Antoine Lacassagne
CENTRE DE LUTTE CONTRE LE CANCER DE NICE

CANCERS DU SEIN A HAUT RISQUE : Traitements médicaux en 2025

Dr BAILLEUX Caroline

12 Juin 2025

Définition du haut risque ?

Risque de récidive à distance à 5 ans

- < 10 % faible risque
- ≥ 10 % et < 20%: risque intermédiaire
- **> 20 % : haut risque**

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CENTRE DE LUTTE CONTRE LE CANCER DE NICE

HER2 + et Triple négatif

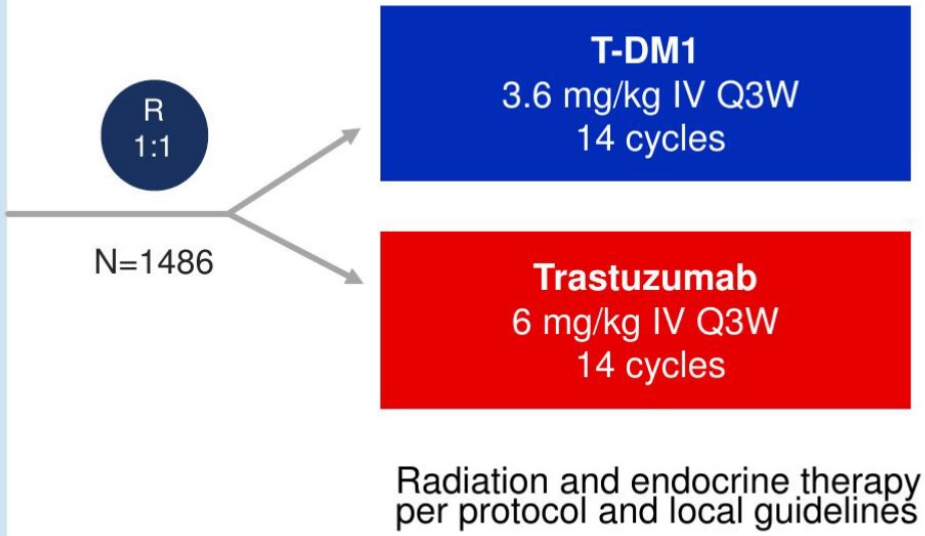
Résidu tumoral après CTNA

Cancers du sein HER2 +

Cancers du sein HER2 +

KATHERINE Study Design

- cT1-4/N0-3/M0 at presentation (cT1a-b/N0 excluded)
- Centrally confirmed HER2-positive breast cancer
- Neoadjuvant therapy must have consisted of
  - Minimum of 6 cycles of chemotherapy
    - Minimum of 9 weeks of taxane
    - Anthracyclines and alkylating agents allowed
    - All chemotherapy prior to surgery
  - Minimum of 9 weeks of trastuzumab
    - Second HER2-targeted agent allowed
- Residual invasive tumor in breast or axillary nodes
- Randomization within 12 weeks of surgery

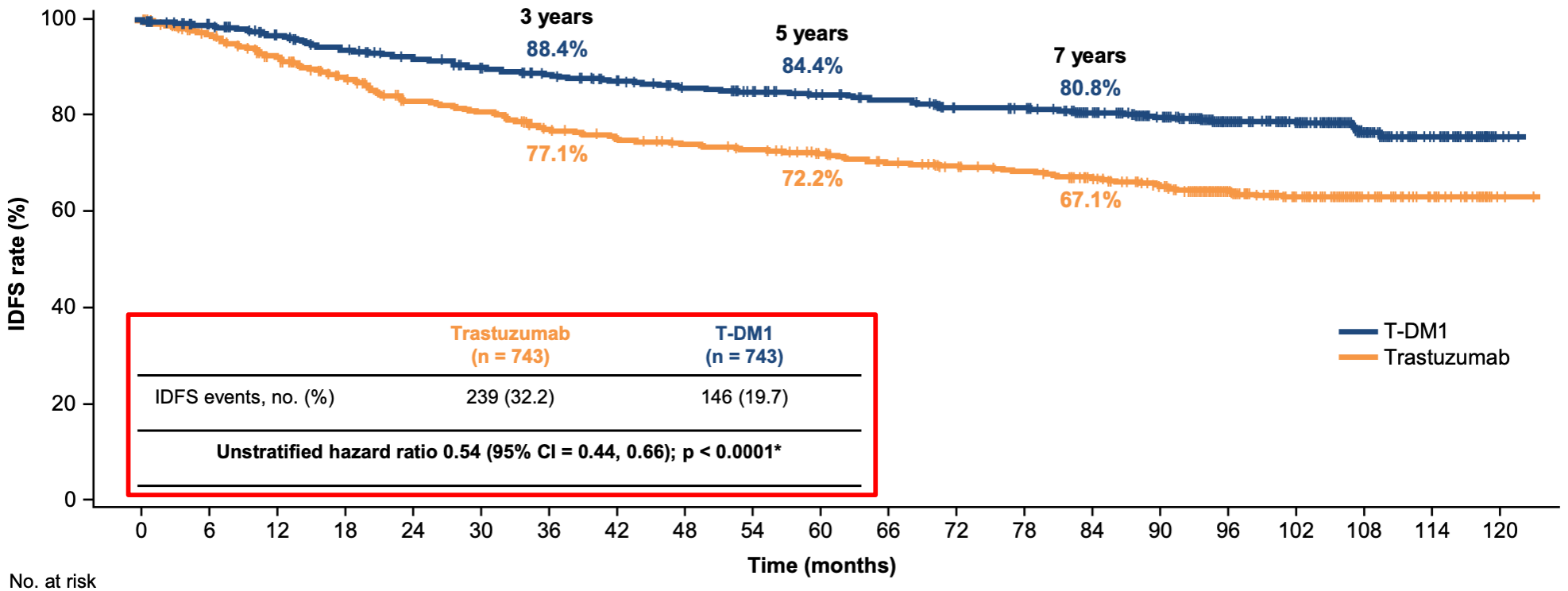


Stratification factors:

- Clinical presentation: Inoperable (stage cT4 or cN2–3) vs operable (stages cT1-3N0-1)
- Hormone receptor: ER or PR positive vs ER negative and PR negative/unknown
- Preoperative therapy: Trastuzumab vs trastuzumab plus other HER2-targeted therapy
- Pathological nodal status after neoadjuvant therapy: Positive vs negative/not done

Loibl et al.
SABCS 2023

KATHERINE IDFS final analysis; median follow-up 8.4 years (101 months)



	Trastuzumab (n = 743)	T-DM1 (n = 743)
IDFS events, no. (%)	239 (32.2)	146 (19.7)
Unstratified hazard ratio 0.54 (95% CI = 0.44, 0.66); p < 0.0001*		

No. at risk																					
Trastuzumab	743	677	636	595	556	540	511	495	485	475	460	444	431	421	397	368	238	187	74	42	2
T-DM1	743	708	682	658	637	620	605	591	574	561	548	537	521	516	481	443	281	236	89	50	3

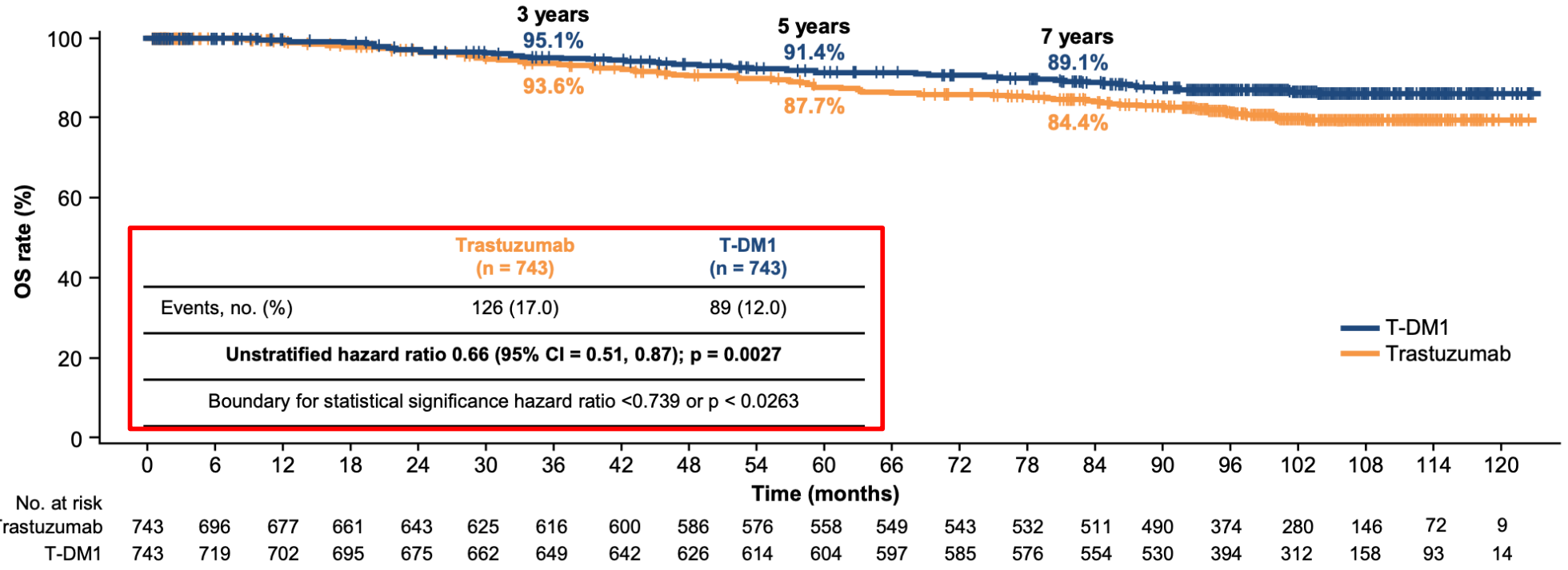
* p-value for IDFS is now exploratory given the statistical significance was established at the primary analysis.
CI, confidence interval; IDFS, invasive disease-free survival; T-DM1, ado-trastuzumab emtansine.

M-CR-00

Loibl et al.
SABCS 2023

San Antonio Breast Cancer Symposium®, December 5–9, 2023

KATHERINE 2nd OS interim analysis; median follow-up 8.4 years (101 months)



Significant reduction in risk of death by 34% with T-DM1

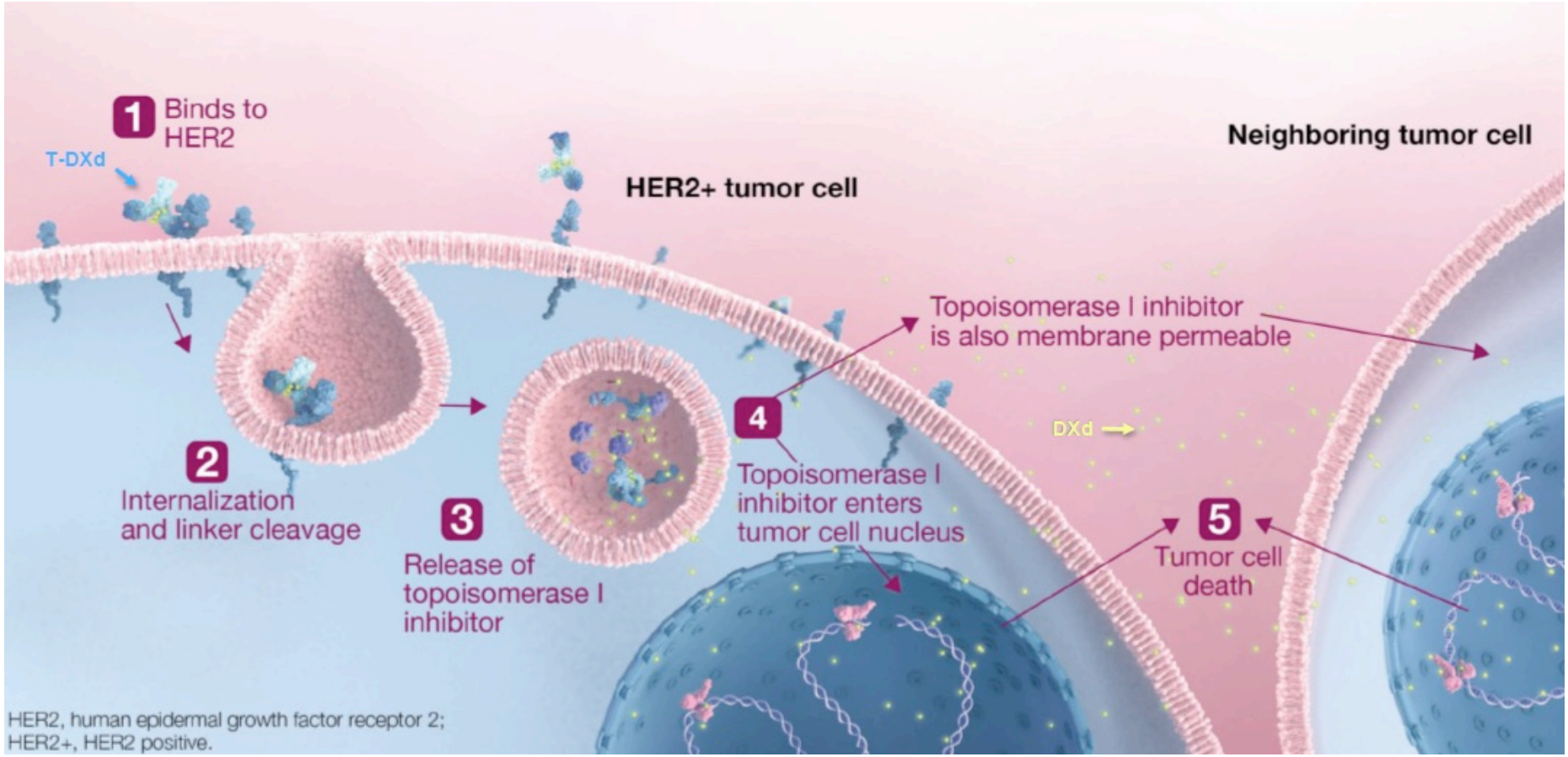
M-CR-00

CI, confidence interval; OS, overall survival; T-DM1, ado-trastuzumab emtansine.

