Highlights Setting Precoce: TNBC

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ESMO

Disclosure Information

Personal financial interests

- **Consultant or advisor:** Roche, Lilly, Novartis, AstraZeneca, Pfizer, Seagen, Gilead, MSD, Exact Sciences, Pierre Fabre, Menarini
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- **Research support (to the Institution):** Gilead

Non-financial interests

- Chair of the ESMO Young Oncologists Committee
- Member of the national council of the Italian Association of Medical Oncology (AIOM)

Outline

- Introduction
- Systemic treatment
- Beyond systemic treatment
- Conclusions

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Where Are We in TNBC ?

SABCS SAN ANTONIO BREAST CANCER SYMPOSIUM®
DECEMBER 5-9, 2023 | @SABCSSanAntonio

SAN ANTONIO BREAST CANCER SYMPOSIUM®

Recent advances in triple-negative breast cancer

Melinda Telli, MD
Associate Professor of Medicine
Stanford University School of Medicine
Director, Breast Cancer Program
Stanford Cancer Institute

Triple-negative breast cancer diagnosis 2007

Where we were then

- Adjuvant therapy consisted of anthracycline and taxane-based combinations
- Selective use & targeting of other standard cytotoxics not optimized
- No approved targeted therapies
- No clear treatment standard in the metastatic disease setting
  - Survival after relapse 12-18 months

Telli M, SABCS 2023

Where Are We in eTNBC ?

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What we have achieved

Advances in early-stage TNBC

- ✓ **Adjuvant capecitabine improves disease-free & overall survival**
- ✓ **Pembrolizumab addition to neoadjuvant chemotherapy improves event-free survival**
- ✓ **Adjuvant olaparib improves disease-free & overall survival in gBRCA1/2 mutation-associated high-risk breast cancer**
- ✓ **Carboplatin addition to neoadjuvant anthracycline and taxane-based chemotherapy improves disease-free & overall survival**

Telli M, SABCS 2023

Neoadjuvant vs. Adjuvant Settings in eTNBC

ASCO special articles

Neoadjuvant Chemotherapy, Endocrine Therapy, and Targeted Therapy for Breast Cancer: ASCO Guideline

Larissa A. Korde, MD[1]; Mark R. Somerfield, PhD[2]; Lisa A. Carey, MD[3]; Jennie R. Crews, MD[4]; Neelima Denduluri, MD[5]; E. Shelley Hwang, MD[6]; Seema A. Khan, MD[7]; Sibylle Loibl, MD, PhD[8]; Elizabeth A. Morris, MD[9]; Alejandra Perez, MD[10]; Meredith M. Regan, ScD[11]; Patricia A. Spears, BS[2]; Preeti K. Sudheendra, MD[12]; W. Fraser Symmans, MD[13]; Rachel L. Yung, MD[4]; Brittany E. Harvey, BS[2]; and Dawn L. Hershman, MD[14]

THE BOTTOM LINE

Neoadjuvant Chemotherapy, Endocrine Therapy, and Targeted Therapy for Breast Cancer: ASCO Clinical Practice Guideline

Guideline Question

What is the optimal use of neoadjuvant therapy for women with invasive, nonmetastatic breast cancer?

Target Population

Patients with nonmetastatic breast cancer.

Target Audience

Medical oncologists, surgical oncologists, radiologists, pathologists, oncology nurses, patients or caregivers or advocates, and oncology advanced practice providers.

Methods

An Expert Panel was convened to develop clinical practice guideline recommendations based on a systematic review of the medical literature.

CLINICAL QUESTION 1

Which patients with breast cancer are appropriate candidates for neoadjuvant systemic therapy?

Recommendations

Recommendation 1.1. Neoadjuvant chemotherapy is the treatment of choice for patients with inflammatory breast cancer or those with unresectable or locally advanced disease at presentation whose disease may be rendered resectable with neoadjuvant treatment (Type: informal consensus; Evidence quality: low; Strength of recommendation: strong).

Recommendation 1.2. Tumor histology, grade, stage and estrogen, progesterone, and HER2 expression should routinely be used to guide clinical decisions as to whether or not to pursue neoadjuvant chemotherapy. There is insufficient evidence to support the use of other immunochemical markers, morphological markers (eg, tumor-infiltrating lymphocytes) or genomic profiles to guide a clinical decision as to whether or not to pursue neoadjuvant chemotherapy (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).

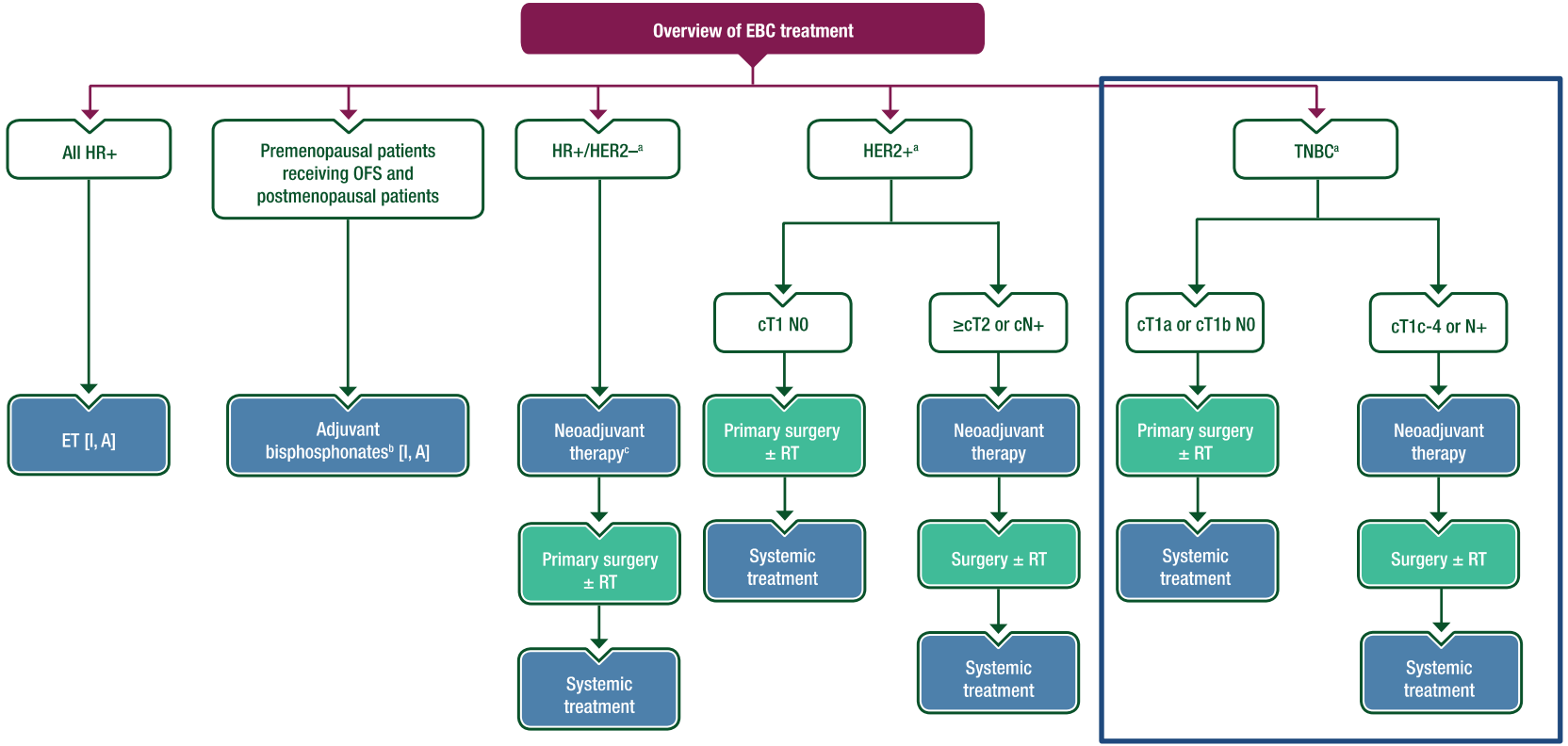
Recommendation 1.3. Neoadjuvant systemic therapy should be offered to patients with high-risk HER2-positive or triple-negative breast cancer (TNBC) in whom the finding of residual disease would guide recommendations related to adjuvant therapy (Type: evidence-based; benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Recommendation 1.4. Neoadjuvant systemic therapy may be offered to reduce the extent of surgery (breast-conserving surgery and axillary lymph node dissection). Chemotherapy with or without targeted therapy, or endocrine therapy (if hormone receptor–positive [HR-positive]) may be offered (Type: evidence-based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 1.5. In patients for whom a delay in surgery is preferable (eg, for genetic testing required for surgical treatment decision making, to allow time to consider reconstructive options) or unavoidable, neoadjuvant systemic therapy may be offered (Type: informal consensus; benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

Korde LA et al, J Clin Oncol 2021;39(13):1485-505

Neoadjuvant vs. Adjuvant Settings in eTNBC



Loibl S et al, Ann Oncol 2024;35(2):159-82

Outline

- Introduction
- **Systemic treatment**
- Beyond systemic treatment
- Conclusions

