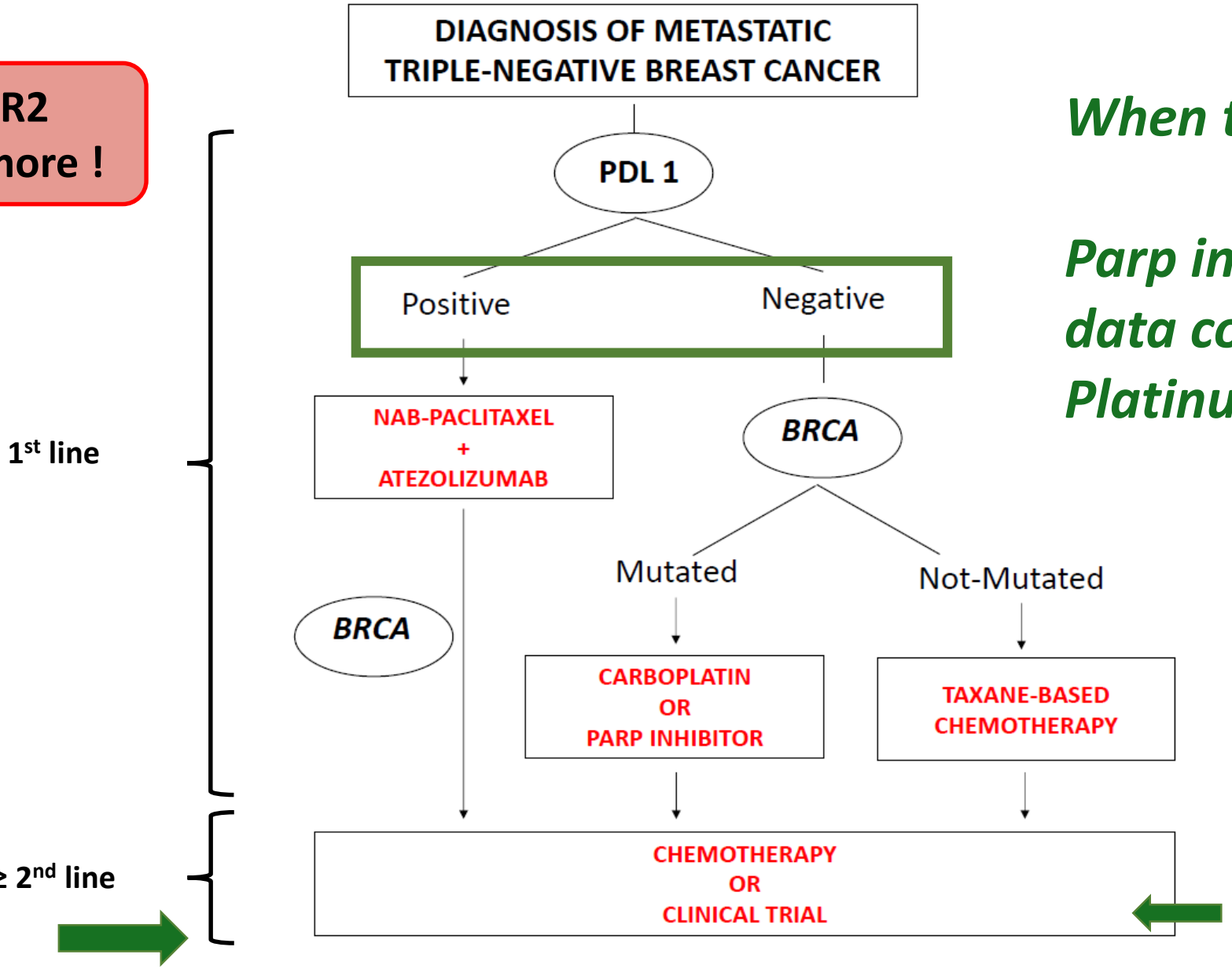


BRCA mutant, any PLD1

Emens LA et al. J Natl Cancer Inst 2021

Secondo lo scenario terapeutico in evoluzione in TNBC
……alla luce di nuovi marcatori biologici e nuovi farmaci

ER, PR and HER2
not enough anymore !