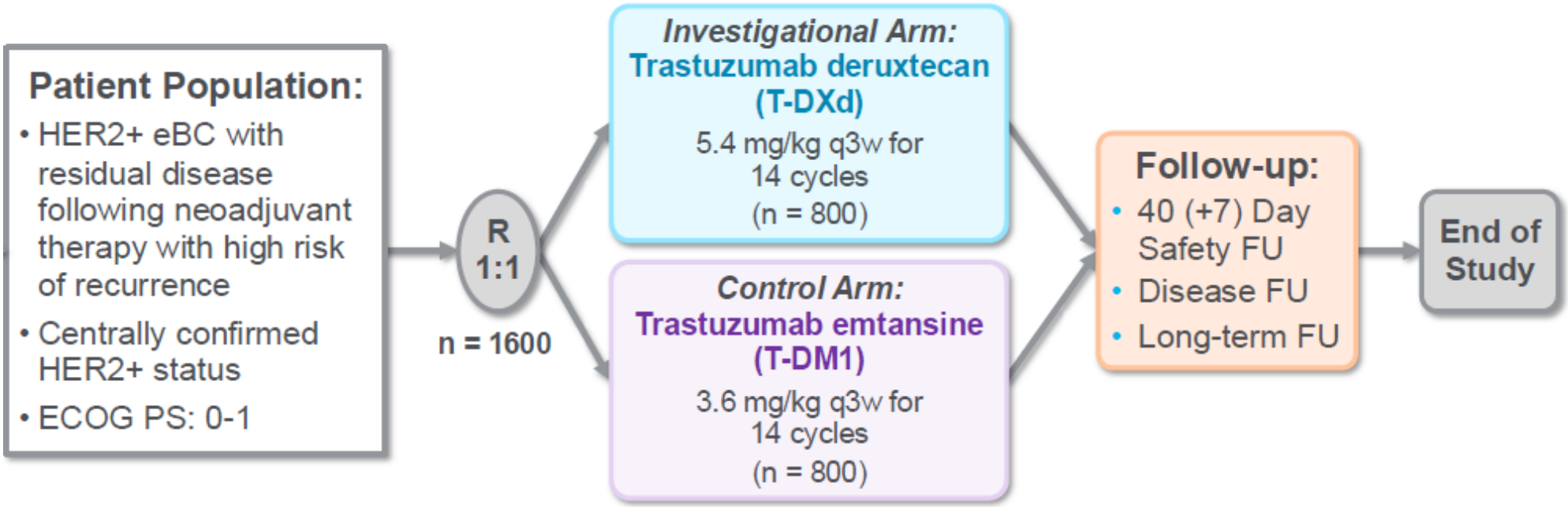
Loibl et al.
SABCS 2023

Cancers du sein HER2 + : à venir ?

Ac conjugués : T-DXd



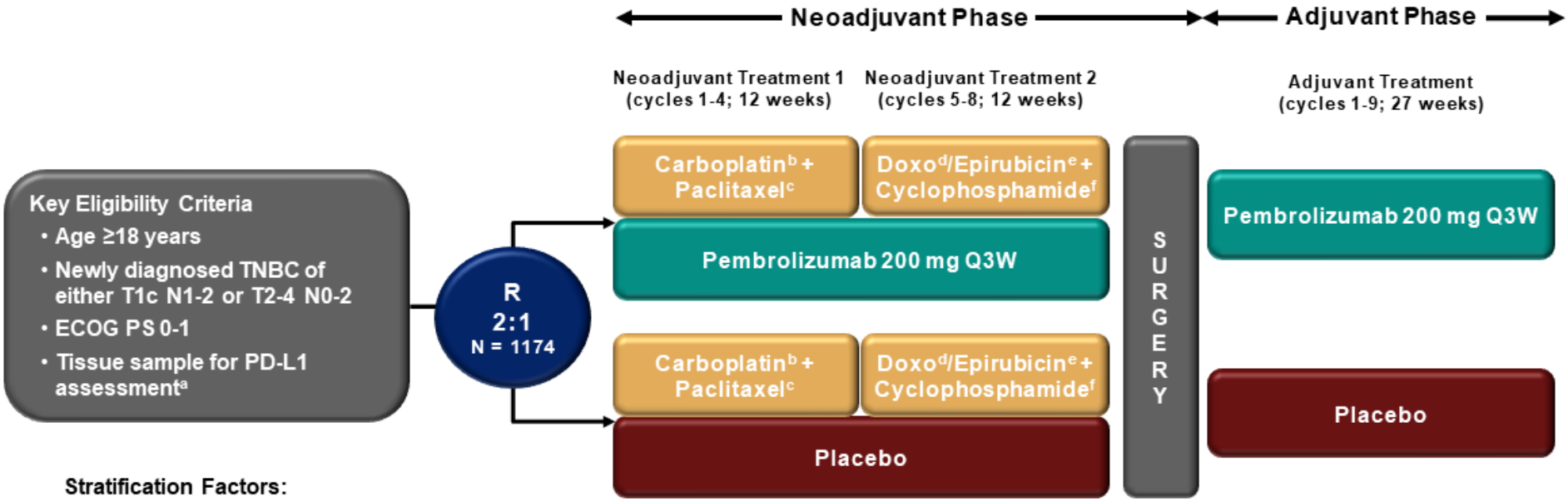
DESTINY-BREAST 05



Cancers du sein TN

Cancers du sein TN

KEYNOTE-522 Study Design (NCT03036488)



Stratification Factors:

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

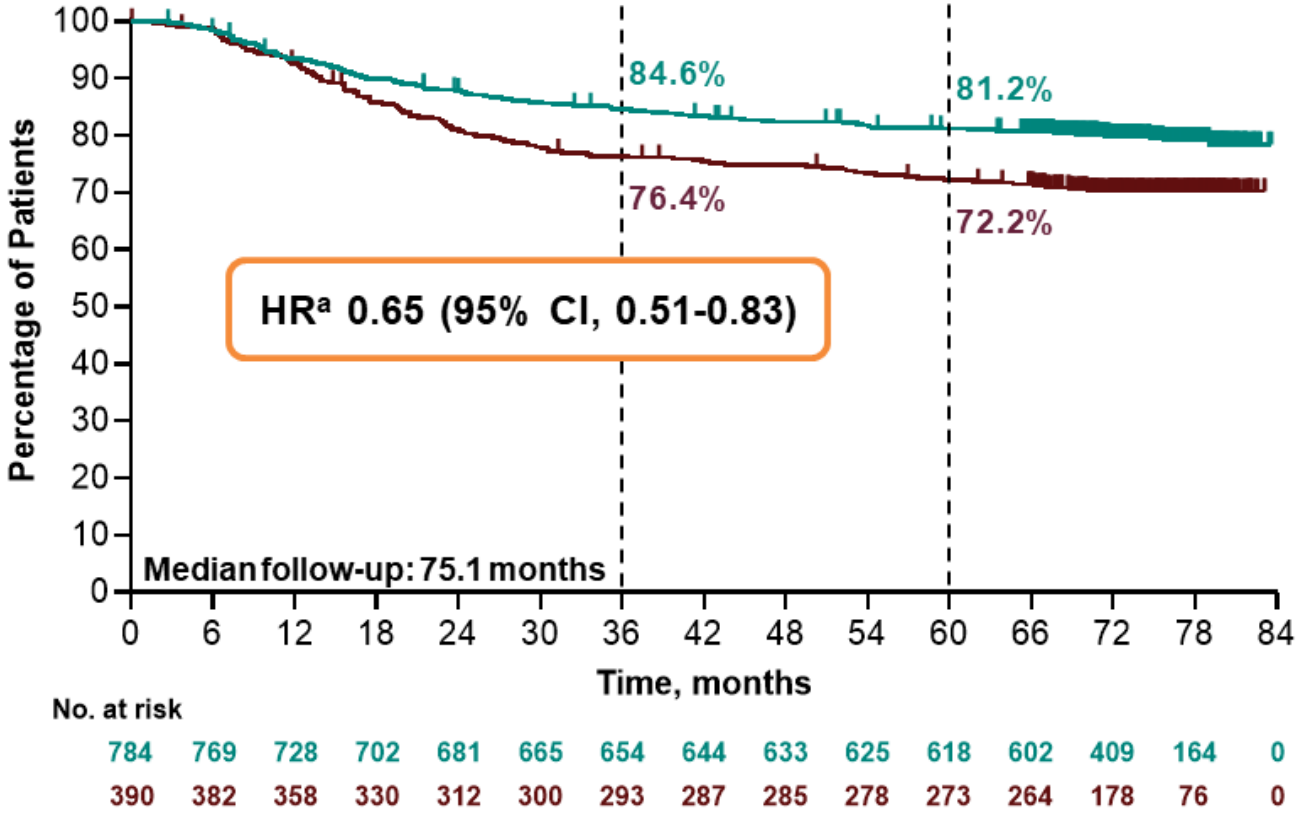
Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post-treatment included)

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

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

Peter Schmid, Esmo 2024

Updated Event-Free Survival

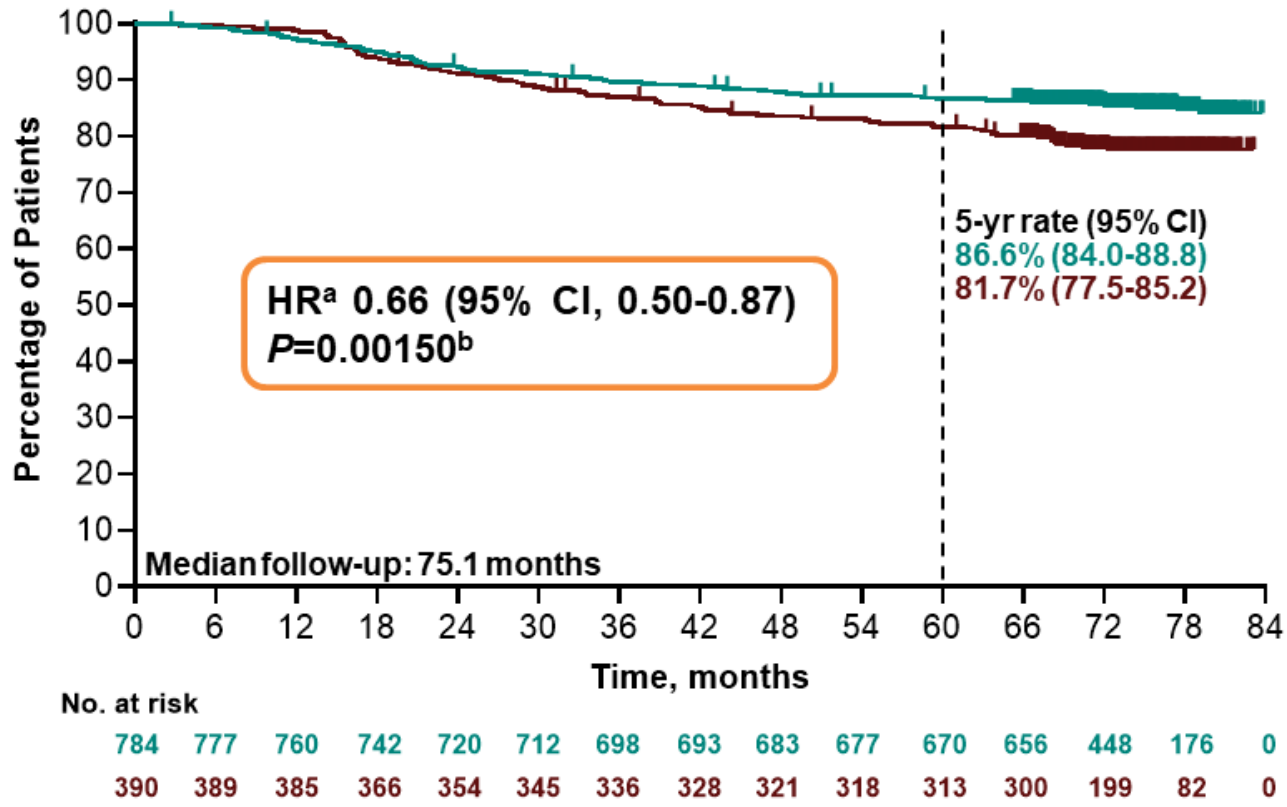


	Pts w/ Event
Pembro + Chemo/Pembro	20.3%
Placebo + Chemo/Placebo	29.2%

[a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. Data cutoff date: March 22, 2024