Neoadjuvant Chemo-immunotherapy in eTNBC

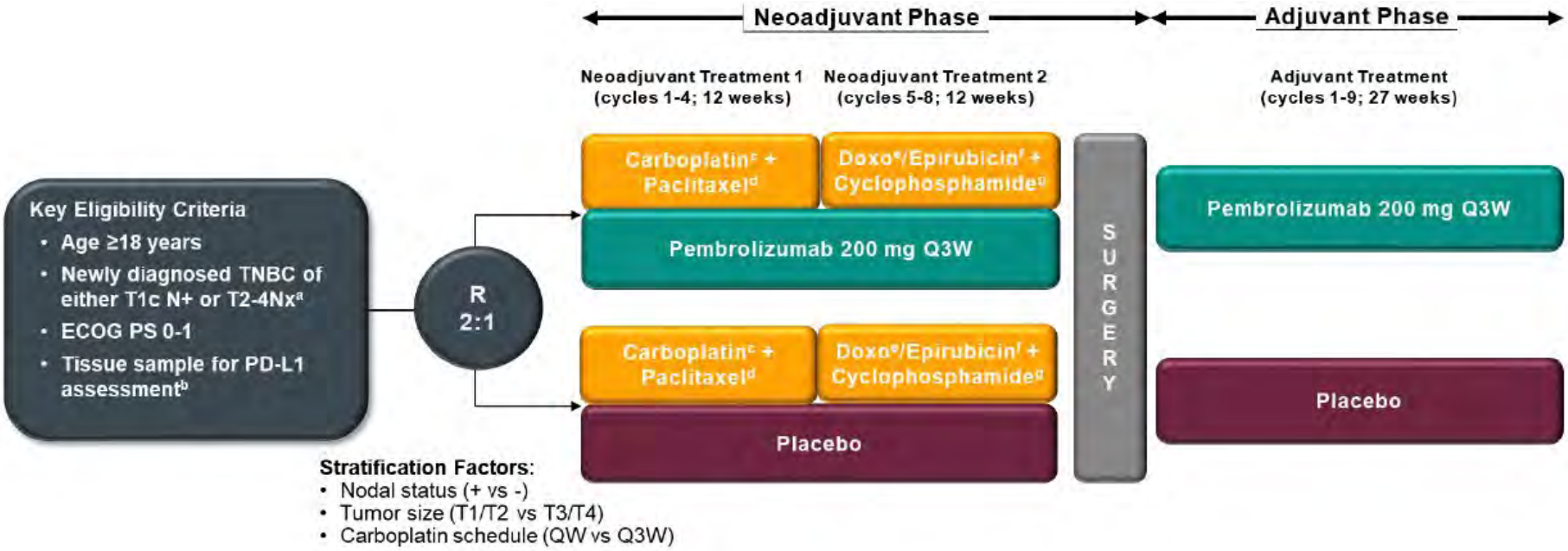
NEOADJUVANT IO TRIALS IN eTNBC

	KEYNOTE-522	IMpassion031	Neo-TRIP	GeparNUEVO	Neo-PACT
Phase	III	III	III	II	II
N. pts	1,174	333	280	174	117
ICI agent	Pembro	Atezo	Atezo	Durvalumab	Pembro
Neoadj regimen	Anthra + Tax + Carbo	Anthra + Tax	Carbo + Tax	Anthra + Tax	Carbo + Tax
Adj regimen	Pembro	Atezo	AC/EC/FEC	-	-
PD-L1+	82%	46%	56%	87.3%	46%
pCR with ICI	65% (Δ14%) (95% CI 59.9-69.5)	58% (Δ16%) (95% CI 50-65%)	49% (Δ4%) (95% CI 40-57.2%)	53% (Δ9%) (95%CI 42.5-61.4%)	60% (95% CI 51-70%)
Median follow-up	39.1 months	39 months	-	43.7 months	-
EFS (HR)	0.63 (sig) (95% CI 0.48-0.82)	0.76 (95% CI 0.47-1.21)	NR	0.31 (sig) (95% CI 0.13-0.74)	NR
OS (HR)	0.72 (NS) (95% CI 0.51-1.02)	0.56 (95% CI 0.30-1.04)	NR	0.24 (sig) (95% CI 0.08-0.72)	NR

Schmid P et al, N Engl J Med 2020;382(9):810-21. Schmid P et al, N Engl J Med 2022;386(6):556-67. Mittendorf EA et al, Lancet 2020;396(10257):1090-100. Barrios CH et al, ESMO Breast 2023
Gianni L et al, Ann Oncol. 2022;33(5):534-43. Loibl S et al, Ann Oncol. 2022;33(11):1149-58. Sharma P et al, ASCO22

Neoadjuvant Chemo-immunotherapy in eTNBC

KEYNOTE-522 trial

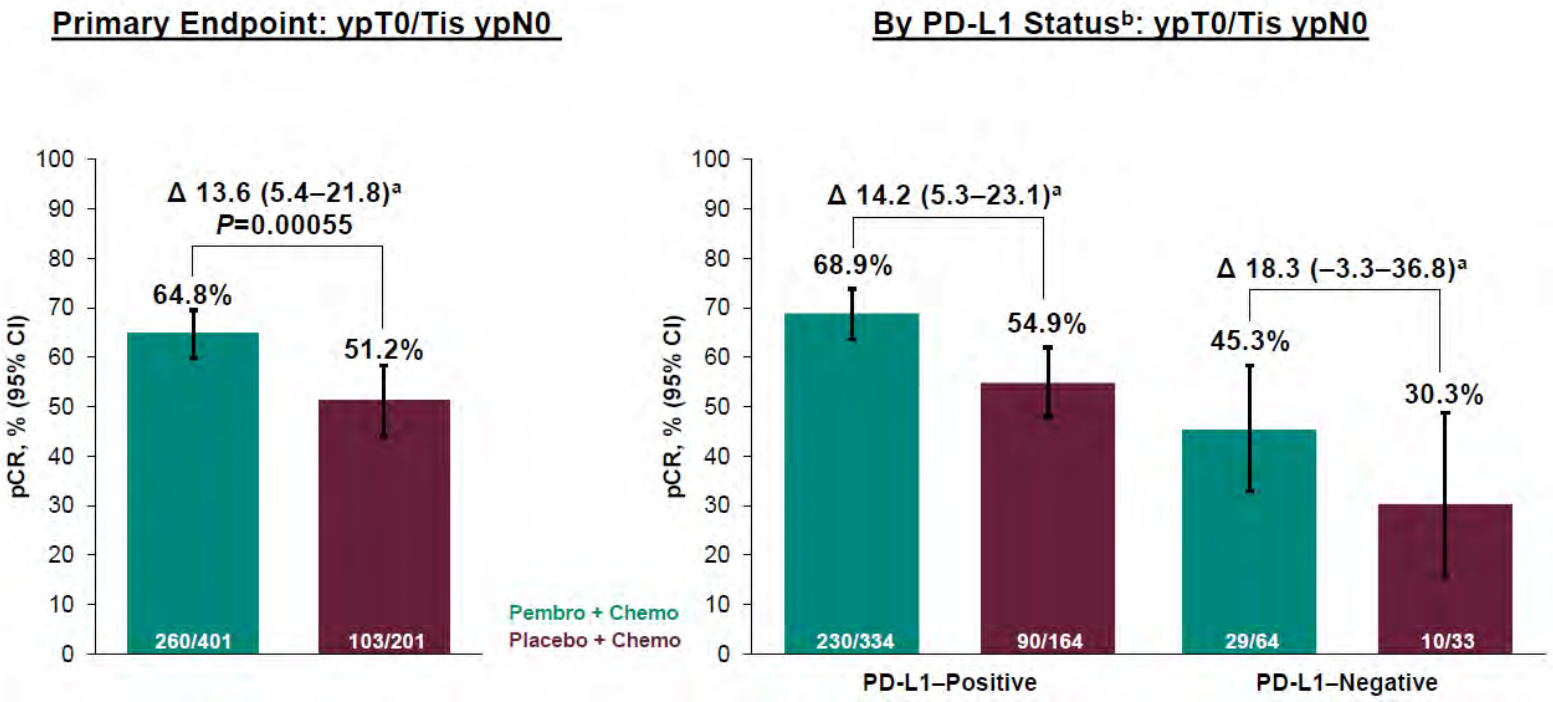


PD-L1+ 82% - T1/T2 74% - N+ 51% - Carboplatin weekly 57%

Schmid P et al, N Engl J Med 2020;382(9):810-21. Schmid P et al, N Engl J Med 2022;386(6):556-67

Neoadjuvant Chemo-immunotherapy in eTNBC

KEYNOTE-522 trial



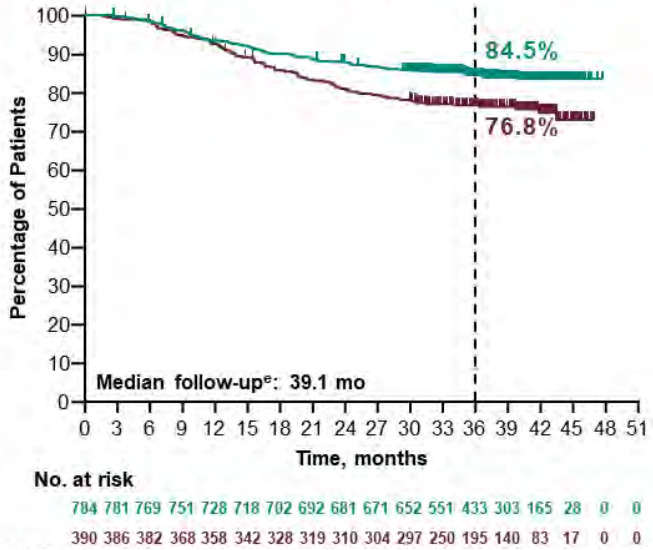
Schmid P et al, N Engl J Med 2020;382(9):810-21

