Friday January 26, 2024
BREAST CANCER DEBATE OF THE YEAR 2023

Stage III Luminal BC in BRCA mutated patient
who did not reach pCR : Olaparib or cdk4/6 inhibitor ?

Olaparib : C. Duhem - CHL

Cdk4/6 Inhibitor : H Denys -UGent

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BREAST CANCER DEBATE OF THE YEAR 2023

Stage III Luminal BC in BRCA mutated patient
who did not reach pCR : Olaparib or cdk4/6 inhibitor ?

Olaparib : C. D...

...Denys -UGent

CHL KRIIBSZ...
DÉPISTER ENCADRER...

...RSITEIT

This is not a debate

Luxembourg vs Belgium
Olympia vs MonarchE (NATALEE)
To test or not to test every High Risk Pt...

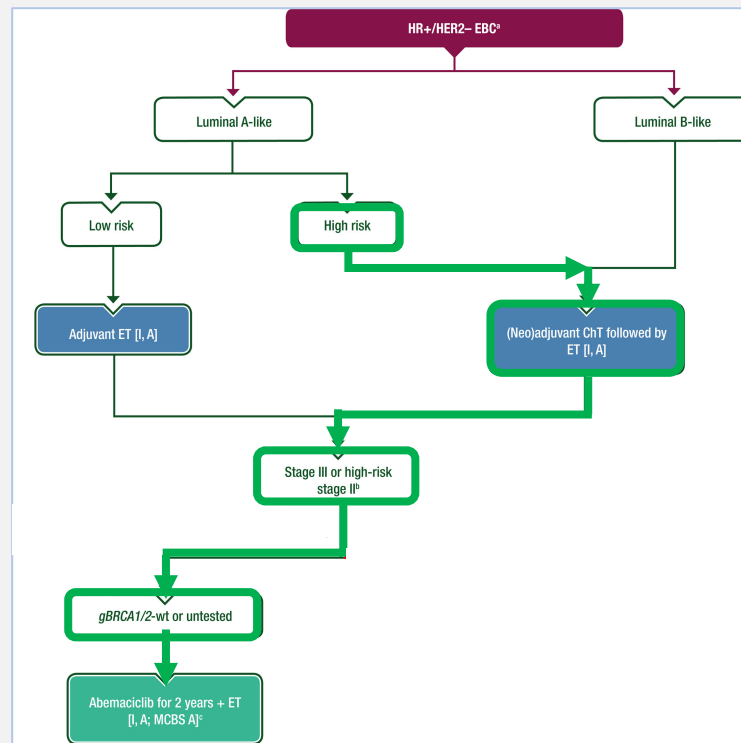**It's about**

answering a clearly asked question

St III Luminal BC in BRCA Mutated Pt
who did not reach pCR : OLAPARIB or Cdk4/6 i ?

Early breast cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up

LOIBL S et al Ann Oncol 2024

St III Luminal BC in BRCA Mutated Pt
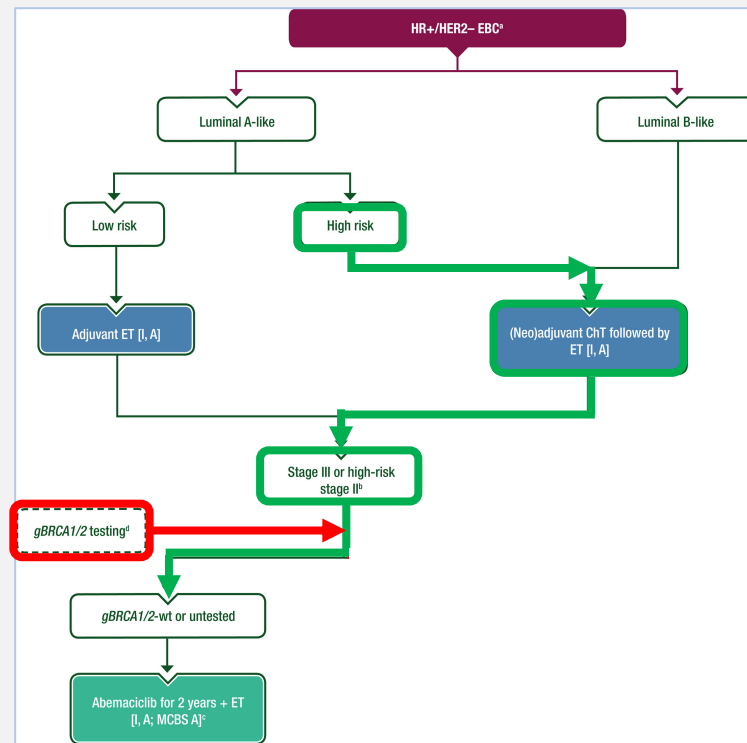# who did not reach pCR : OLAPARIB or Cdk4/6 i ?