Peter Schmid, Esmo 2024

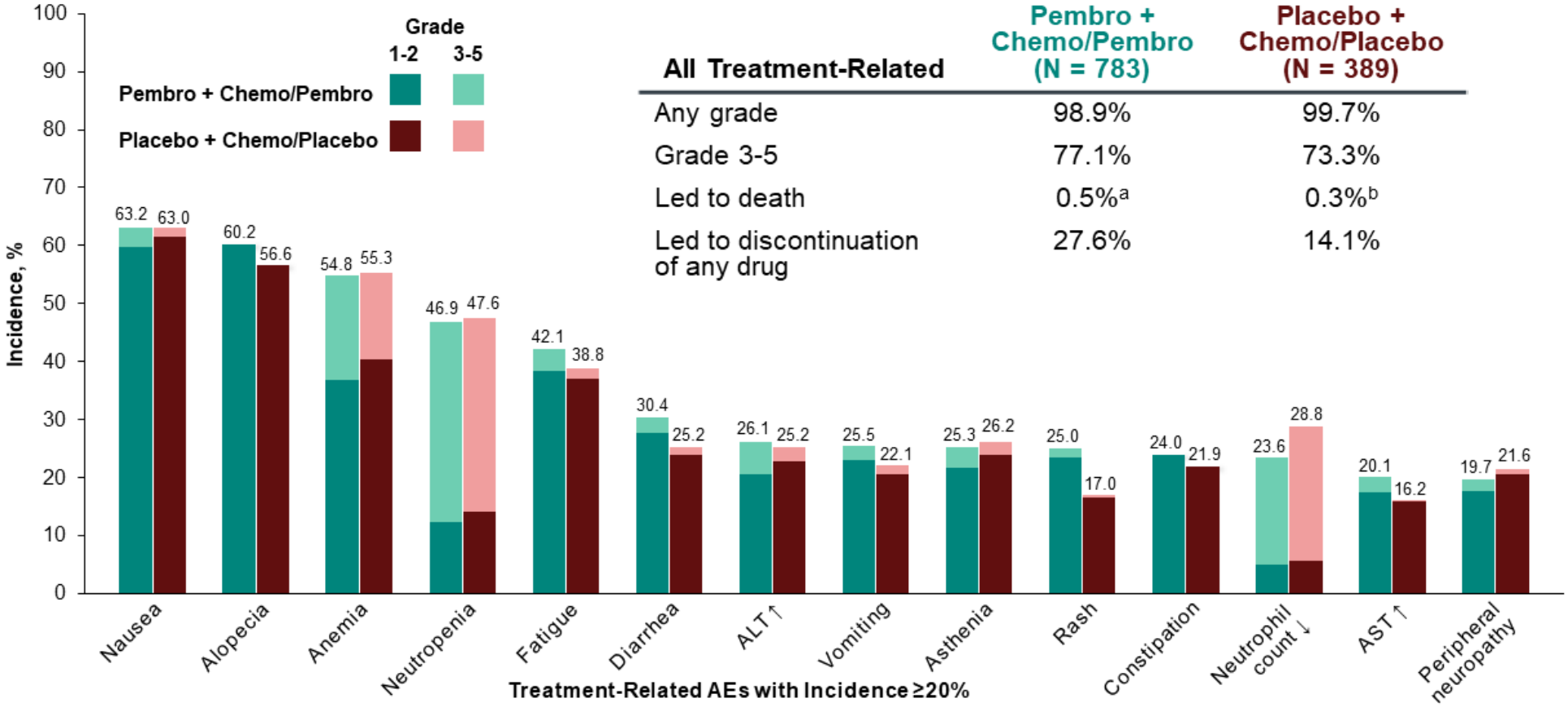
Key Secondary Endpoint: Overall Survival



	Pts w/ Event
Pembro + Chemo/Pembro	14.7%
Placebo + Chemo/Placebo	21.8%

[a]The unstratified piecewise HR was 0.87 (95% CI, 0.57-1.32) before the 2-year follow-up and 0.51 (95% CI, 0.35-0.75) afterwards. The weighted average HR with weights of number of events before and after 2-year follow-up was 0.66. With 200 events (67.3% information fraction), the observed *P*-value crossed the prespecified nominal boundary of 0.00503 (1-sided) at this interim analysis. Data cutoff date: March 22, 2024.

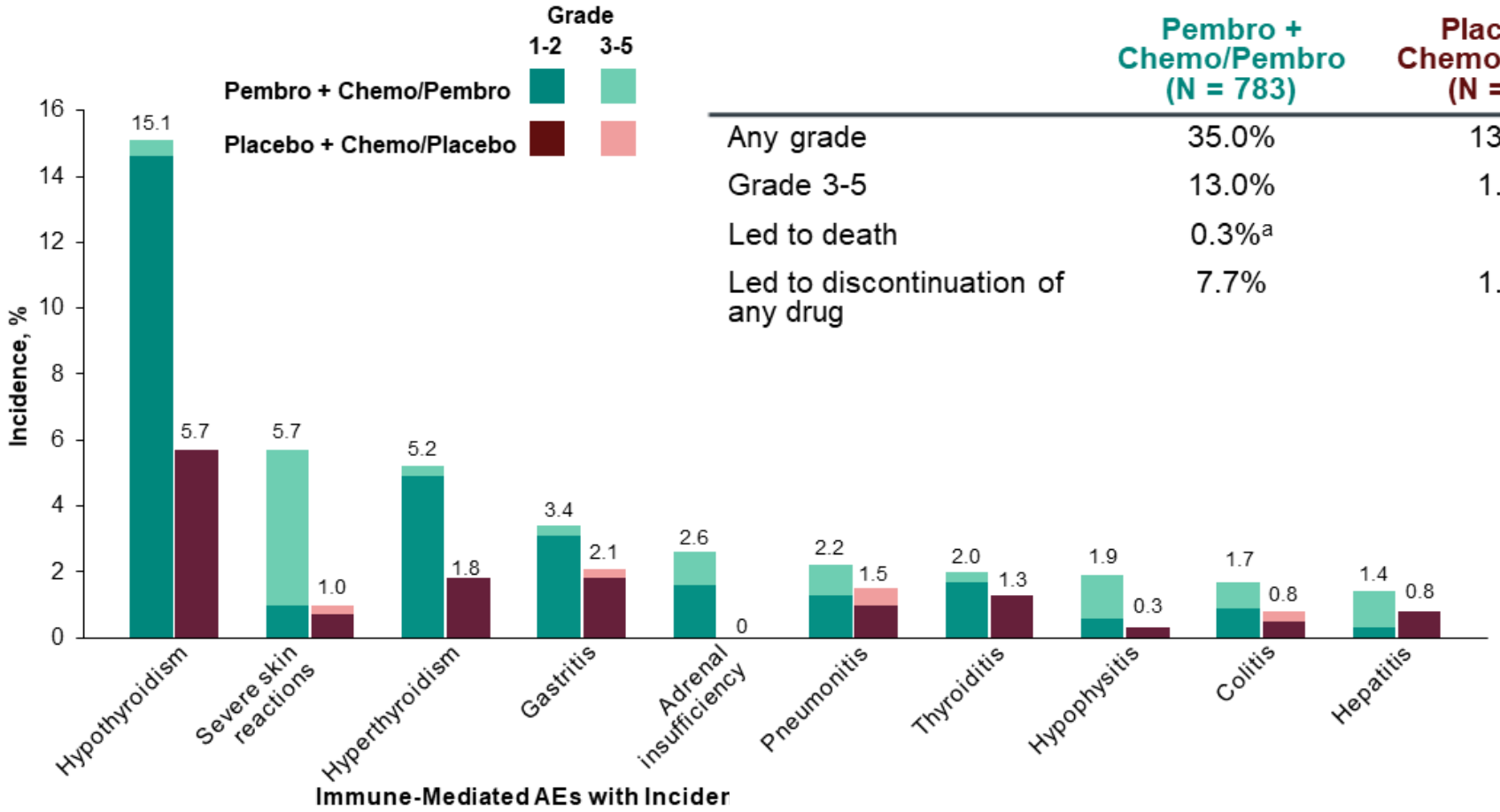
Treatment-Related Adverse Events



All Treatment-Related	Pembro + Chemo/Pembro (N = 783)	Placebo + Chemo/Placebo (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	27.6%	14.1%

[a]1 patient from sepsis and multiple organ dysfunction syndrome; 1 patient from pneumonitis; 1 patient from pulmonary embolism; 1 patient from autoimmune encephalitis. [b]1 patient from septic shock.
Data cutoff date: March 22, 2024.

Immune-Mediated Adverse Events

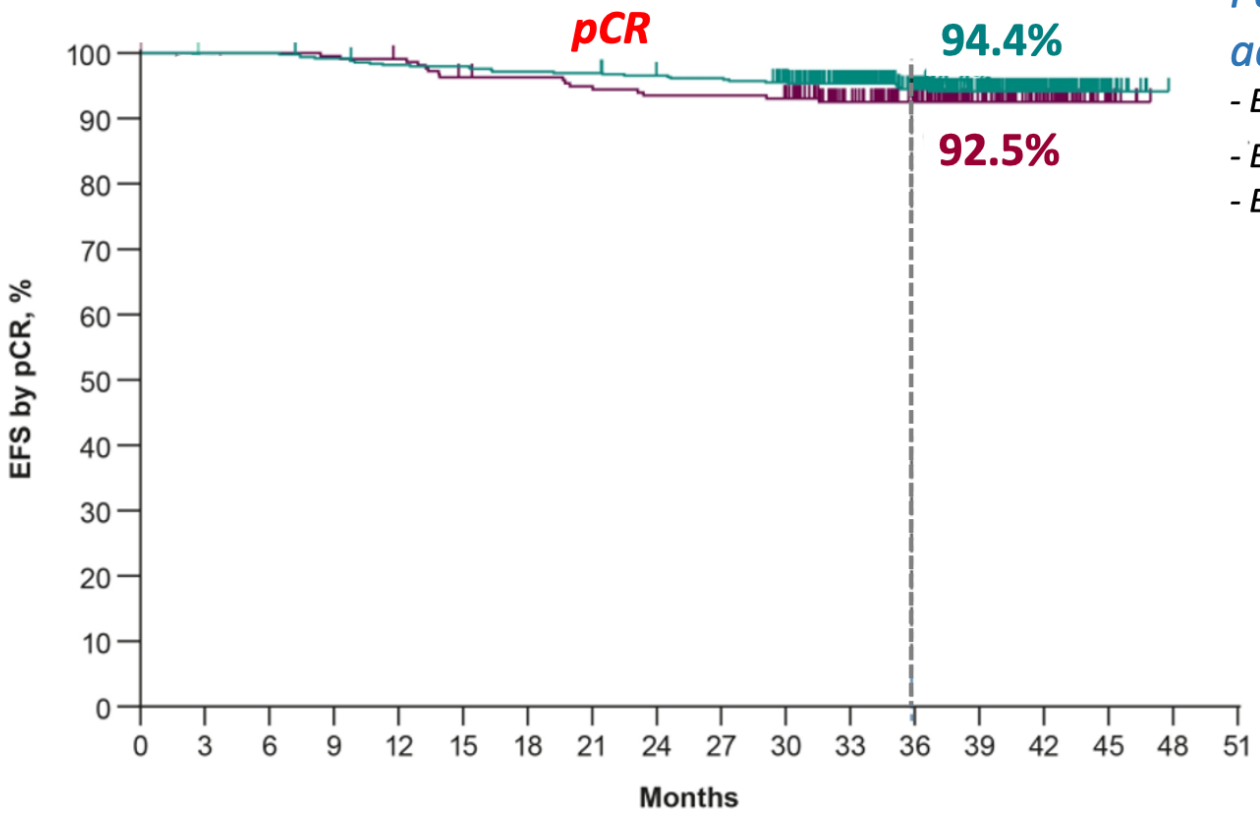


	Pembro + Chemo/Pembro (N = 783)	Placebo + Chemo/Placebo (N = 389)
Any grade	35.0%	13.1%
Grade 3-5	13.0%	1.5%
Led to death	0.3%[a]	0
Led to discontinuation of any drug	7.7%	1.0%

[a]1 patient from pneumonitis and 1 patient from autoimmune encephalitis. Considered regardless of attributi
Data cutoff date: March 22, 2024.