Neoadjuvant Chemo-immunotherapy in eTNBC

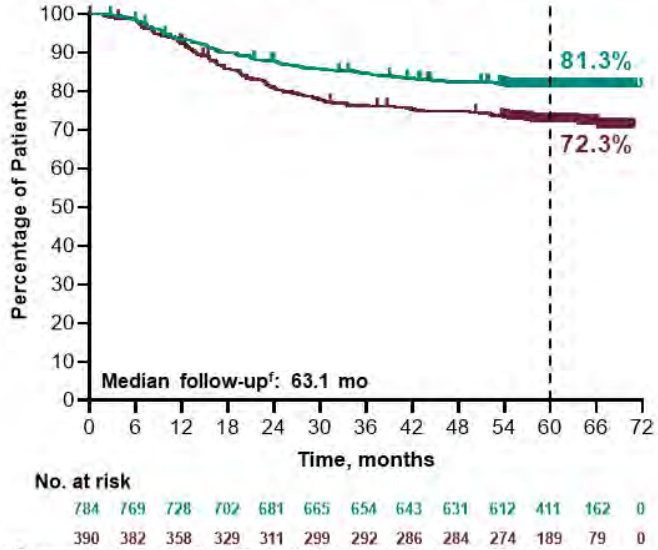
KEYNOTE-522 trial

EFS at IA4 and IA6

IA4[a]	Events	HR (95% CI)	*P* value
Pembro + Chemo/Pembro	15.7%	0.63[c] (0.48–0.82)	0.00031[d]
Placebo + Chemo/Placebo	23.8%		



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

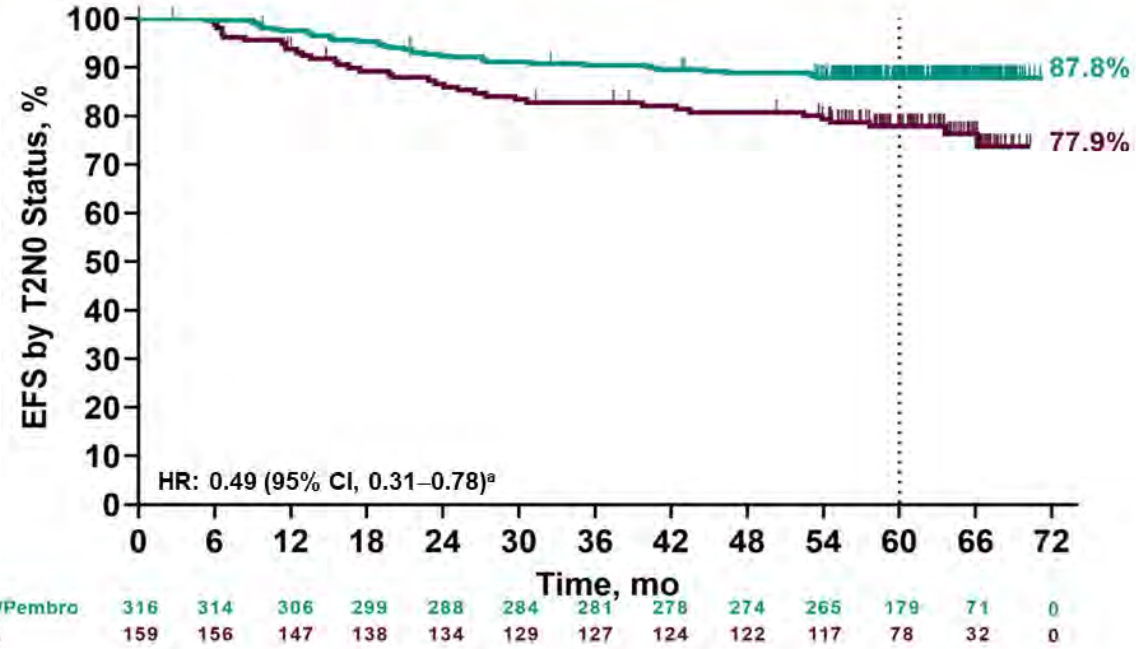


Schmid P et al, SABCS 2023

Neoadjuvant Chemo-immunotherapy in eTNBC

KEYNOTE-522 trial

EFS at IA6 in Patients With Baseline T2N0



Schmid P et al, SABCS 2023

Neoadjuvant Chemo-immunotherapy in eTNBC

KEYNOTE-522 trial: open questions

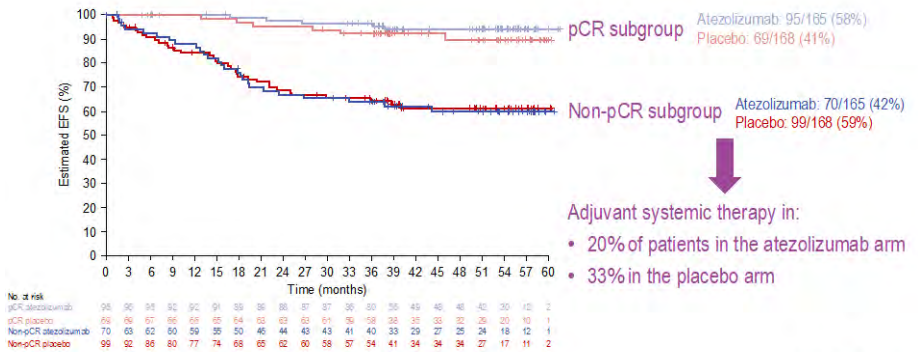
- **Optimal chemotherapy backbone ?**
  - **Platinum-based chemotherapy**
  - **Anthracycline-based chemotherapy**
  - **Dose-dense schedule**

- **Which post-neoadjuvant treatment ?**
  - **Pembrolizumab following pCR**
  - **Capecitabine in patients with no pCR**
  - **Olaparib in *BRCA* patients with no pCR**

Neoadjuvant Chemo-immunotherapy in eTNBC
Post-neoadjuvant Considerations

EFS according to pCR

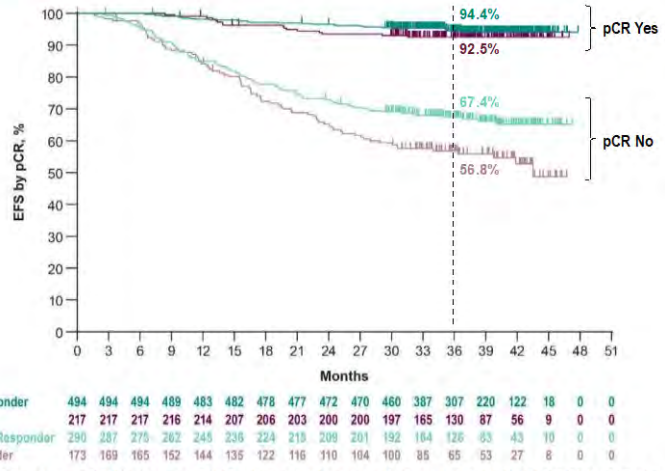
IMpassion031



Adjuvant systemic therapy in:

- 20% of patients in the atezolizumab arm
- 33% in the placebo arm

KEYNOTE-522



Barrios CH et al, ESMO Breast 2023. Schmid P et al, N Engl J Med 2022;386(6):556-67

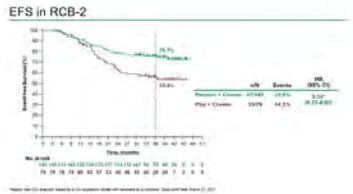
Lambertini M, ESMO Breast 2023

Neoadjuvant Chemo-immunotherapy in eTNBC
Post-neoadjuvant Considerations

ESMO BREAST CANCER

Lambertini M, ESMO Breast 2023

Neoadjuvant Chemo-immunotherapy in eTNBC
Post-neoadjuvant Considerations



ESMO BREAST CANCER

Lambertini M, ESMO Breast 2023

Neoadjuvant Chemo-immunotherapy in eTNBC

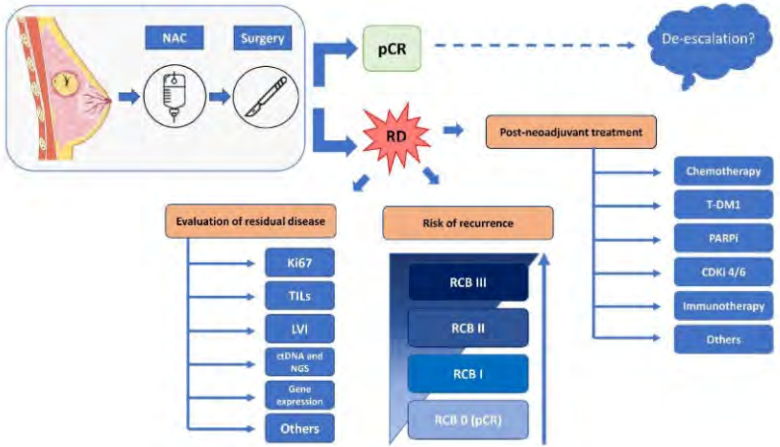
Post-neoadjuvant Considerations

In patients without pCR: let's escalate treatment ! Ok, but how ?