1st line

≥ 2nd line

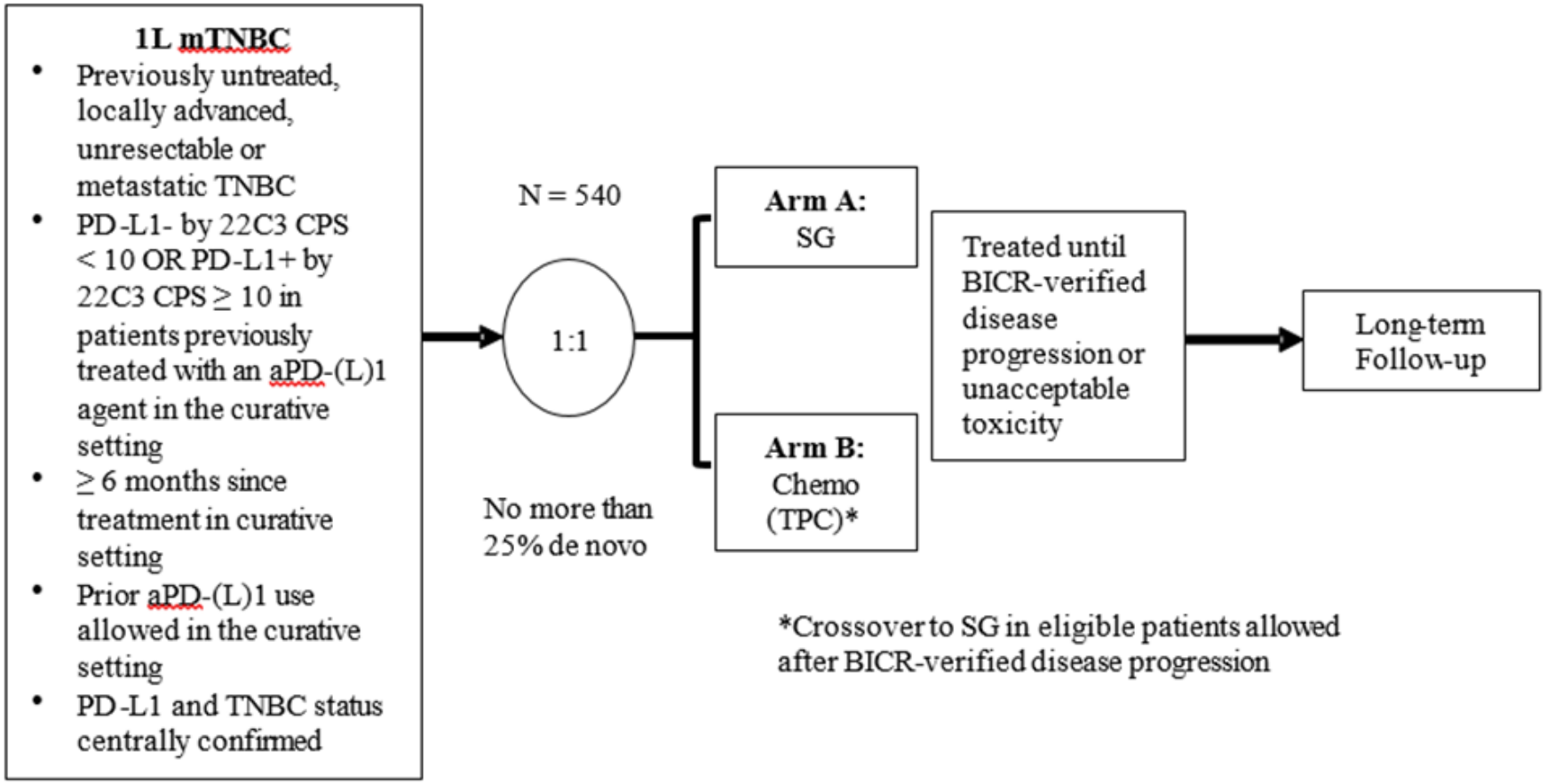
Sacituzumab

When to test BRCA???