Peter Schmid, Esmo 2024

EFS by pCR

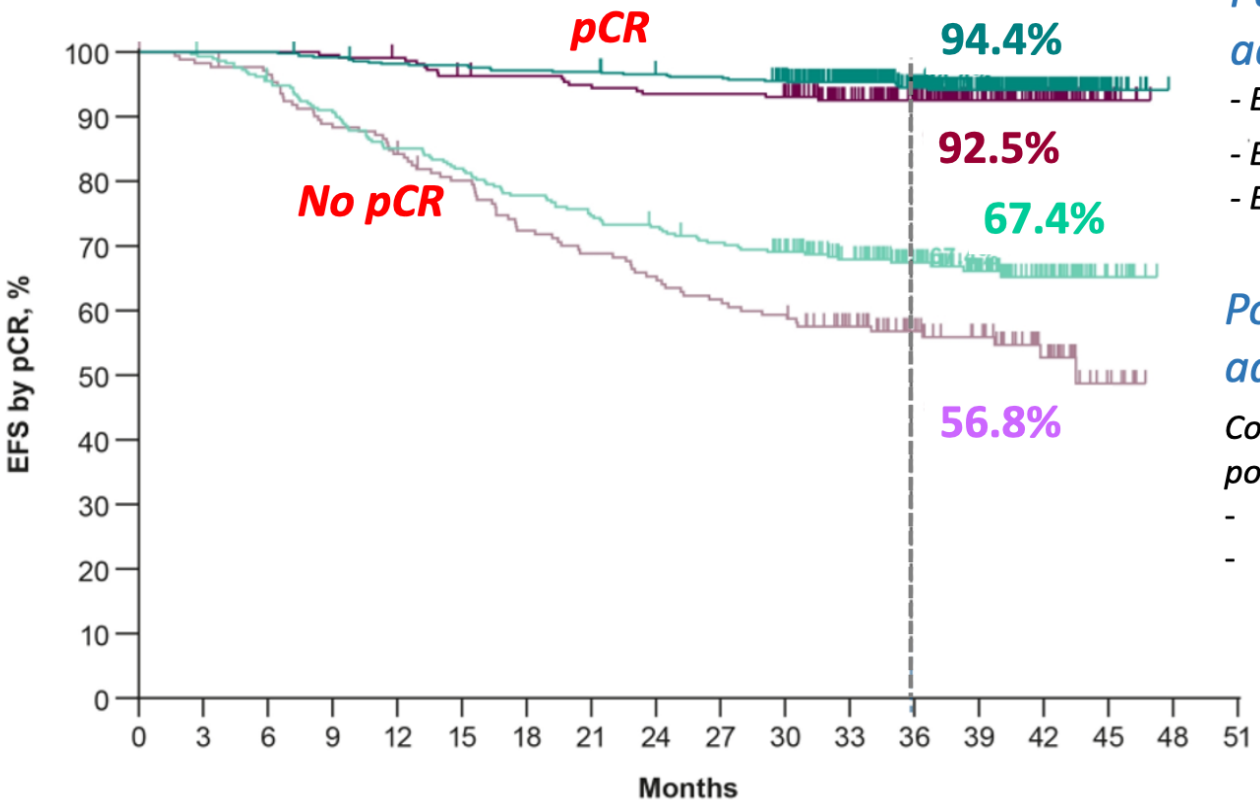


Poursuite du pembrolizumab adjuvant en cas de pCR ?

- *Essai OptimICE-pCR*
- *Essai SWOG 1418: pembro adjuvant si RD*
- *Essai A-BRAVE: Ave adjuvant si RD*

Schmid, *ESMO* 2021

EFS by pCR



Poursuite du pembrolizumab adjuvant en cas de pCR ?

- Essai OptimICE-pCR

- Essai SWOG 1418: pembro adjuvant si RD

- Essai A-BRAVE: Ave adjuvant si RD

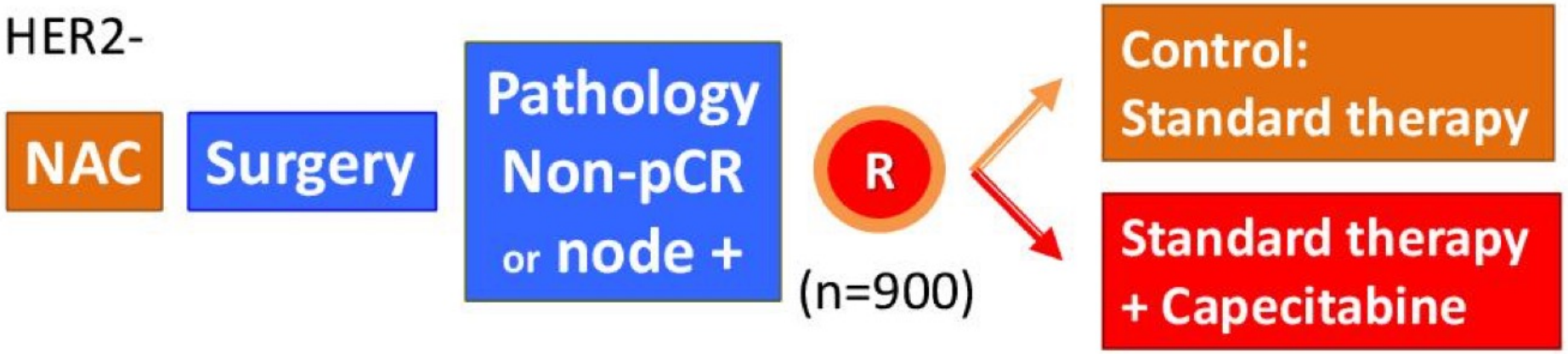
Poursuite du pembrolizumab adjuvant en cas de non pCR

Conciliation avec les autres traitements post néoadjuvant apportant un bénéfice:

- *Capécitabine (all comers) (CAPPA)*
- *Olaparib (gBRCA)*

Schmid, *ESMO* 2021

CREATE-X: Trial Design

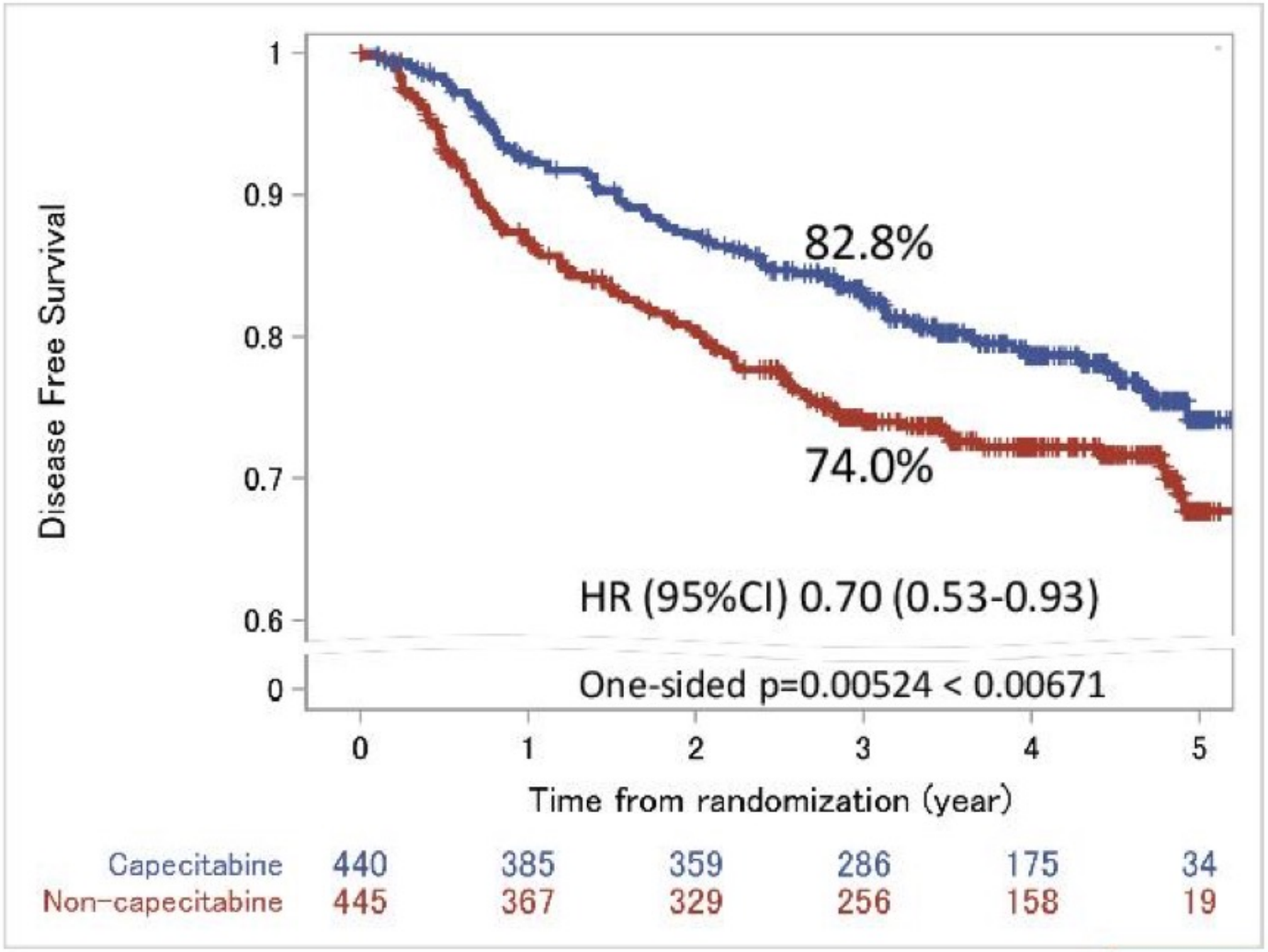


Stratification factors:
ER, Age, NAC, ypN,
5FU and institution

Standard therapy:
HR+: Hormone therapy
HR-: No further systemic treatment

Lee S-J. et al., SABCS 2015, S1-07

CREATE-X: Disease free Survival



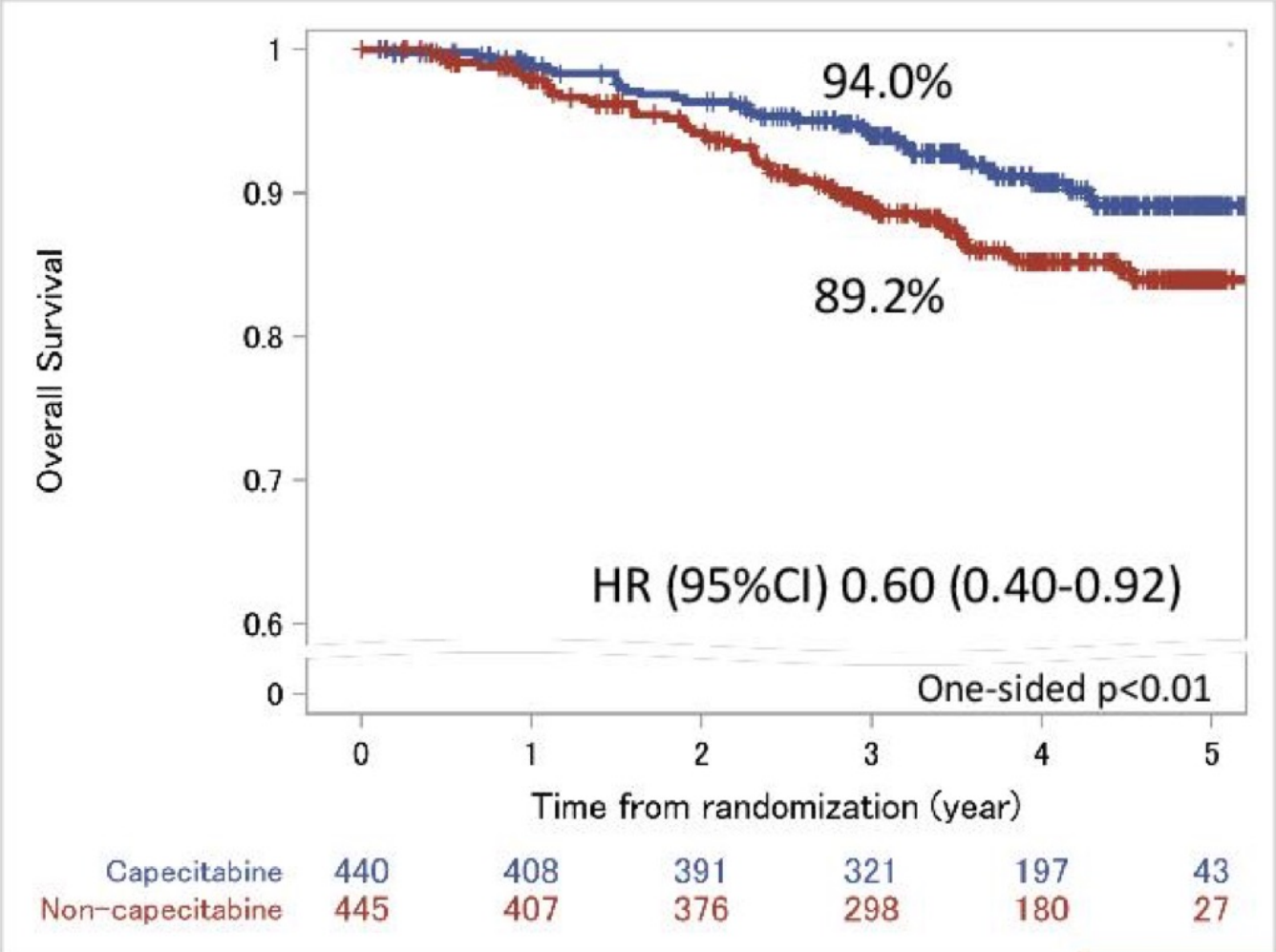
5yr DFS

74.1% Capecitabine

67.7% Control

Lee S-J. et al., SABCS 2015, S1-07

CREATE-X: Overall Survival



5yr OS

89.2% Capecitabine

83.9% Control

Lee S-J. et al., SABCS 2015, S1-07

Question 49 : Cancers du sein précoces RH- et HER+

2024

- Après traitement néoadjuvant selon les modalités de l'étude KEYNOTE-522 et de maladie résiduelle, il est acceptable après discussion en RCP du rapport bénéfice/risque et discussion avec la patiente, d'initier un traitement par capécitabine pour une durée de 6 mois concomitamment à la poursuite du pembrolizumab adjuvant.