Adjuvant systemic therapy in patients without pCR

Adjuvant systemic therapy, n (%)	Atezolizumab + CT (n=70)	Placebo + CT (n=99)
Any[a]	14 (20)	33 (33)
Capecitabine	4 (6)	26 (26)
Other chemotherapy[b]	9 (13)	5 (5)
Olaparib	0	0
Other targeted therapy	1 (1)	2 (2)
Endocrine therapy	1 (1)	3 (3)

[a]More than one therapy category possible
[b]Includes paclitaxel, platinum, anthracycline-containing regimens and gemcitabine

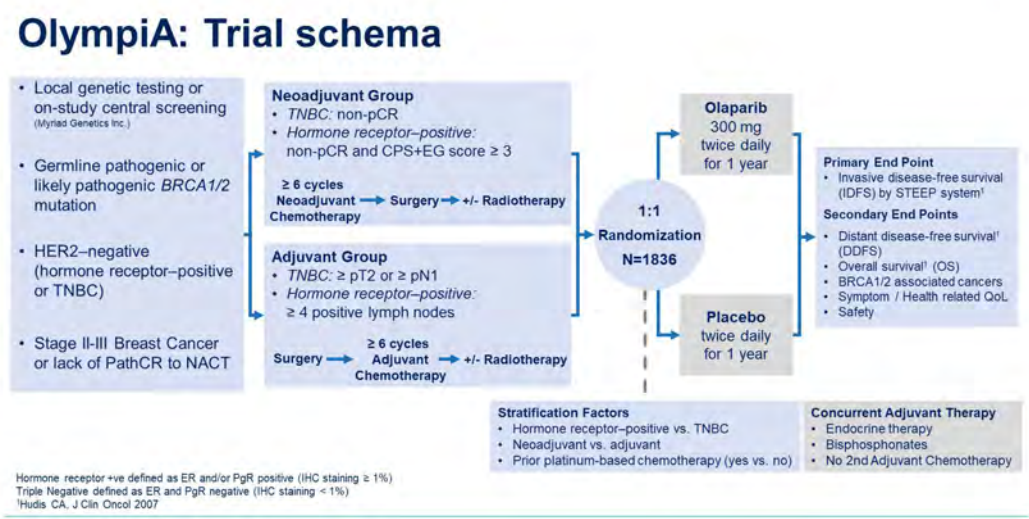


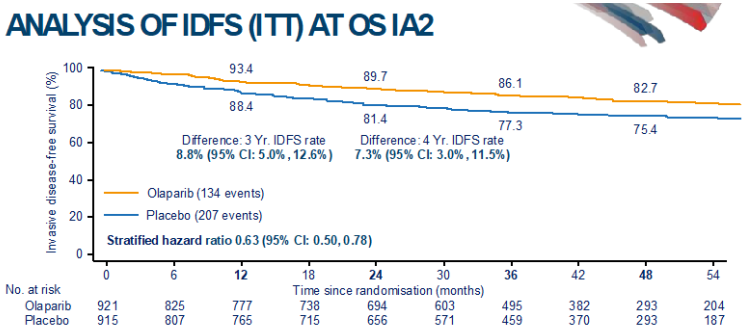
Barrios CH et al, ESMO Breast 2023. Agostinetto E et al, Cancers 2022;14(21):5467

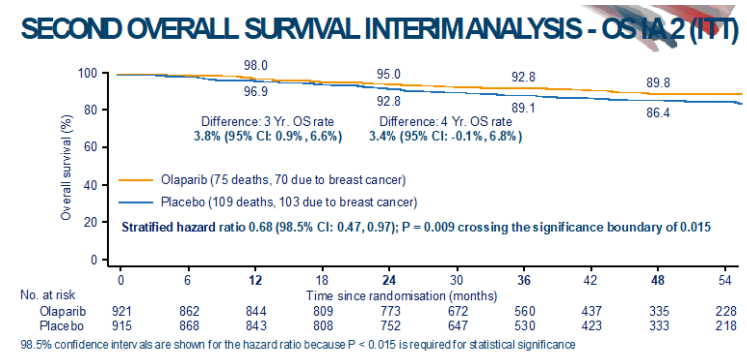
Lambertini M, ESMO Breast 2023

Adjuvant PARPi in *BRCA* Carriers with eTNBC

OlympiA trial



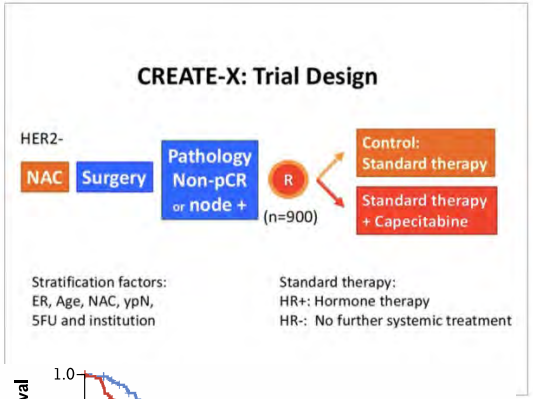


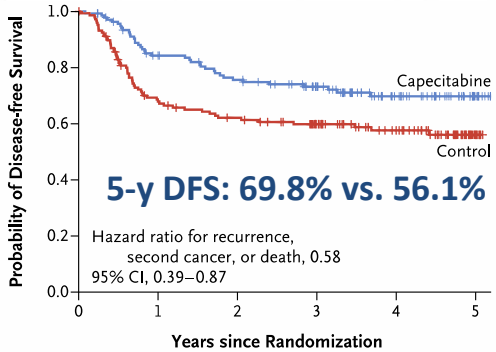


Tutt A et al, N Engl J Med 2021;384(25):2394-405. Geyer CE et al, Ann Oncol 2022;33(12):1250-68

Adjuvant Capecitabine +/- ICI in eTNBC

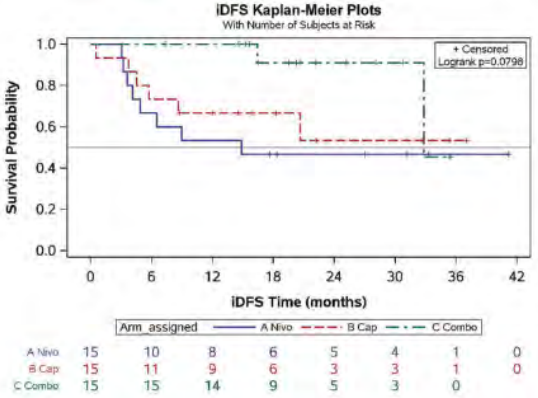
CreateX trial





No. at Risk						
Capecitabine	139	109	96	76	42	11
Control	147	95	84	69	47	6

OXEL trial

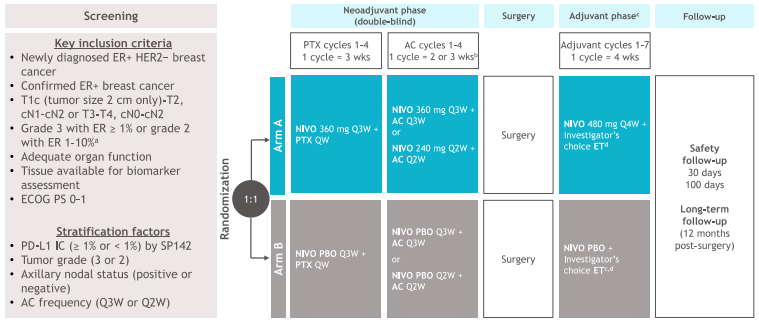


Event	Arm A Nivolumab (*N* = 15)		Arm B Capecitabine (*N* = 15)		Arm C Nivolumab and Capecitabine (*N* = 15)	
	All Grades	Grade 3	All Grades	Grade 3	All Grades	Grade 3
	Number of patients (%)					
Endocrine disorders: Hypothyroidism	3 (20)	0	0	0	2 (13.3)	0
Gastrointestinal disorders						
Abdominal pain	0	0	2 (13.3)	0	5 (33.3)	1 (6.7)
Diarrhea	1 (6.7)	0	7 (46.7)	0	7 (46.7)	2 (13.3)
Nausea	0	0	4 (26.7)	0	2 (13.3)	0
Oral mucositis	0	0	3 (20)	2 (13.3)	3 (20)	0
General disorders: fatigue	6 (40)	0	5 (33.3)	0	4 (26.7)	2 (13.3)
Musculoskeletal and connective tissue disorders: arthralgia	5 (33.3)	0	1 (6.7)	0	0	0
Nervous system disorders: Peripheral sensory neuropathy	0	0	3 (20)	0	4 (26.7)	0
Skin and subcutaneous tissue disorders						
Palmar-plantar erythrodysesthesia syndrome	0	0	7 (46.7)	0	5 (33.4)	0
Skin and subcutaneous tissue disorders	0	0	1 (6.7)	0	4 (26.7)	0

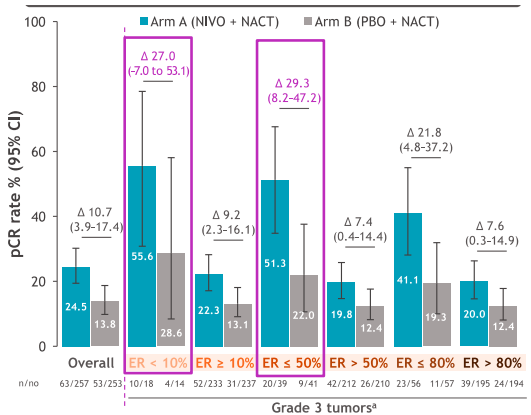
Masuda N et al, N Engl J Med 2017;376(22):2147-59. Lynce F et al, Nat Commun 2024;15(1):2691