Early breast cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up

LOIBL S et al Ann Oncol 2024

St III Luminal BC in BRCA Mutated Pt who did not reach pCR : OLAPARIB or Cdk4/6 i ?

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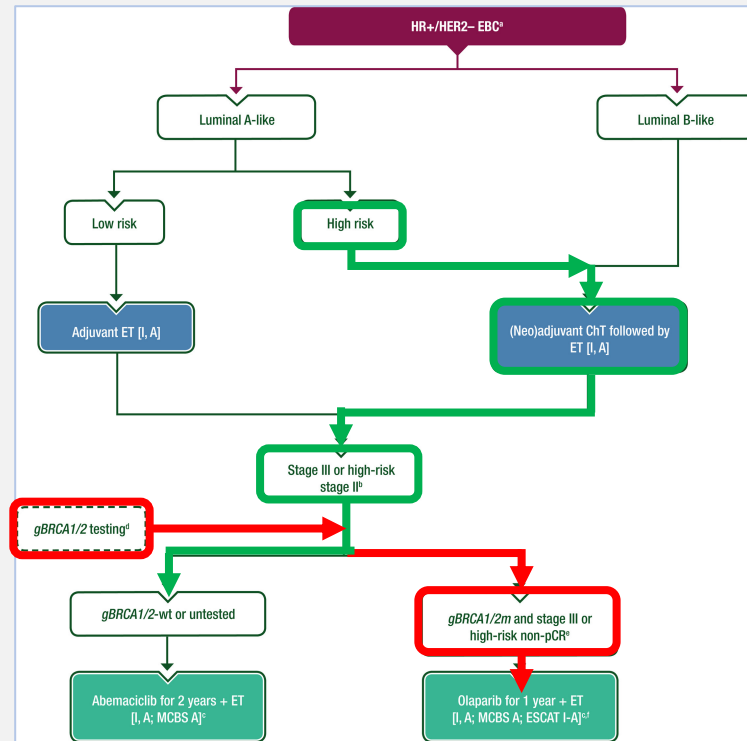
LOIBL S et al Ann Oncol 2024

In a High Risk gBRCA mut Pt Would you prefer to give:

A targeted Tt improving IDFS AND OS in a biomarker selected population (ESCAT I-A) tackling the vulnerability of cancer cells

Or

An other Tt improving IDFS only in unselected population

...(potentially) less effective in this subgroup ?

St III Luminal BC in BRCA Mutated Pt
who did not reach pCR : OLAPARIB or Cdk4/6 i ?

Early breast cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up

Luminal A-like

Low risk

High risk

Adjuvant ET [I, A]

Stage III or high-risk stage II[b]

gBRCA1/2 testing[d]

gBRCA1/2-wt or untested

Abemaciclib for 2 years + ET [I, A; MCBS A][c]
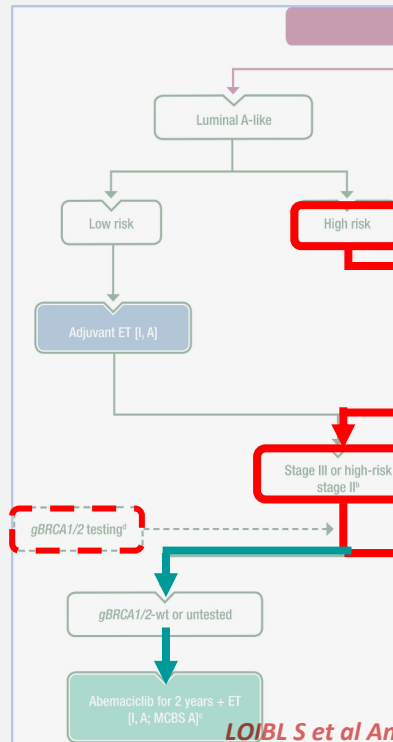
Olaparib for 1 year + ET [I, A; MCBS A; ESCAT I-A][c,f]

LOIBL S et al Ann Oncol 2024

Pt : Would you to give

IDFS AND OS (LOE 1) in cted population

DFS only in unselected ly less effective in this selected pop

St III Luminal BC in BRCA Mutated Pt who did not reach pCR

BREAST CANCER DEBATE OF THE YEAR 2023

Integration of new agents in the landscape of available (Neo)Adjuvant treatments for high risk Pts

✓ **Controversies about the way to combine/sequence/ choose the best option(s)**

✓ **Unlikely that new clinical trials will answer these questions**

✓ **Recommendations → through indirect evidences , extrapolation from the advanced setting etc...**

1) In favor of Olaparib

1) Population

2) Efficacity - Sensitivity to treatment

3) Toxicity - Compliance

4) Cost-effectiveness

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St III Luminal BC in BRCA Mutated Pt
who did not reach pCR : OLAPARIB or Cdk4/6 i ?

No restriction for nodal involvement or CPS+ EG sore

St III Luminal BC in BRCA Mutated Pt
who did not reach pCR : OLAPARIB or Cdk4/6 i ?