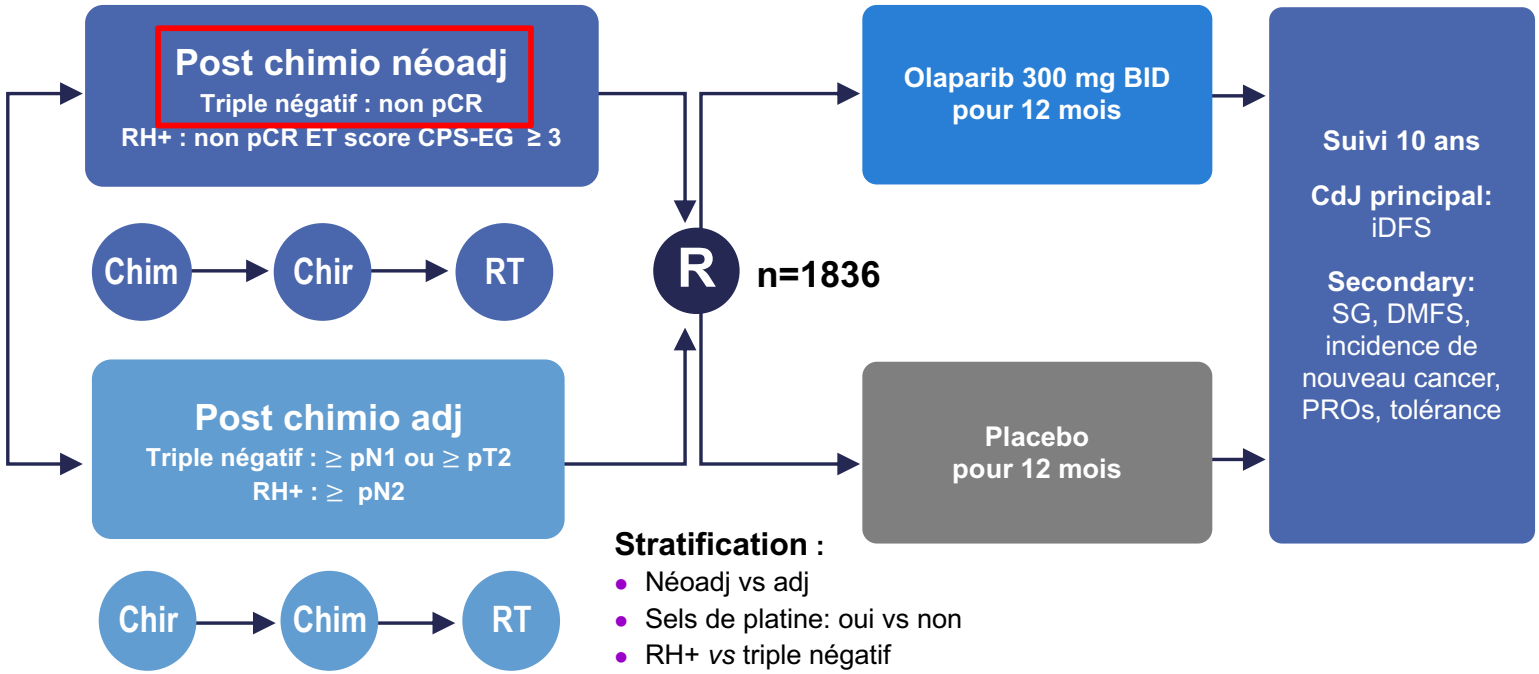
	D'accord	Pas d'accord	Abstention
Experts	58%	8%	33%
Salles	75%	16%	9%

On attend avec impatience l'ouverture de l'étude CAPPA …

OLYMPIA

Olaparib en adjuvant pour les patients porteurs de mutation BRCA1 ou BRCA2 avec cancer du sein à haut risque

- Cancer du sein HER2 négatif à haut risque avec mutation germinale de BRCA1 ou 2
- Après chimio (néo)adjuvante au moins 6 cycles avec anthracycline et/ou taxanes
- ECOG 0-1
- Pas de dysfonction d'organe



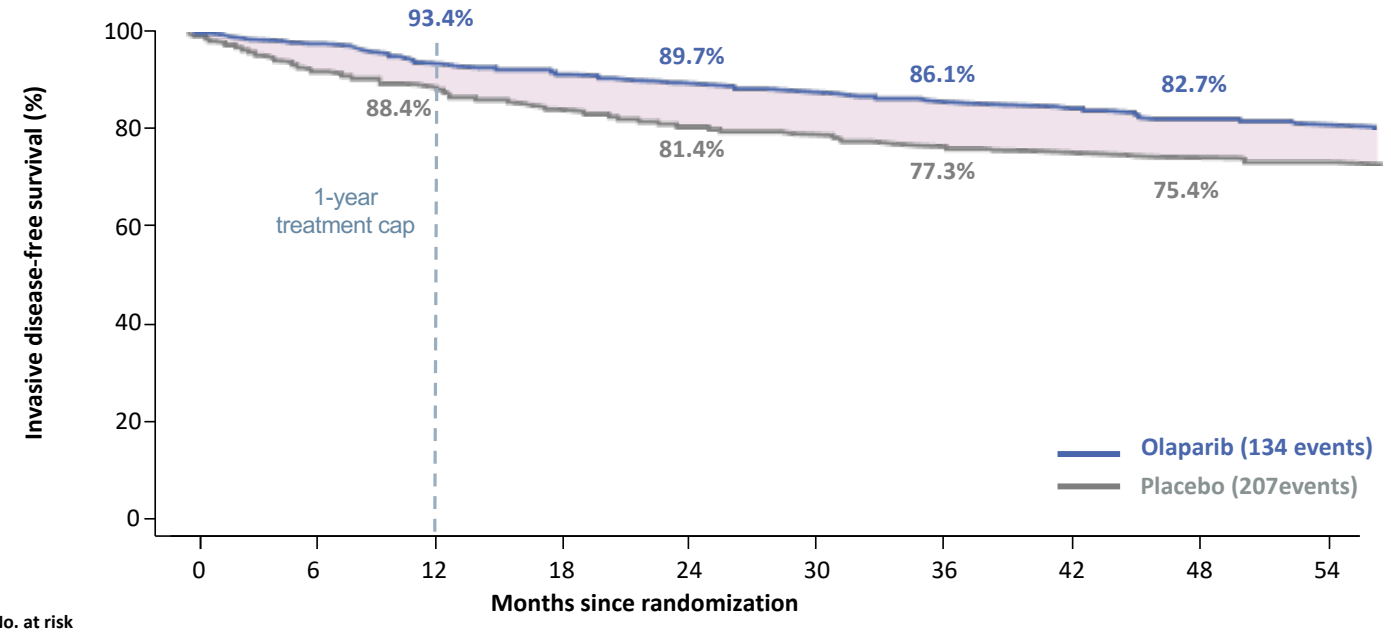
iDFS : Survie sans maladie invasive ; SG : Survie globale ; DMFS : Survie sans métastases à distance ; PROs : critères rapportés par les patients

A.N.J. Tutt, et al., ASCO2021, Abs #LBA1

OLYMPIA

IDFS benefit associated with olaparib was maintained with 1-year additional follow-up†

Exploratory Analysis



HR 0.63
95% CI 0.50–0.78

No. at risk										
Olaparib	921	825	777	738	694	603	495	382	293	204
Placebo	915	807	765	715	656	571	459	370	293	187

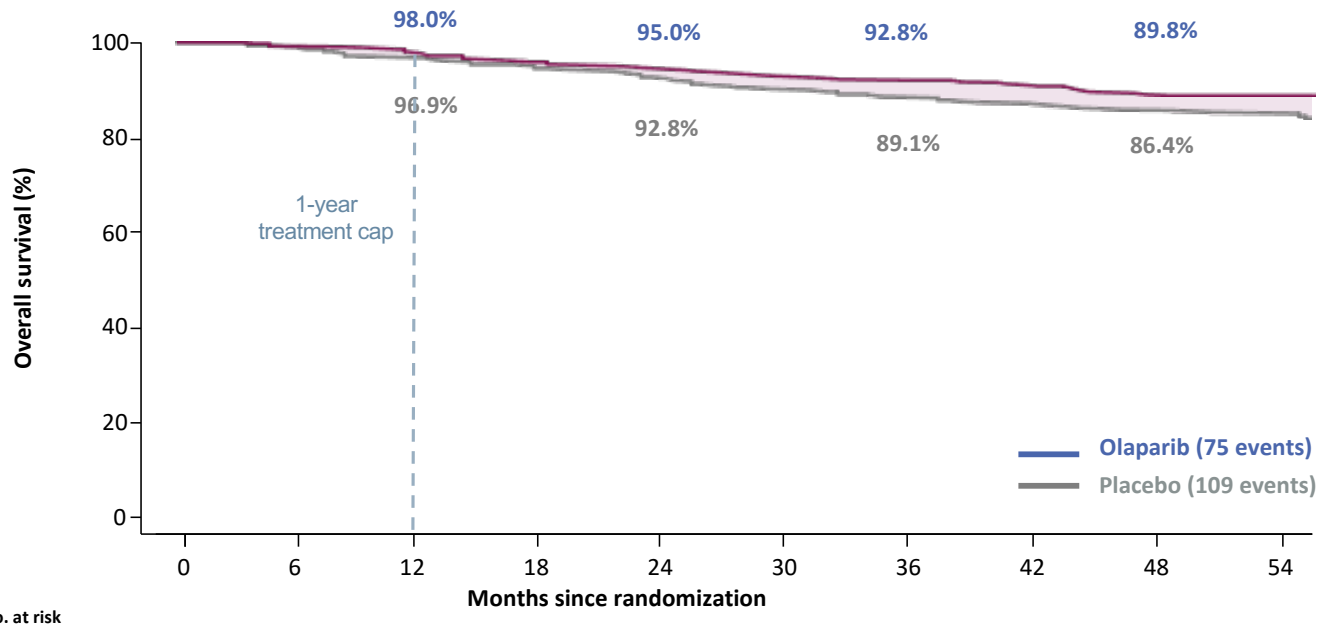
- †IDFS analysis is descriptive at OS IA2; ‡DCO2 12 July 2021 (at 330 IDFS events, 25% data maturity)
- Tutt J, Garber J, Gelber R, et al. Pre-specified event driven analysis of Overall Survival in the OlympiA Phase III trial of adjuvant olaparib in germline BRCA1/2 mutation associated breast cancer. [Presentation]. Presented at ESMO Virtual Plenary; March 16-18, 2022.

ABBREVIATIONS

OLYMPIA

Olaparib demonstrated a significant OS benefit with 90% of patients alive at 4-years in the olaparib arm

Secondary endpoint: overall survival



No. at risk										
Olaparib	921	862	844	809	773	672	560	437	335	228
Placebo	915	868	843	808	752	647	530	423	333	218

OS at DCO2

HR 0.68†
98.5% CI 0.47–0.97
p=0.009

4-year OS rate

Olaparib (n=921)	**89.8%**
Placebo (n=915)	**86.4%**

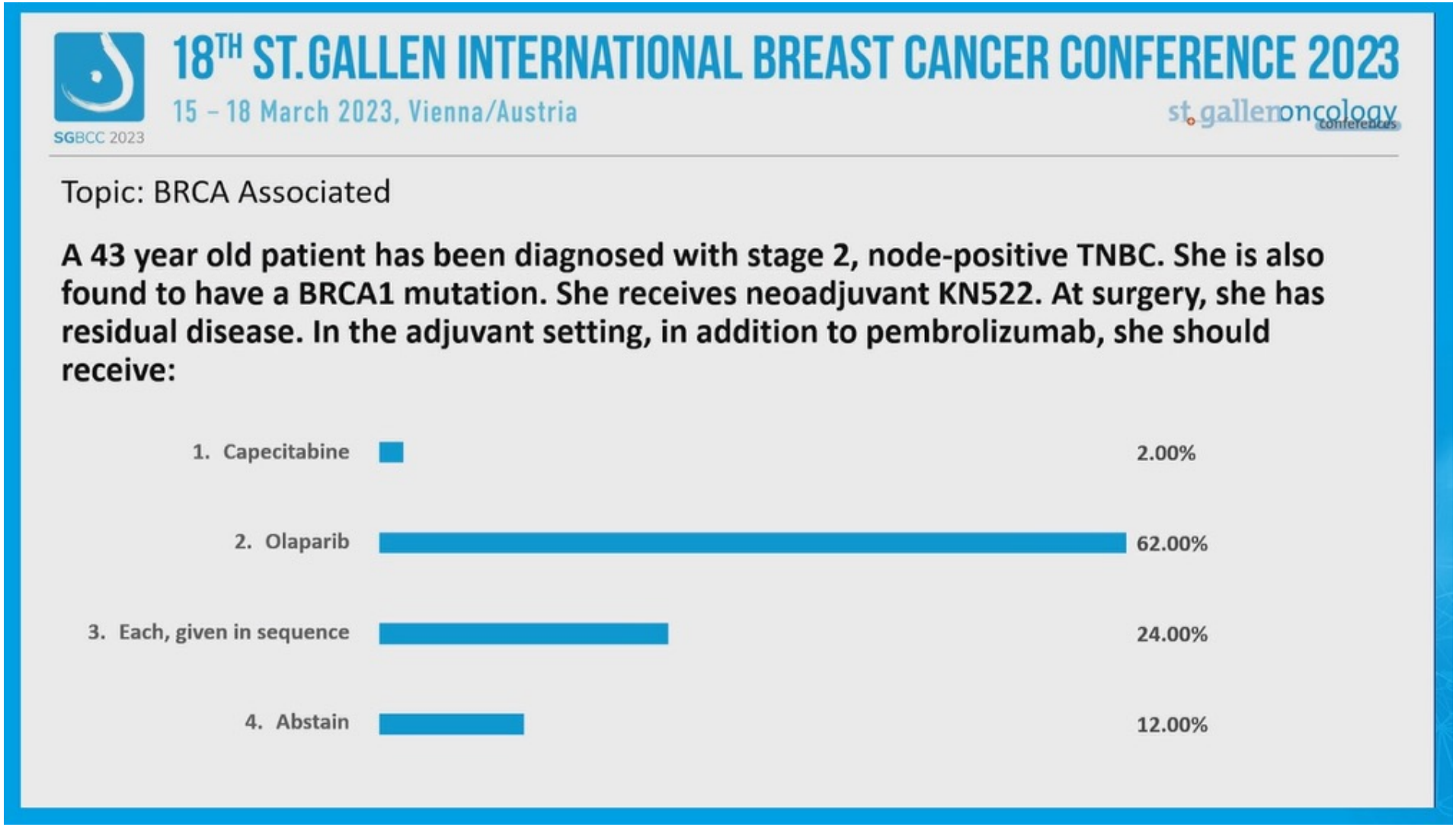
Difference 3.4%
95% CI -0.1–6.8

- *Data from the pre-specified second interim analysis of OS (at ~330 IDFS events); cut-off date July 2021 (DCO2), data maturity 9%; †Non-proportional hazards; 98.5% CI is shown for the HR for OS because p<0.015 is required to indicate statistical significance for this endpoint

1. Tutt A, Garber J, Gelber R, et al. Pre-specified event driven analysis of Overall Survival in the OlympiA Phase III trial of adjuvant olaparib in germline BRCA1/2 mutation associated breast cancer. [Presentation]. Presented at ESMO Virtual Plenary; March 16-18, 2022 2. In House Data, AstraZeneca. Data on file SD-2020-ALL-0088

ABBREVIATIONS

PEMBROLIZUMAB + OLAPARIB ?