Neoadjuvant Chemo-immunotherapy in ER-low

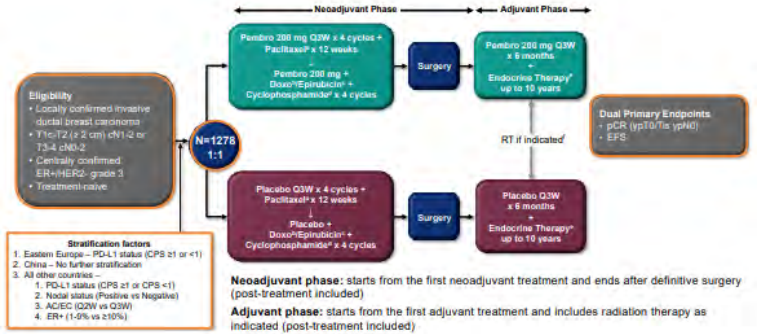
CheckMate 7FL trial



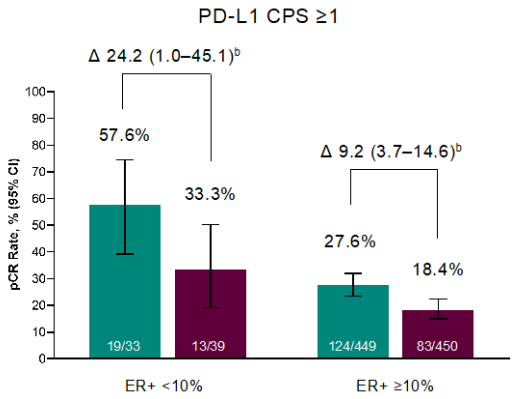
pCR by ER status



KEYNOTE-756 trial



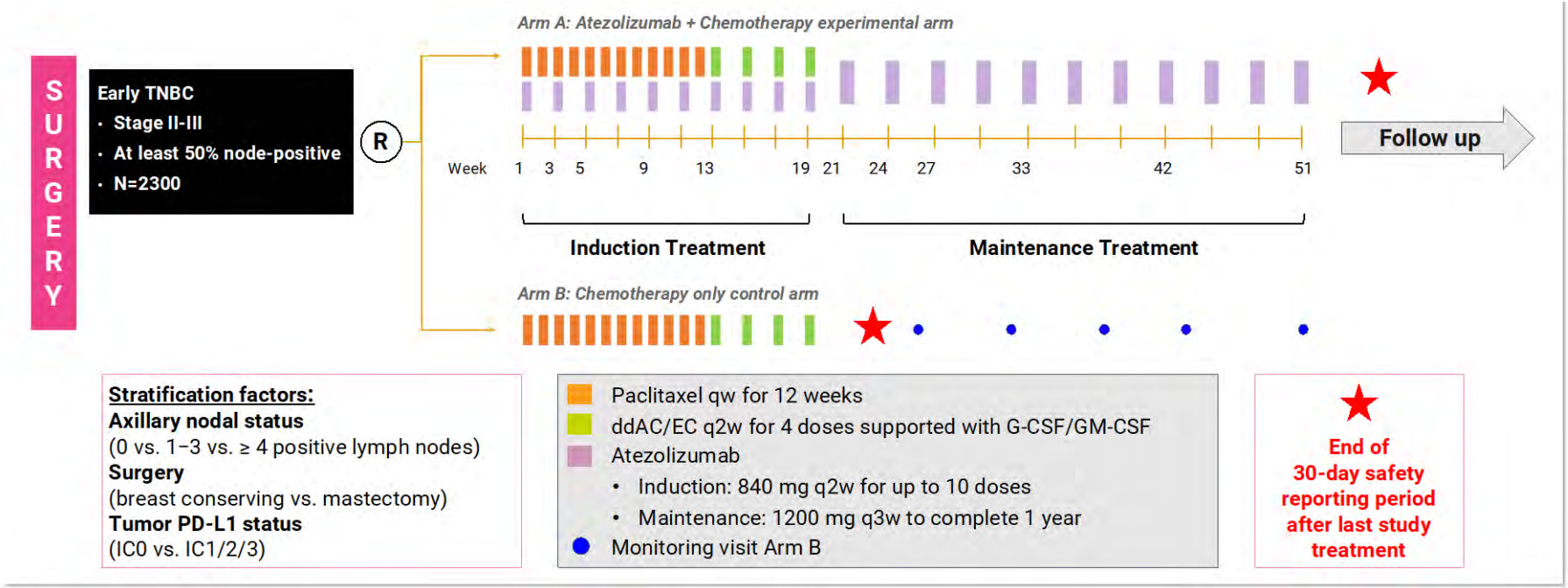
pCR by ER status



Loi S et al, ESMO 2023. Loi S et al, SABCS 2023. Cardoso F et al, ESMO 2023. O'Shaughnessy J et al, SABCS 2023

Adjuvant Chemo-immunotherapy in eTNBC

ALEXANDRA/IMpassion030 trial



PD-L1+ 71% - T1/T2 94% - N+ 48%

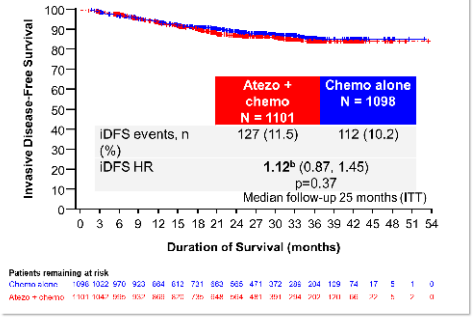
McArthur H et al, EBCC-14

Adjuvant Chemo-immunotherapy in eTNBC

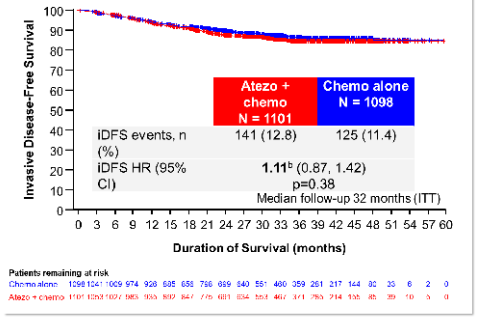
ALEXANDRA/IMpassion030 trial

iDFS IA and Final Analysis
Primary Efficacy Endpoint (ITT population)

Interim Analysis[a]



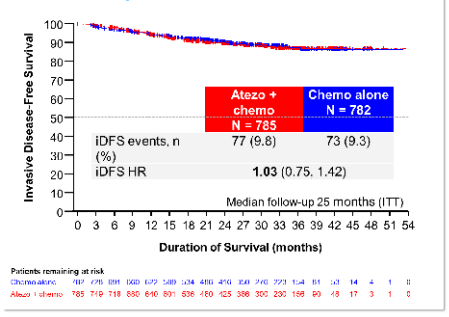
Final Analysis



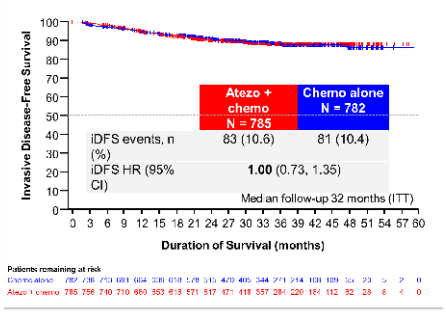
iDFS: defined as the interval from randomization until date of first occurrence of an iDFS event
[a]IA results previously presented at SABCs 2023 (database of 17 Feb 2023, not cleaned)
[b]Stratified by PD-L1 status, Surgery, and Axillary Nodal Status

iDFS PDL1+ IA and Final Analysis
Secondary Endpoint (ITT population)

Interim Analysis[a]



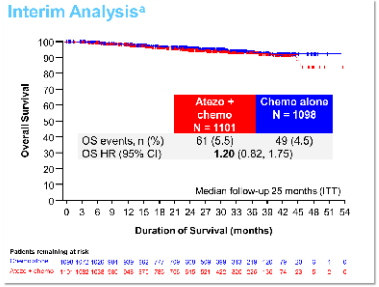
Final Analysis



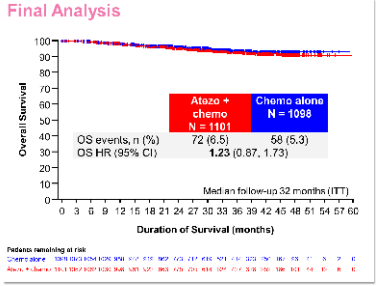
[a]IA results previously presented at SABCS 2023 (database of 17 Feb 2023, not cleaned)

Overall Survival IA and Final Analysis
Secondary Enpoint (ITT population)

Interim Analysis[a]



Final Analysis



Overall Survival (OS): defined as the interval between randomization until death from any cause.
[a]IA results previously presented at SABCS 2023 (database of 17 Feb 2023, not cleaned), one patient in the atezo arm who died 25 Dec 2022 not taken into account (data issue, not cleaned)

McArthur H et al, EBCC-14

(Neo)Adjuvant Chemo-immunotherapy in eTNBC

Ongoing large trials with ICIs in eTNBC

Trial	No.	Treatment	Setting	Primary Endpoint
A-BRAVE (NCT02926196)	474	Avelumab x 1yr vs. observation	Stratum A: high risk primary surgery (after standard CT) Stratum B: no-pCR after NACT	• DFS in all pts • DFS in post-NACT pts
SWOG S1418/ NRG BR006 (NCT02954874)	1,155	Pembrolizumab x 1yr vs. observation	No pCR after NACT	• iDFS in all pts • iDFS in PD-L1+
GeparDouze (NCT03281954)	1,520	P + C + Atezolizumab → AC/EC + Atezolizumab x 1yr vs. P+C → AC/EC	T2 or T3 if cN0 or cN1 with negative biopsy or T1c, T2, or T3 if cN1 with positive biopsy or cN2 or cN3	• pCR • EFS

Outline

- Introduction
- Systemic treatment
- **Beyond systemic treatment**
- Conclusions

Do We Always Need Chemotherapy in eTNBC ?