Parp in first Line? No data comparing to Platinum!!

ASCENT 03

Figure 1. Study Schema

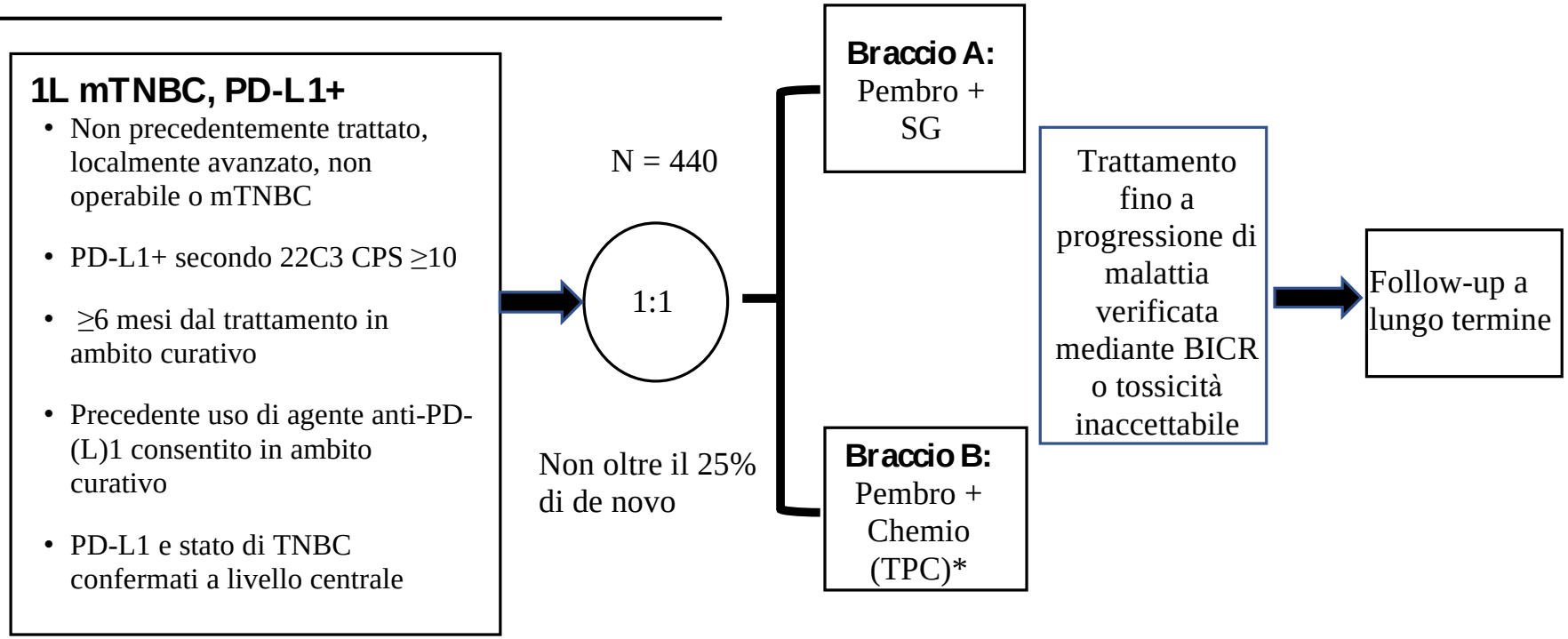


Stratification Factors:

- De novo vs recurrent disease within 6-12 months of treatment in the curative setting vs recurrent disease > 12 months of treatment in the curative setting
- Geographic region (US/Canada/Western Europe vs rest of world)

Primary End Point: PFS
Key Secondary End Points: OS, ORR, PROs, and Safety

ASCENT 04



*Crossover a SG per pazienti eleggibili consentito dopo la progressione verificata mediante BICR

Fattori di stratificazione

- Malattia de novo rispetto a recidivante tra i 6 e 12 mesi dal completamento del trattamento in ambito curativo rispetto a malattia recidivante che si manifesta >12 mesi dal completamento del trattamento in ambito curativo**