On attend avec impatience l'ouverture de l'étude PEMBOLA …

Cancers du sein TN : à venir ?

Cancers du sein TN : à venir ?

2 stratégies en cours d'exploration ADC + Immunothérapie :

- Renforcer le traitement néoadjuvant pour tous
- Renforcer le traitement adjuvant uniquement pour les patientes en l'absence de réponse complète

Cancers du sein TN : à venir ?

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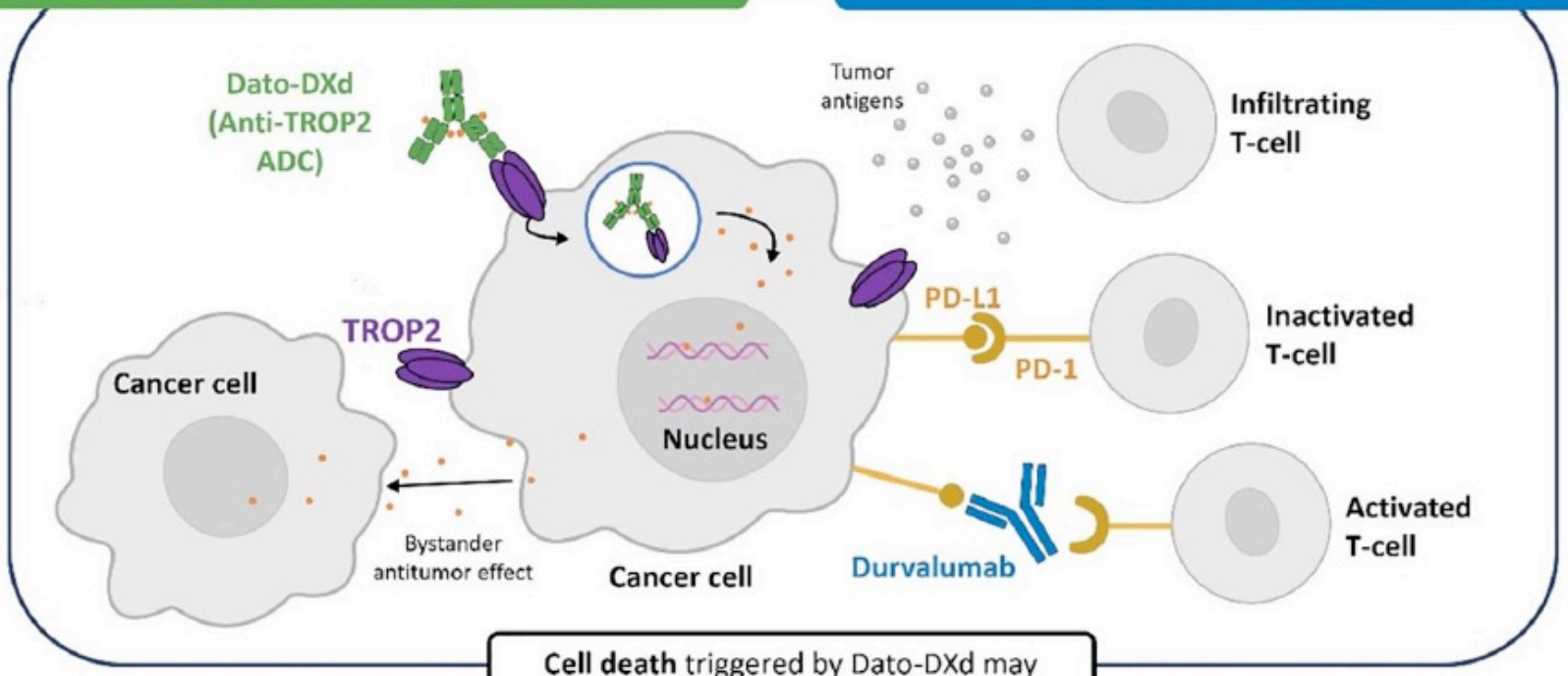
TROPION BREAST-04

Dato-DXd binds to TROP2, is internalized into cancer cells and releases a DNA topoisomerase-I inhibitor payload, leading to DNA damage and apoptosis

Durvalumab blocks PD-L1 binding with PD-1/CD80 (B7.1), preventing immune suppression and maintaining antitumor activity

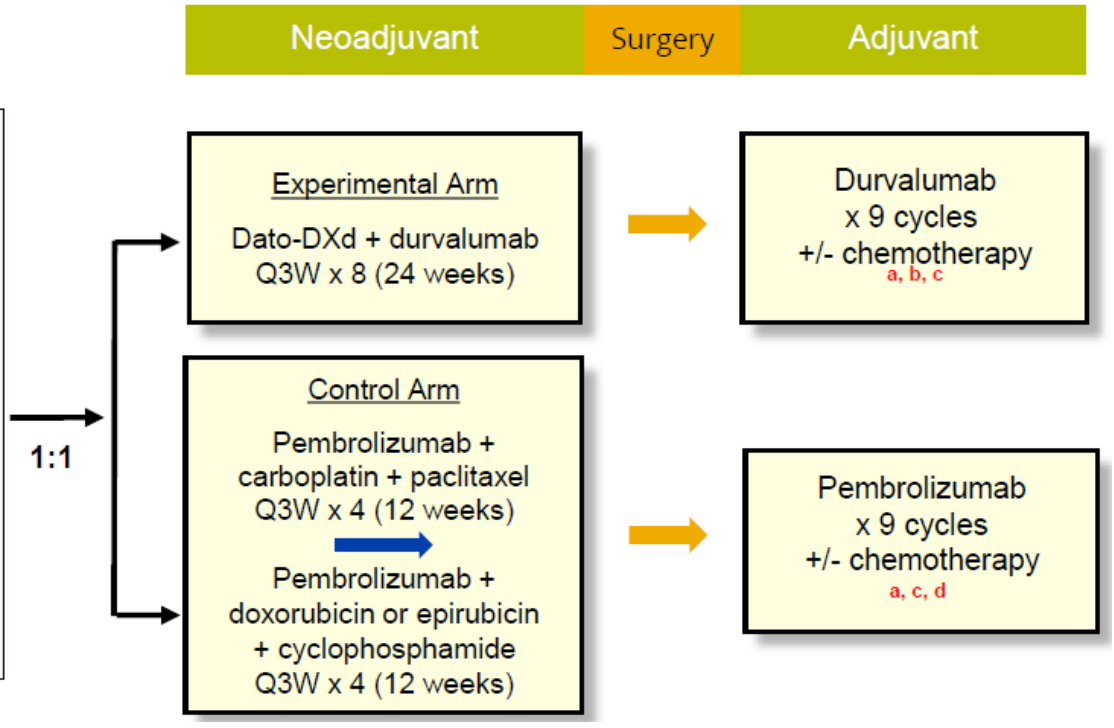


Cell death triggered by Dato-DXd may **promote T-cell recruitment and activation,** enhancing the effects of durvalumab

TROPION : BREAST 04

Key Eligibility Criteria

- Histologically confirmed Stage II or III unilateral or bilateral primary invasive breast cancer.
- TNBC (ER and PR < 1%) or hormone receptor-low breast cancer (ER and/or PR 1% to < 10%, neither hormone receptor may be ≥ 10%), and HER2-negative. [e, f]
- No evidence of distant disease.
- No prior surgery, radiation, or systemic anticancer therapy.
- ECOG PS 0 or 1.
- Adequate hematologic and organ function.



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2 stratégies en cours d'exploration ADC + Immunothérapie :

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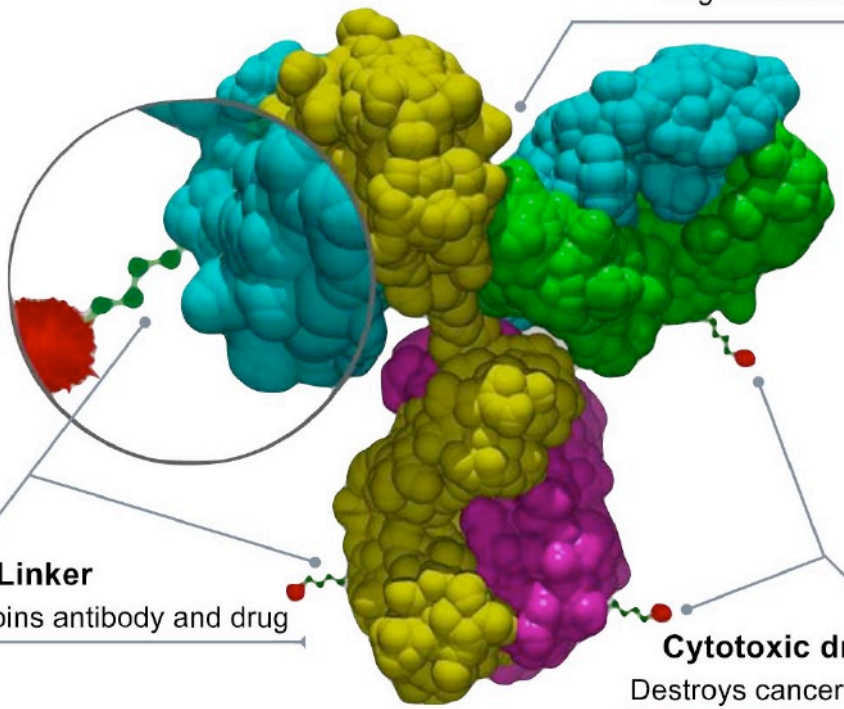
Sacituzumab tirumotecan (sac-TMT)



Antibody
Targets cancer cells

- TROP2
- Overexpressed on cancer cells
- Elevated TROP2 expression associated with tumor invasion, aggression, progression, and metastasis

- TL033
- Designed to optimize ADC stability
- Bystander effect

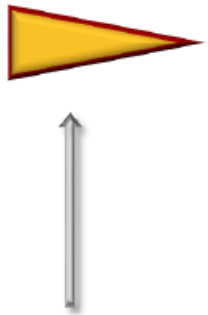
Linker
Joins antibody and drug

Cytotoxic drug
Destroys cancer cells

- Topoisomerase I inhibitor belotecan derivative
- Arrest cell cycle at the G2/S stage, leading to cell death
- Average DAR 7.4 (7-8)

TROFUSE

- Centrally confirmed TNBC (ER<1%, PR<1%, HER2-)
- Non-pCR after at least 5 cycles of pembrolizumab and chemotherapy, including 1 cycle of anthracycline-based neoadjuvant therapy
- Randomization within 12 weeks of definitive surgery
- Adjuvant RT if indicated, completed before randomization



RANDOMIZATION 1:1

Arm 1

Pembrolizumab 400 mg q6w x 5 doses
+
sac-TMT 4 mg/kg q2w x 12 doses

Arm 2

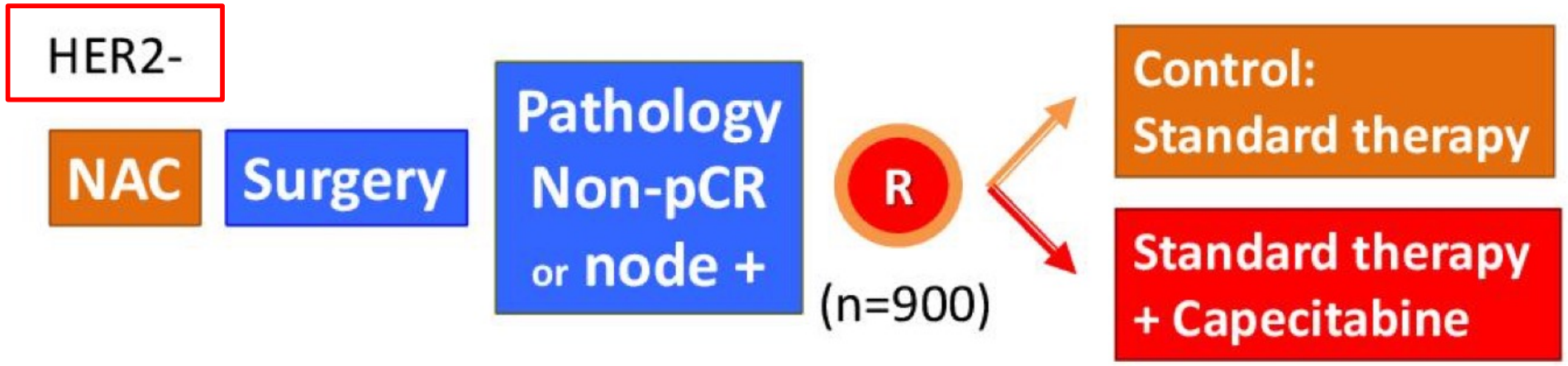
Treatment of Physician's Choice (TPC)
Pembrolizumab 400 mg q6w x 5 doses
or
Pembrolizumab 400 mg q6w x 5 doses and capecitabine 1000 mg/m2 to 1250 mg/m2 BID on Days 1-14 and Days 22-35 every 42 days x 4 (2 weeks on, 1 week off)