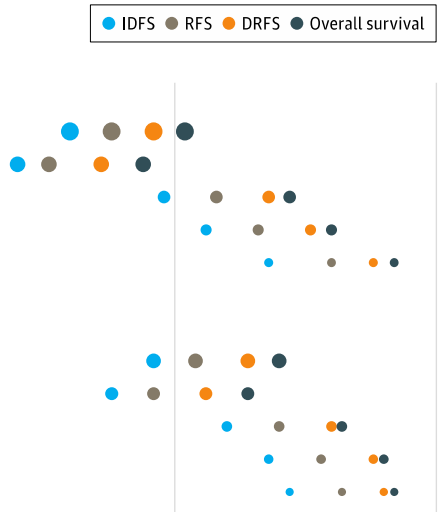
Research

JAMA | Original Investigation

Tumor-Infiltrating Lymphocytes in Triple-Negative Breast Cancer

Roberto A. Leon-Ferre, MD; Sarah Flora Jonas, PhD; Roberto Salgado, MD, PhD; Sherene Loi, MBBS, PhD; Vincent de Jong, MD; Jodi M. Carter, MD, PhD; Torsten O. Nielsen, MD, PhD; Samuel Leung, Msc; Nazia Riaz, MD, PhD; Stephen Chia, MD; Gérôme Jules-Clément, MS; Giuseppe Curigliano, MD, PhD; Carmen Criscitiello, MD, PhD; Vincent Cockenpot, MD; Matteo Lambertini, MD, PhD; Vera J. Suman, PhD; Barbro Linderholm, MD, PhD; John W. M. Martens, MD, PhD; Carolien H. M. van Deurzen, MD, PhD; A. Mieke Timmermans, BSc; Tatsunori Shimoi, MD, PhD; Shu Yazaki, MD; Masayuki Yoshida, MD, PhD; Sung-Bae Kim, MD, PhD; Hee Jin Lee, MD, PhD; Maria Vittoria Dieci, MD; Guillaume Bataillon, MD; Anne Vincent-Salomon, MD, PhD; Fabrice André, MD, PhD; Marleen Kok, MD, PhD; Sabine C. Linn, MD, PhD; Matthew P. Goetz, MD; Stefan Michiels, PhD; for the International Immuno-Oncology Biomarker Working Group

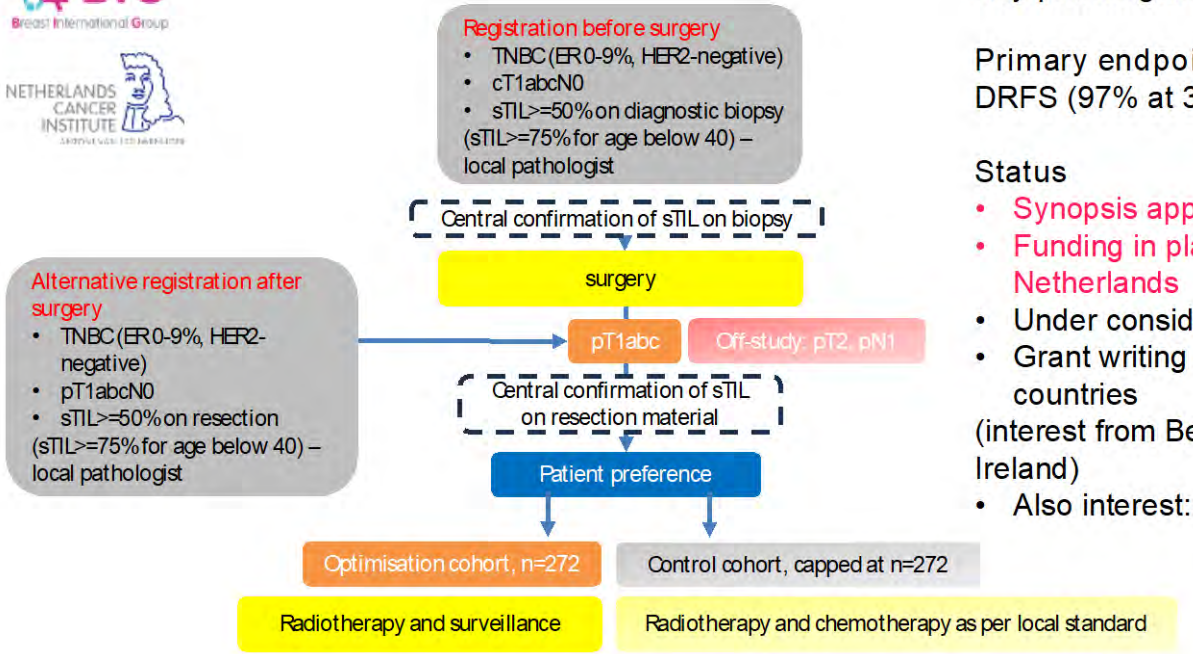
		Estimated survival, % (bootstrapped 95% CI)			
	No. (%)	5-y iDFS	5-y RFS	5-y DRFS	5-y Overall survival
All patients (N = 1966)					
TIL levels, %					
0-100	1966	65 (63-67)	69 (67-71)	73 (71-75)	76 (75-78)
<30	1300 (66)	60 (58-63)	63 (61-66)	68 (66-70)	72 (69-74)
≥30	666 (34)	74 (71-77)	79 (77-82)	84 (81-86)	86 (84-88)
≥50	417 (21)	78 (74-81)	83 (80-86)	88 (85-90)	90 (88-93)
≥75	168 (9)	84 (80-89)	90 (86-93)	94 (91-97)	96 (93-98)
Stage I (n = 1081)[a]					
TIL levels, %					
0-100	1081	73 (70-75)	77 (75-79)	82 (80-83)	85 (83-87)
<30	728 (67)	69 (66-72)	73 (70-76)	78 (75-80)	82 (79-84)
≥30	353 (33)	80 (76-83)	85 (82-88)	90 (87-92)	91 (88-94)
≥50	226 (21)	84 (80-88)	89 (86-93)	94 (91-96)	95 (92-97)
≥75	108 (10)	86 (80-92)	91 (87-95)	95 (92-98)	96 (93-99)



Leon-Ferre RA et al, JAMA 2024;331(13):1135-44

Do We Always Need Chemotherapy in eTNBC ?

EORTC 2257: OPTImisation of treatMent for pAtients with low stage triple-negative breast cancer patients with high sTIL (OPTImaL



PI: Marleen Kok, NKI, Netherlands
Key-pathologist: Roberto Salgado

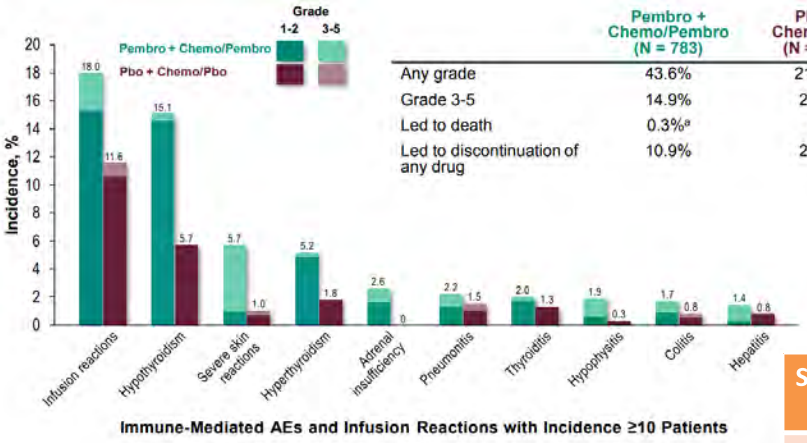
Primary endpoint
DRFS (97% at 3-yrs considered a success)

Status
- Synopsis approved by EORTC
- Funding in place to start in the Netherlands
- Under consideration by ECOG
- Grant writing ongoing for European countries

(interest from Belgium, Germany, Italy, Ireland)
- Also interest: Australia, Japan

Sharma P & Thomas A, SABCS 2023

Let's Pay Extra Attention to IO-related Toxicities !