Endpoint primario: PFS in popolazione ITT
Principali endpoint secondari: OS
Altri endpoint secondari: ORR, PRO e sicurezza

Tropion Breast 03

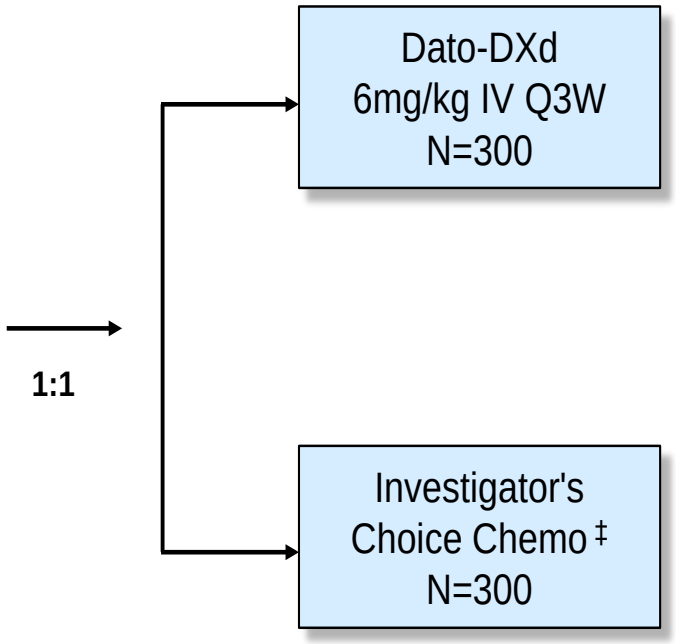
Study Design

Key Eligibility Criteria

- Locally recurrent inoperable or metastatic TNBC
- No prior chemotherapy or targeted systemic therapy for metastatic breast cancer
- Not candidate for PD-1/PD-L1 inhibitor therapy†
- Measurable disease as defined by RECIST v1.1
- Mandatory tumor sample
- ECOG PS 0 or 1
- Adequate hematologic and end-organ function

Stratification factors:

- Geographic location (US/Canada/EU vs rest of world)
- DFI mo vs prior DFI>12 mo)
- PD-L1 status (positive vs negative)