Stratification factors

1. Residual tumor and lymph node status:
   a. [Tumor < 1 cm (ypT1mi – T1b), ypN0] (capped at ~15%)
   vs
   b. [Tumor ≥ 1 cm (ypT1c+), ypN0] or [No tumor or tumor < 1 cm (ypT0 – T1b), ypN1]
   vs
   c. [Tumor ≥1 cm (ypT1c+), ypN1] or [No tumor or any tumor size (ypT0+), ypN2+]
2. TROP2 expression per IHC (low vs medium vs high).
3. Intention to use capecitabine (yes [capped at ~60%] vs no)

Cancers du sein RH + à haut risque
Quelles armes thérapeutiques en plus de l'OLAPARIB et de la CAPECITABINE

CREATE-X: Trial Design



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Lee S-J. et al., SABCS 2015, S1-07

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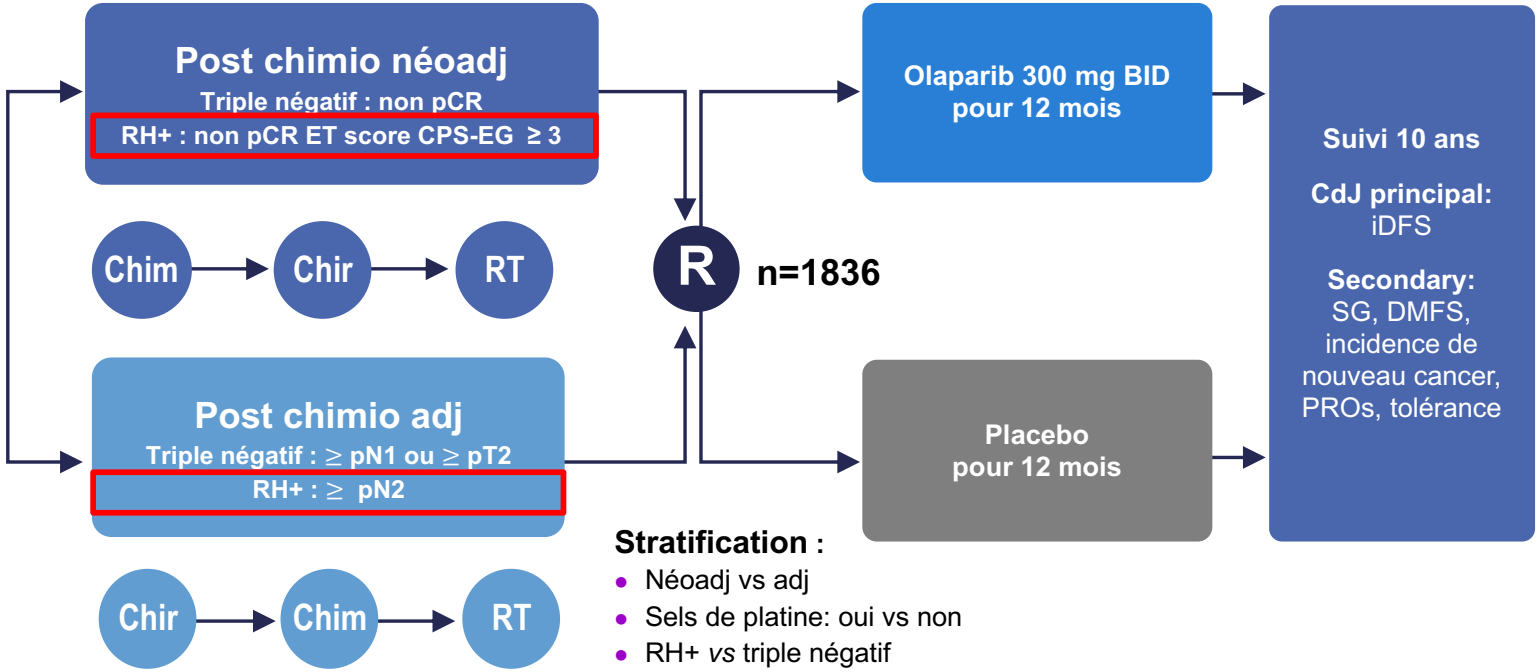

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A.N.J. Tutt, et al., ASCO2021, Abs #LBA1

CDK4/6 Inhibiteurs en adjuvant : les études

	PALLAS[1,2]	PENELOPE-B[3,4]	monarchE[5,6]	NATALEE[7,8]
N	5796	1250	5637	5101
Sex	Men and women	Women	Men and women	Men and women
Menopausal status	Pre- and postmenopausal	Pre- and postmenopausal	Pre- and postmenopausal	Pre- and postmenopausal
Disease severity	• Stage II • Stage III • N0, N1, N2, N3	• Residual invasive disease after neoadjuvant therapy ≥16 weeks (including 6 weeks of taxane) • CPS-EG ≥3 or score 2 if ypN+ • N0, N1, N2, N3	• Cohort 1: ≥4 ALN or 1-3 ALN + tumor size ≥5 cm and/or grade 3 • Cohort 2: 1-3 ALN + Ki-67 ≥20%	• Stage III (N0 and N1) • Stage IIB and IIA N1 • Stage IIA N0 G3 or N0 G2 with Ki-67 ≥20% or high risk by genetic test • Stage II pts capped at 40% of enrollment
CDK4/6i, dose	PAL 125 mg QD* (3 weeks on/1 week off)	PAL 125 mg QD * (3 weeks on/1 week off)	ABE 150 mg BID	RIB 400 mg QD * (3 weeks on/1 week off)
ET partner	AI or TAM ± LHRH agonist	Standard adjuvant ET	Standard adjuvant ET (eg, AI, TAM, LHRH agonist)	LET or ANA
Duration of CDK4/6i therapy	2 years	~13 months	Up to 2 years	3 years

References: 1. Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT02513394. Accessed March 15, 2022; 2. Mayer E, et al. *Lancet Oncol*. 2021;22:212-222. 3. Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT01864746. Accessed March 15, 2022; 4. Loibl S, et al. *J Clin Oncol*. 2021;39:1518-1530; 5. Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT03155997. Accessed March 15, 2022; 6. Johnston S, et al. J Clin Oncol. 2020;38:3987-3998. 7. Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT03701334. Accessed March 15, 2022; 8. Slamon D, et al. ASCO 2019. Poster TPS597.

CDK4/6 Inhibiteurs en adjuvant : les études

	PALLAS[1,2]	PENELOPE-B[3,4]	monarchE[5,6]	NATALEE[7,8]
N	5796	1250	5637	5101
Sex	Men and women	Women	Men and women	Men and women
Menopausal status	Pre- and postmenopausal	Pre- and postmenopausal	Pre- and postmenopausal	Pre- and postmenopausal
Disease severity	• Stage II • Stage III • N0, N1, N2, N3	• Residual invasive disease after neoadjuvant therapy ≥16 weeks (including 6 weeks of taxane) • CPS-EG ≥3 or score 2 if ypN+ • N0, N1, N2, N3	• Cohort 1: ≥4 ALN or 1-3 ALN + tumor size ≥5 cm and/or grade 3 • Cohort 2: 1-3 ALN + Ki-67 ≥20%	• Stage III (N0 and N1) • Stage IIB and IIA N1 • Stage IIA N0 G3 or N0 G2 with Ki-67 ≥20% or high risk by genetic test • Stage II pts capped at 40% of enrollment
CDK4/6i, dose	PAL 125 mg QD* (3 weeks on/1 week off)	PAL 125 mg QD * (3 weeks on/1 week off)	ABE 150 mg BID	RIB 400 mg QD * (3 weeks on/1 week off)
ET partner	AI or TAM ± LHRH agonist	Standard adjuvant ET	Standard adjuvant ET (eg, AI, TAM, LHRH agonist)	LET or ANA
Duration of CDK4/6i therapy	2 years	~13 months	Up to 2 years	3 years

pas d'AMM dans cette indication

AMM dans cette indication

AMM dans cette indication
En attente du remboursement

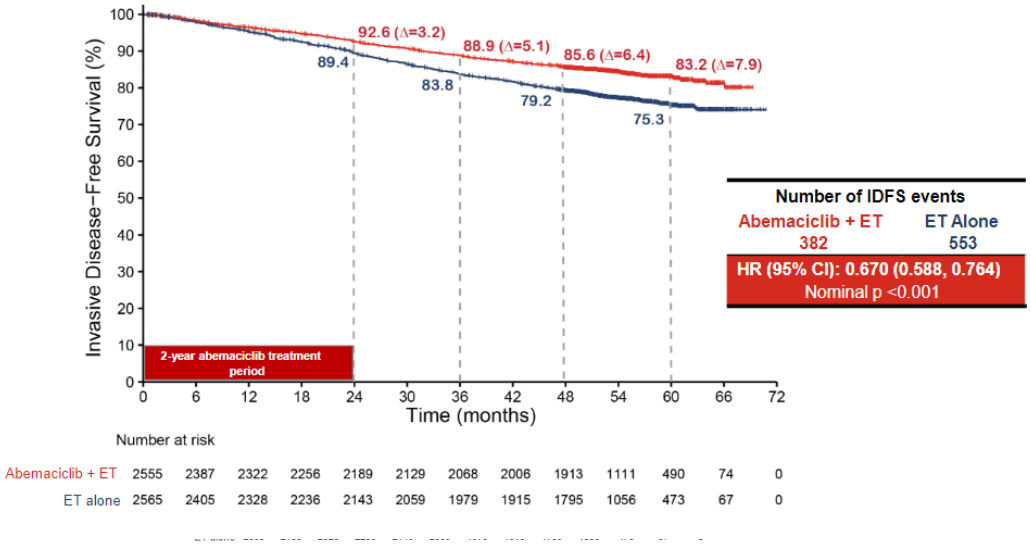
References: 1. Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT02513394. Accessed March 15, 2022; 2. Mayer E, et al. *Lancet Oncol*. 2021;22:212-222. 3. Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT01864746. Accessed March 15, 2022; 4. Loibl S, et al. *J Clin Oncol*. 2021;39:1518-1530; 5. Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT03155997. Accessed March 15, 2022; 6. Johnston S, et al. J Clin Oncol. 2020;38:3987-3998. 7. Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT03701334. Accessed March 15, 2022; 8. Slamon D, et al. ASCO 2019. Poster TPS597.

Critères d'inclusion NATALEE et monarchE

AJCC anatomical staging	TN (M0)	NATALEE	monarchE
Phase IIA	T0N1	✓	Only if G3 or Ki-67 ≥ 20%
	T1N1	✓	Only if G3 or Ki-67 ≥ 20%
	T2N0	Only if G3; or G2 with Ki-67 ≥20% or genomic high risk[a]	✗
Phase IIB	T2N1	✓	Only if G3 or Ki-67 ≥20%
	T3N0	✓	✗
Phase IIIA	T0N2	✓	✓
	T1N2	✓	✓
	T2N2	✓	✓
	T3N1	✓	✓
	T3N2	✓	✓
Phase IIIB	T4N0	✓	✗
	T4N1	✓	Only if the tumour is ≥5 cm or G3 or Ki-67 ≥20%
	T4N2	✓	✓
Phase IIIC	Any TN3	✓	✓

Survie sans maladie invasive

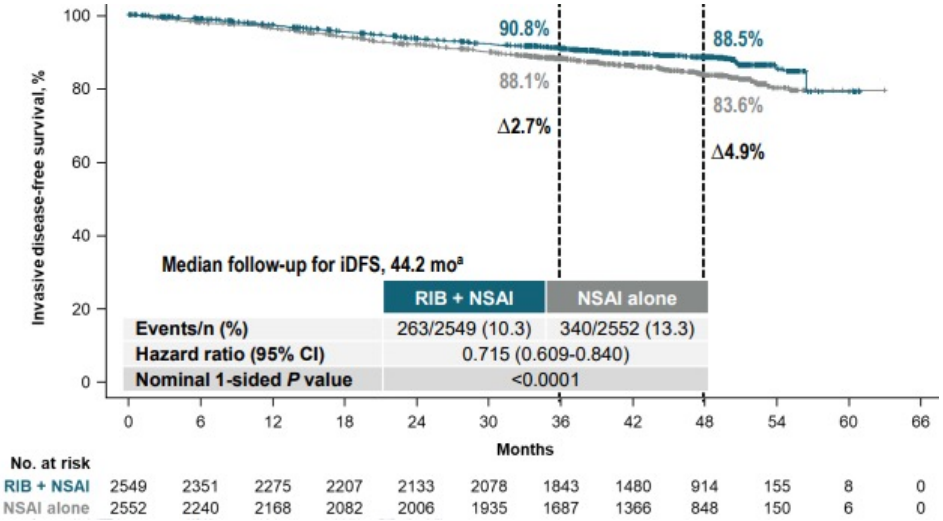
MONARCHE : IDFS à 5 ans



33% reduction in the risk of developing an IDFS event
The KM curves continue to separate and the absolute difference in IDFS rates between arms was 7.9% at 5 years