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

	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%

Safety	Any Grade (n=577)	Grade 3+	KN522, Any Grade (n= 783)	KN522 Grade 3+
Adverse Drug Event (ADE) Causing Dose Reductions	217 (37.6%)		No equivalent reported	
ADE Causing Early Discontinuation	228 (39.5%)		216 (27.7%)	
Patients who experienced an immune-related adverse effect (irAE)?	412 (71.4%)	184 (31.9%)	262 (33.5%)	101 (12.9%)

- If patients had an ADE that caused a dose reduction, they were significantly more likely to have residual disease (P = 0.039).
- There was no difference in pCR for patients who discontinued treatment early vs. those who did not.
- For example, high rates of all grade hepatitis/transaminitis (19.9%), hypothyroidism (18%) and adrenal insufficiency (7.8%) were observed. See our poster for a complete list of all grade and G3+ irAEs.

Schmid P et al, N Engl J Med 2022;386(6):556-67. Hofherr ML et al, SABCS 2023

Let's Pay Extra Attention to IO-related Toxicities !

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO OPEN CANCER HORIZONS

REVIEW

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

M. Garutti[1*], M. Lambertini[2,3] & F. Puglisi[1,3,4]

PMID	Adverse effect	Evidence	Drug	Sample size
28039179	Primary hypogonadism	Bilateral orchitis	Anti-PD1 + anti-CTLA4	1
30936376	Primary hypogonadism	Epididymo-orchitis + encephalitis	Anti-PD1	1
32556068	Primary hypogonadism	Altered spermatogenesis	Anti-PD1 + anti-CTLA4	7
33613847	Primary hypogonadism	Testosterone deficiency	Anti-PD1 and/or anti-CTLA4	49
33299797	Primary hypogonadism	Azoospermia	Anti-PD1 + anti-CTLA4	1
31235040	Primary hypogonadism	Azoospermia	Anti-PD1 and/or anti-CTLA4	22
30861560	Secondary hypogonadism	Metanalysis of endocrine irAEs	Anti-PD1 and/or anti-CTLA4	19922
31021376	Secondary hypogonadism	Metanalysis of irAEs	Anti-PD1 or anti-PDL1	20128
32507965	Secondary hypogonadism	Endocrine irAEs	Anti-PD1 and/or anti-CTLA4	6089
24610577	Secondary hypogonadism	Endocrine irAEs	Anti-CTLA4	256
31235040	Secondary hypogonadism	Isolated hypogonadotropic hypogonadism	Anti-PDL1	1
33646368	Secondary hypogonadism	Increased LH-to-FSH ratio and estradiol	Anti-PD1	22
31235040	Sexuality	No sexual alterations during or after ICIs	Anti-PD1 and/or anti-CTLA4	25
31672171	Sexuality	Autoimmune vulvitis	Anti-PD1	1

Adverse event	Clinical approaches	Unsolved questions
Primary hypogonadism	• Discuss the possibility of infertility linked with the treatment and the strategies of fertility preservation (e.g. cryopreservation)	• Frequency • Duration after discontinuation of immunotherapy • Alteration of sex hormones levels (e.g. testosterone, estradiol) • Impact on fertility, pregnancy, and complicated pregnancy • Impact on libido and sexual life
Secondary hypogonadism	• Discuss the possibility of hypopituitarism-induced infertility linked with the treatment and the strategies of fertility restoration (e.g. hormonal therapy if clinically safe)	• Frequency of secondary hypogonadism • Frequency of isolated secondary hypogonadism • Impact on fertility, pregnancy, and complicated pregnancy • Impact on libido and sexual life

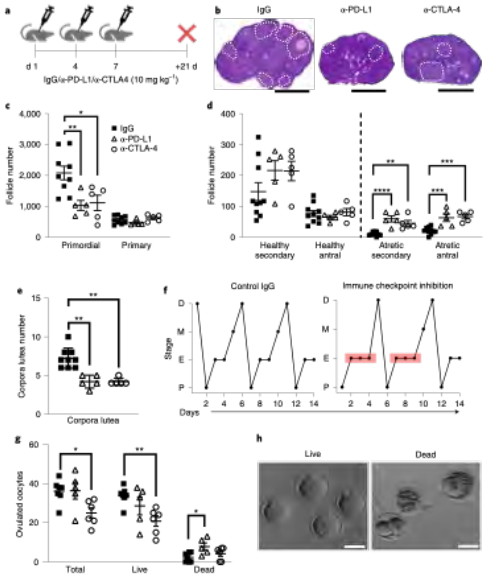
Garutti M et al, ESMO Open 2021;6(5):100276

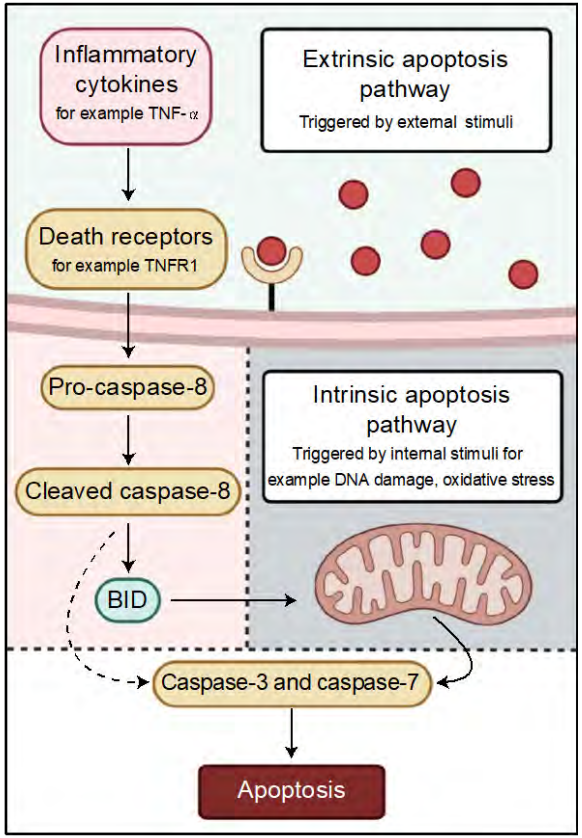
Let's Pay Extra Attention to IO-related Toxicities !

ARTICLES
https://doi.org/10.1038/s43018-022-00413-x
nature cancer

Checkpoint inhibitor immunotherapy diminishes oocyte number and quality in mice

Amy L. Winship[1,7], Lauren R. Alesi[1,7], Sneha Sant[2,3,7], Jessica M. Stringer[1], Aldana Cantavenera[1], Teharn Hegarty[1], Carolina Lliberos Requesens[1], Seng H. Liew[1], Urooza Sarma[1], Meaghan J. Griffiths[1], Nadeen Zerafa[1], Stephen B. Fox[2,3], Emmaline Brown[2,3], Franco Caramia[2], Pirooz Zareie[4], Nicole L. La Gruta[4], Kelly-Anne Phillips[3], Andreas Strasser[5,6], Sherene Loi[2,3,7] and Karla J. Hutt[1,7]





Winship A et al, Nat Cancer 2022;3:1-13

Pregnancy after Breast Cancer in *BRCA* Carriers

Study Design and Participants

- International, multicenter, hospital-based, retrospective cohort study

Key inclusion criteria

- Stage I - III invasive breast cancer
- Diagnosis between January 2000 and December 2020
- Age ≤ 40 years at diagnosis
- Known germline likely pathogenic or pathogenic variants in *BRCA1* and/or *BRCA2* genes

Key exclusion criteria

- Stage IV *de novo* breast cancer
- Lack of data on follow-up or post-treatment pregnancies
- History of ovarian cancer or other malignancies without prior breast cancer
- *BRCA* VUS or *BRCA* healthy carriers

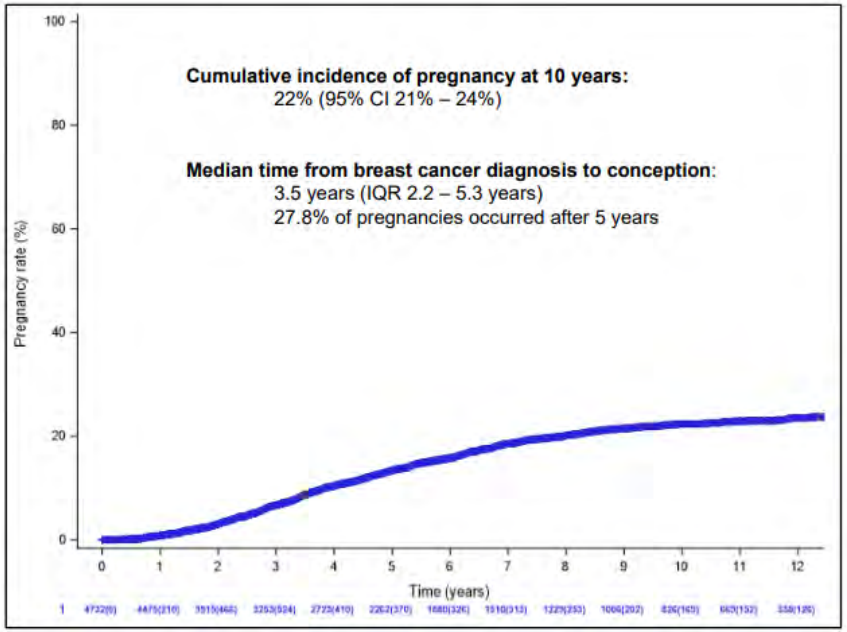
4732 patients from 78 centers – 659 with a pregnancy after breast cancer