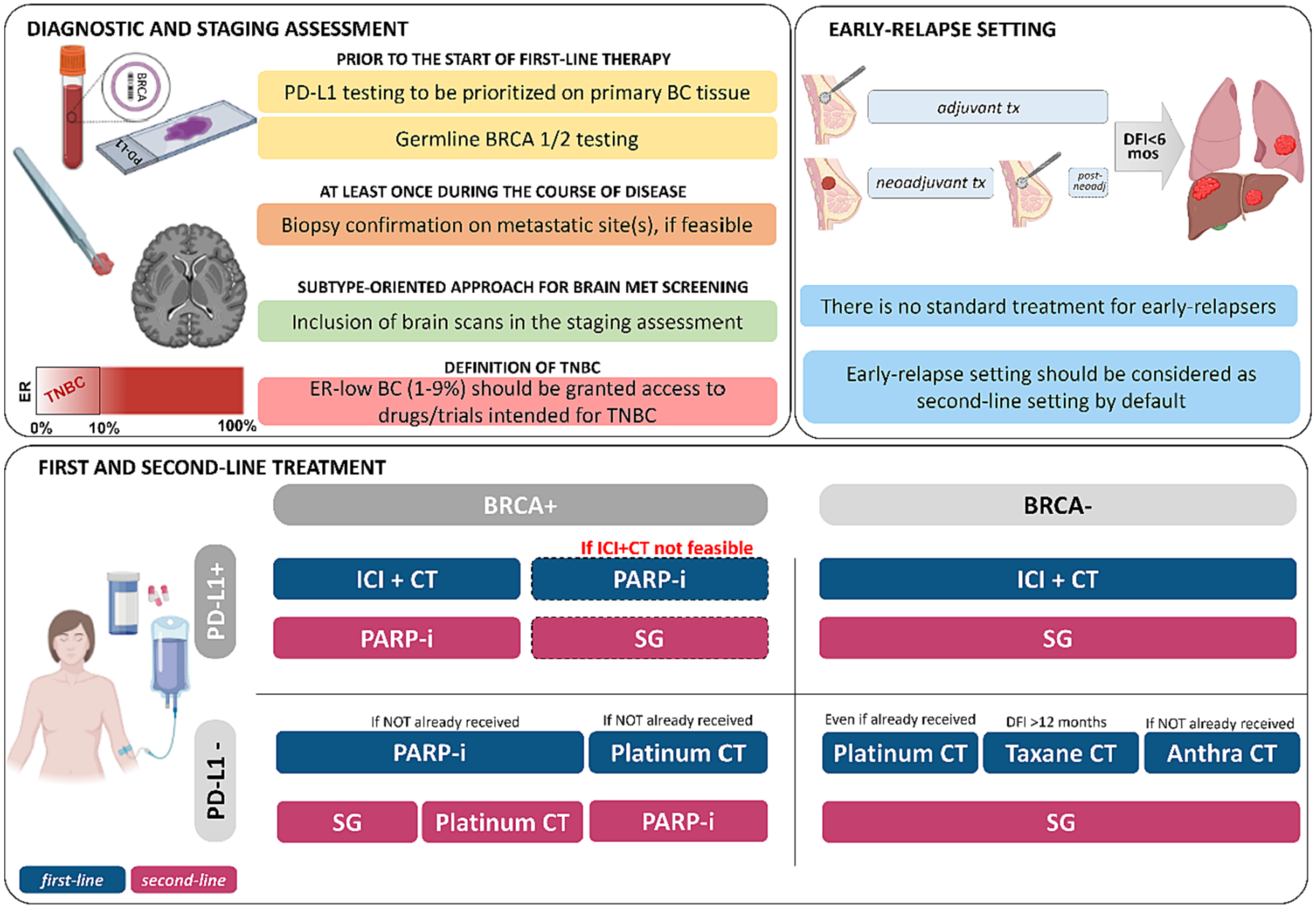


Dual primary endpoints
PFS (BICR), OS

Secondary endpoints
PFS (inv), ORR, DoR, TTD, DCR, PRO, Safety, Tolerability, PK, and Immunogenicity

Exploratory endpoints
TROP2, PD-L1

Response assessment: Scan Q6W for 48 weeks, then Q9W thereafter *until RECIST1.1 disease progression (as assessed by Investigator), regardless of study intervention discontinuation or start of subsequent anticancer therapy. Following disease progression, 1 additional follow-up scan should be performed as per Imaging schedule (i.e., either 6 weeks or 9 weeks later).*



Optimizing choices and sequences in the diagnostic-therapeutic landscape of advanced triple-negative breast cancer: An Italian consensus paper and critical review

F. Miglietta, A. Fabi, D. Generali et al. Cancer Treat Review 2022

Atezolizumab plus nab-paclitaxel as first-line treatment of PD-L1 positive metastatic triple-negative breast cancer: results from the multicentre, real-word ANASTASE study

ClinicalTrials.gov identifier: NCT05609903.

- Retrospective analysis of PD-L1-positive metastatic TNBC patients who completed at least one cycle of atezolizumab and nab-paclitaxel treatment

- Conducted in 29 Italian oncology centers.

- Outcomes : time-to-treatment discontinuation,
objective response rate (ORR),
duration of response,
median progression-free survival (PFS),
time to next treatment or death (TNT-D),
overall survival (OS) rate,
description of second-line therapy after progression.

29 Italian Centers

Fabi et al submitted

Multidisciplinary approach is not enough. Quality of Multidisciplinary Team Important

Cortesly by Dr. Nancy DeMore MUSC Hollings Cancer Center

Atezo ***anticorpo Ventana SP142***
positività di PD- L1 (IC) è >1%

Pembro DAKO 22C3 assay
positività CPS >10