Rastogi P, et al.. J Clin Oncol. 2024

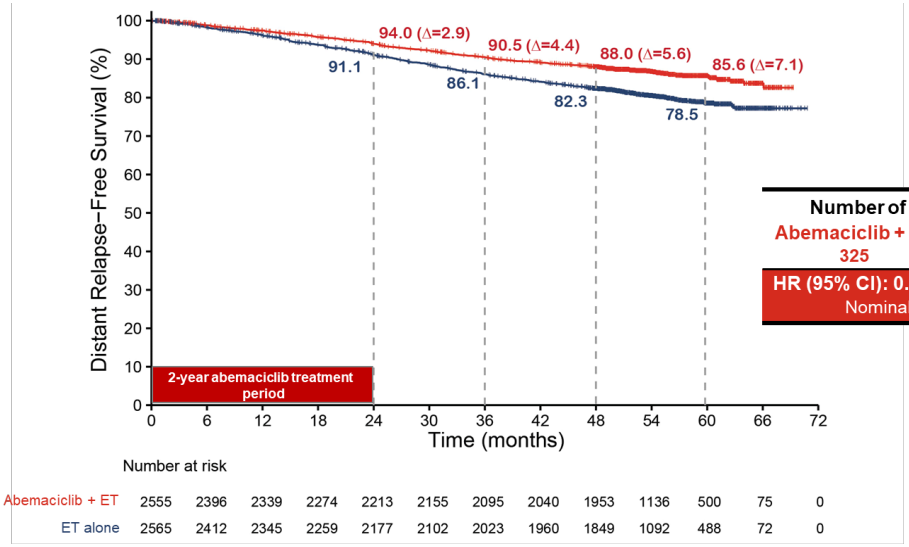
NATALEE : IDFS à 4 ans



Fasching, *ESMO* 2024

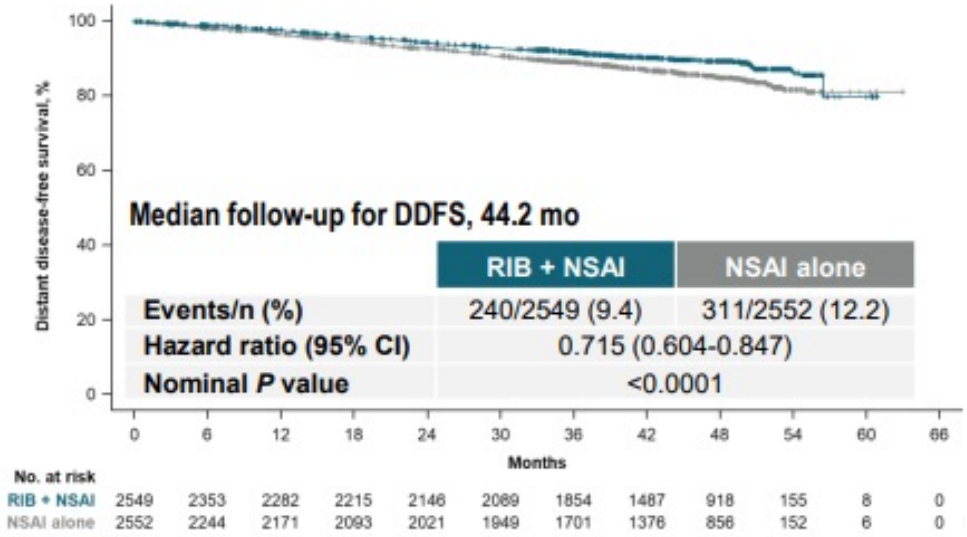
Survie sans récidive à distance

MONARCHE : DRFS à 5 ans



Rastogi P, et al.. J Clin Oncol. 2024

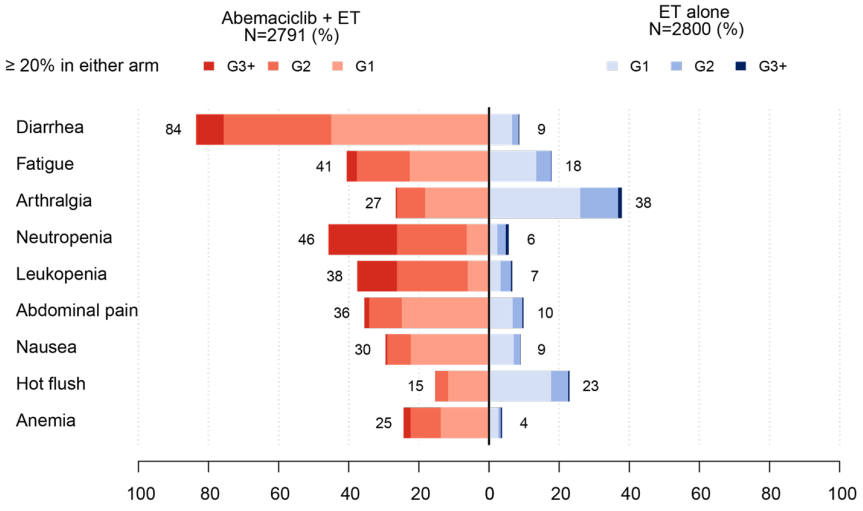
NATALEE : DDFS à 4 ans



Fasching, *ESMO* 2024

Profils de tolérance

MONARCHE



Median duration of abemaciclib: 23.7 months.

Other events of interest, any grade	Abemaciclib + ET N = 2791, %	ET Alone N = 2800, %
VTE	2.5	0.7
PE	1.0	0.1
ILD	3.3	1.3

Abemaciclib dose adjustments due to AEs
- dose holds: 61.7%
- dose reductions: 43.6%
- discontinuations 18.5% [8.9% after dose reduction]

Johnston SRD, et al. Presented at SABCS 2022

NATALEE

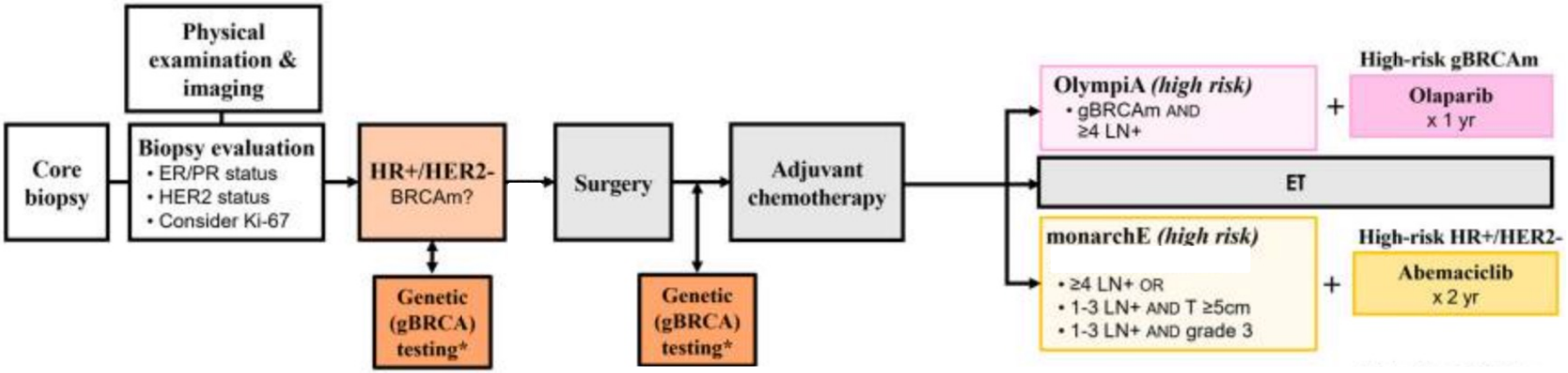
	RIB + NSAI n=2526		NSAI alone n=2441	
AESIs, %	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Neutropenia[a]	62.8	44.4	4.5	0.9
Febrile neutropenia	0.3	0.3	0	0
Liver-related AEs[b]	26.7	8.6	11.4	1.7
QT interval prolongation[c]	5.4	1.0	1.6	0.7
ECG QT prolonged	4.4	0.2	0.8	<0.1
Interstitial lung disease/pneumonitis[d]	1.6	0	0.9	0.1
Clinically relevant AEs, %				
Arthralgia	38.8	1.0	44.4	1.3
Nausea	23.5	0.2	7.9	<0.1
Headache	22.9	0.4	17.2	0.2
Fatigue	22.8	0.8	13.5	0.2
Diarrhea	14.6	0.6	5.5	0.1
VTE[e]	1.1	0.6	0.5	0.3

Rates of discontinuation due to AEs (20.0%) remained stable through all of the data cuts, with a <1.0% increase from the previous cutoff[1,2]

Liver-related AEs were predominantly ALT/AST elevations without concomitant bilirubin increase

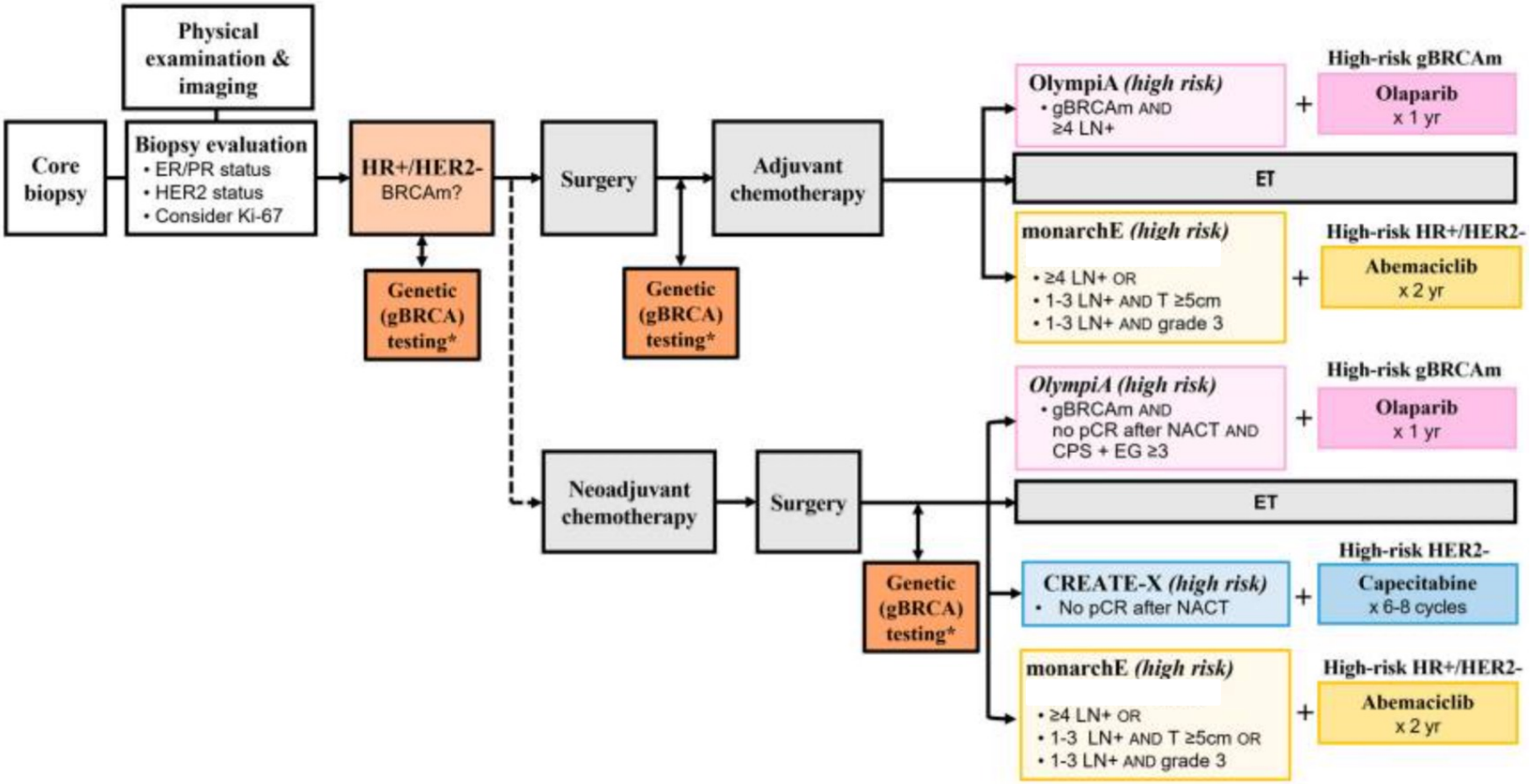
Fasching, *ESMO* 2024

Au final ?



From Henning et al, Current oncology 2023

Au final ?



From Henning et al, Current oncology 2023

Conclusions

- L'introduction de nouvelles molécules a permis d'améliorer le pronostic des cancers du sein à haut risque

- Prochaines étapes :
  - ✓ Nouvelles molécules : SERD oraux
  - ✓ Nouveaux Ac Conjugués : DATO-DXd, Sac-TMT

- Sélection de patientes à très haut risque avec de nouvelles technologies (ADNtc)