Lambertini M, Blondeaux E et al, SABCS 2023 – JAMA 2024;331(1):49-59

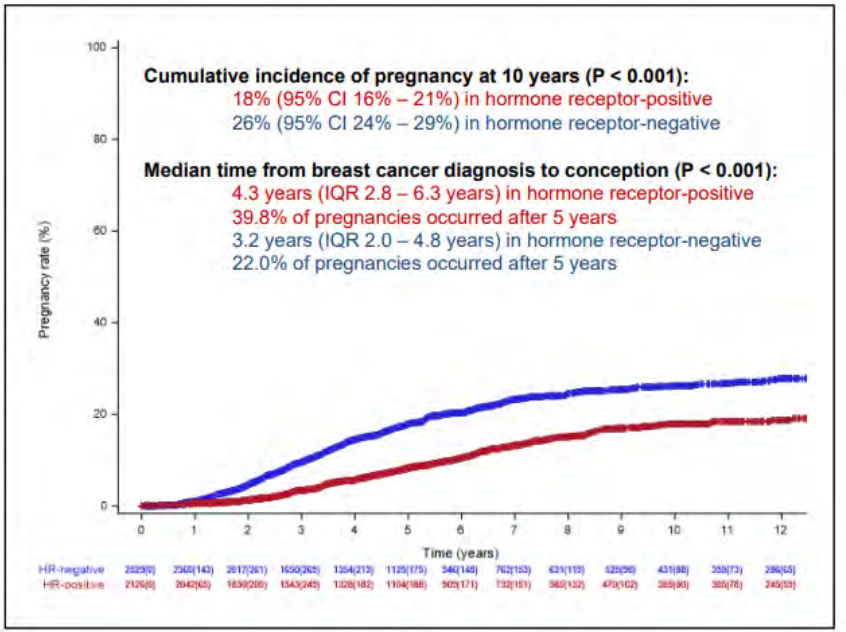
Pregnancy after Breast Cancer in *BRCA* Carriers

Study Results – Cumulative Incidence of Pregnancy

Overall cohort



According to hormone receptor status



Lambertini M, Blondeaux E et al, SABCS 2023 – JAMA 2024;331(1):49-59

Pregnancy after Breast Cancer in *BRCA* Carriers

Study Results – Disease-free Survival

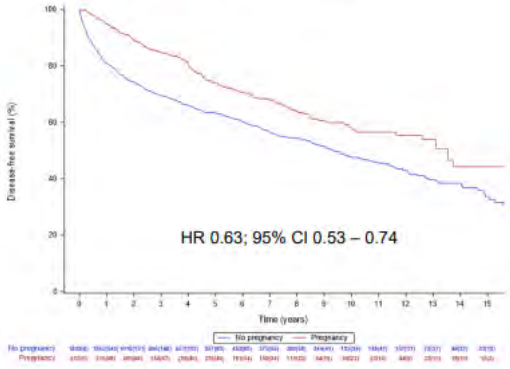
Primary analysis – Extended Cox model with occurrence of pregnancy as a time-varying covariate

Unadjusted HR 0.97; 95% CI 0.82 – 1.15
Adjusted HR* 0.99; 95% CI 0.81 – 1.20

Subgroup analyses	Multivariable HR* (95% CI)	P value for interaction
Specific *BRCA* gene		
BRCA1	0.80 (0.63 – 1.01)	0.007
BRCA2	1.55 (1.12 – 2.16)	
BRCA1 and *BRCA2*	4.49 (0.28 – 72.17)	
BRCA, unknown if 1 or 2	Not evaluable	
Hormone receptor status:		
ER and/or PR positive	1.30 (0.95 – 1.76)	0.009
ER and PR negative	0.76 (0.60 – 0.95)	
Unknown	0.28 (0.04 – 2.21)	
HER2 status:		
HER2 negative	0.61 (0.22 – 1.71)	0.08
HER2 positive	1.07 (0.87 – 1.31)	
Unknown	0.42 (0.17 – 1.02)	
Received chemotherapy:		
No	0.77 (0.39 – 1.52)	0.47
Yes	1.00 (0.82 – 1.23)	
Unknown	0.77 (0.39 – 1.52)	
Received endocrine therapy:		
No	0.85 (0.67 – 1.08)	0.01
Yes	1.55 (1.08 – 2.21)	
Unknown	0.13 (0.01 – 2.95)	

*Adjusted for: region, age, nodal status, hormone receptor status and type of breast surgery

Secondary matched analysis

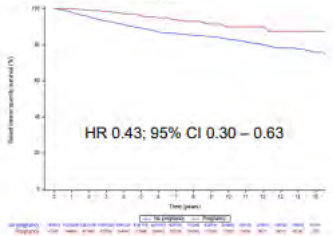


Study Results – Secondary Survival Outcomes

Breast cancer-specific survival

Extended Cox model:
Unadjusted HR 0.53; 95% CI 0.37 – 0.74
Adjusted HR* 0.60; 95% CI 0.40 – 0.88

Secondary matched analysis:

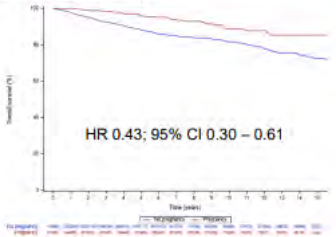


*Adjusted for: region, age, nodal status, hormone receptor status and type of breast surgery

Overall survival

Extended Cox model:
Unadjusted HR 0.52; 95% CI 0.38 – 0.72
Adjusted HR* 0.58; 95% CI 0.40 – 0.85

Secondary matched analysis:

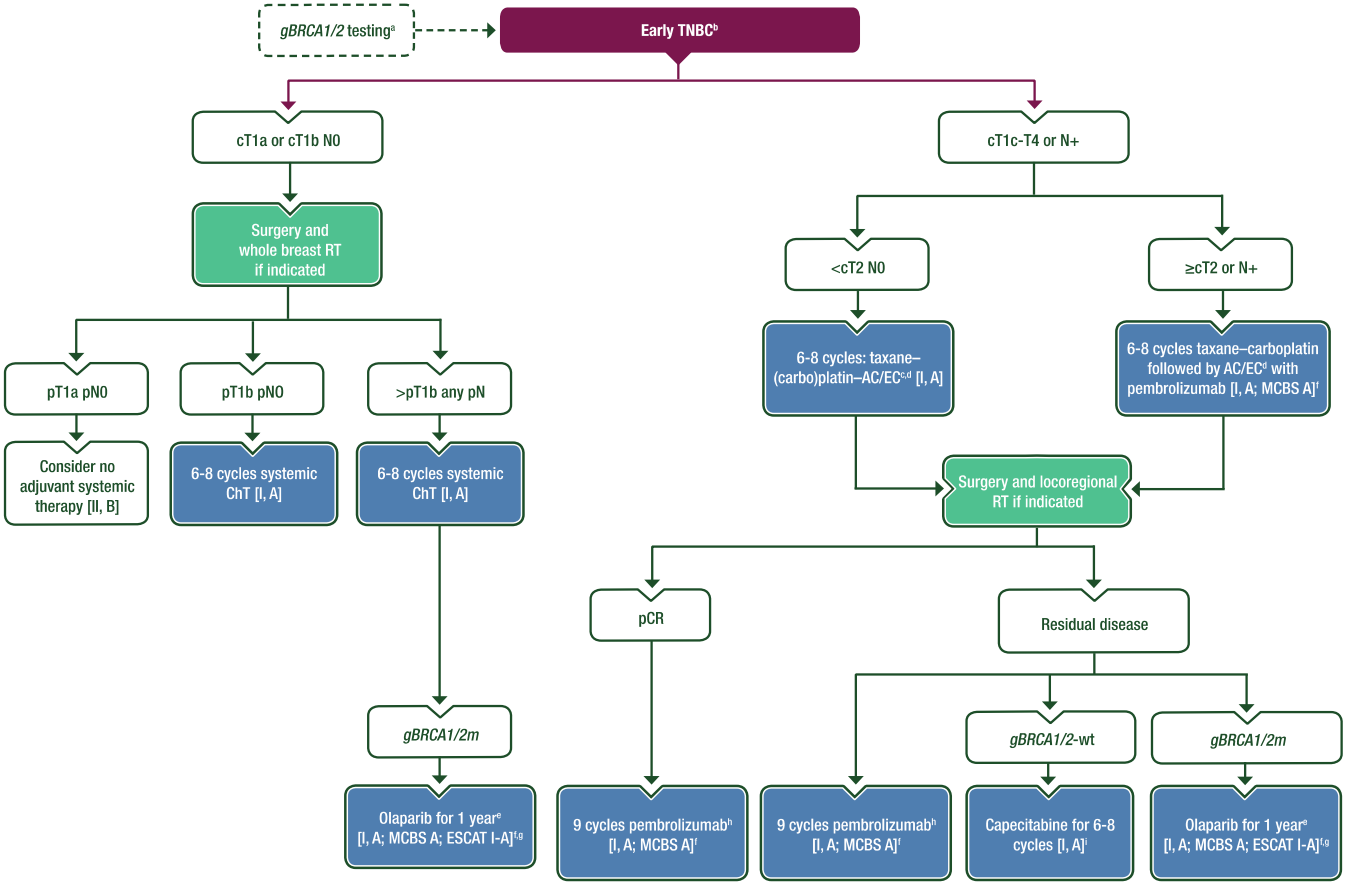


Lambertini M, Blondeaux E et al, SABCS 2023 – JAMA 2024;331(1):49-59

Outline

- Introduction
- Systemic treatment
- Beyond systemic treatment
- **Conclusions**

Conclusions



Loibl S et al, Ann Oncol 2024;35(2):159-82

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