Inclusion criteria and drug approval

	OlympiA	monarchE	Olaparib Drug Label
After neoadjuvant chemotherapy	non-pCR and CPS+EG≥3	≥4 ALN or 1-3 ALN and grade 3 or ≥T3 or Ki67≥20%	High risk
After adjuvant chemotherapy	≥4 ALN	≥4 ALN or 1-3 ALN and grade 3 or ≥T3 or Ki67≥20%	High risk

Pt at very high risk

✓ **Clinical St III**

✓ **No pCR after NAC**
  ➢ RCB ? Luminality? Age? Chemo Component?

✓ **gBRCA mutant !**

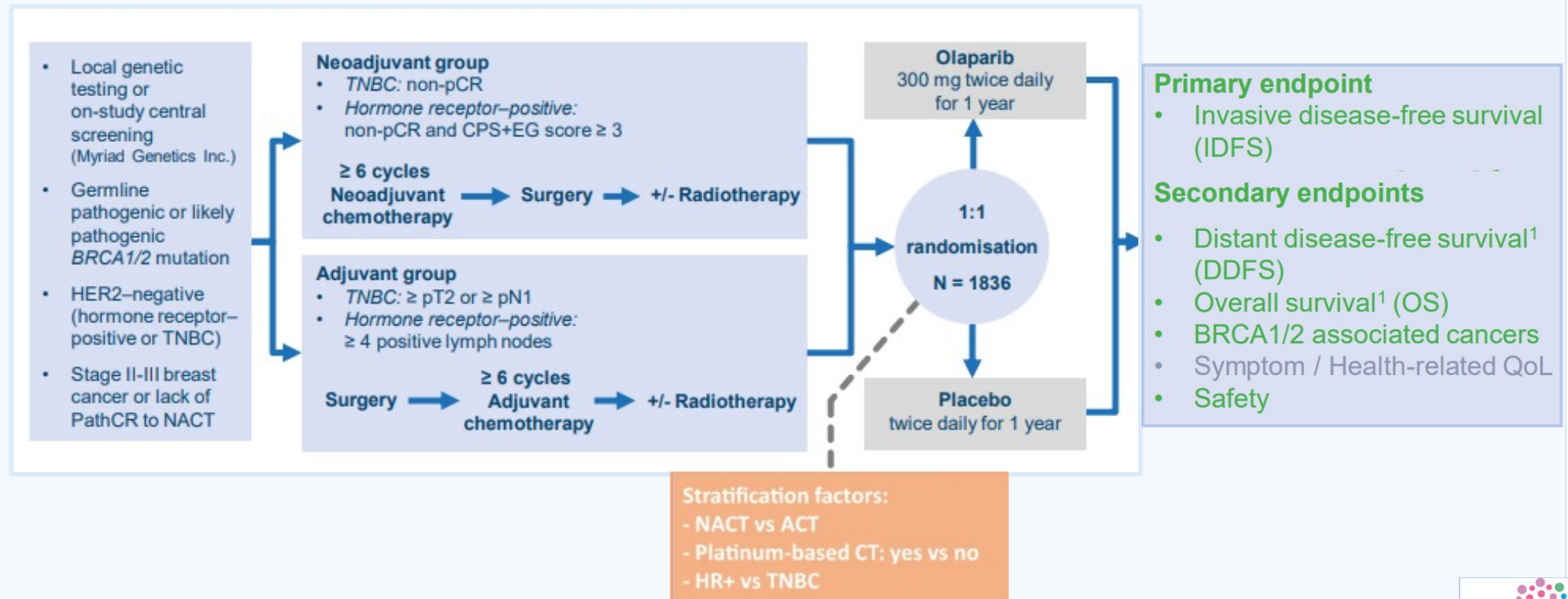- In OLYMPIA Trial (Distant) Relapse Rate in HR + Subgroup = **23% at 3 Y** in control arm
  - Higher RS , Poor prognosis
→ e.a : gBRCA 2 HR+ BC outcome < HR-
Tryggvadottir L, Breast Cancer Res Treat. 2013

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High Risk gBRCA mutant RH + Breast cancer

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjuvant Olaparib for Patients with BRCA1- or BRCA2-Mutated Breast Cancer

High Risk gBRCA mutant RH + Breast cancer

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ORIGINAL ARTICLE

Adjuvant Olaparib for Patients with *BRCA1*- or *BRCA2*-Mutated Breast Cancer

(HR + Group = 18 %)

N= 325

- 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
Hormone receptor–positive: non-pCR and CPS+EG score ≥ 3

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

Adjuvant group
Hormone receptor–positive: ≥ 4 positive lymph nodes

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

1:1 randomisation

Olaparib 300 mg twice daily for 1 year

Stratification factors:
- NACT vs ACT
- Platinum-based CT: y
- HR+ vs TNBC

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy

« CAPECITABINE = SOC for TNBC with post NAC residual disease »
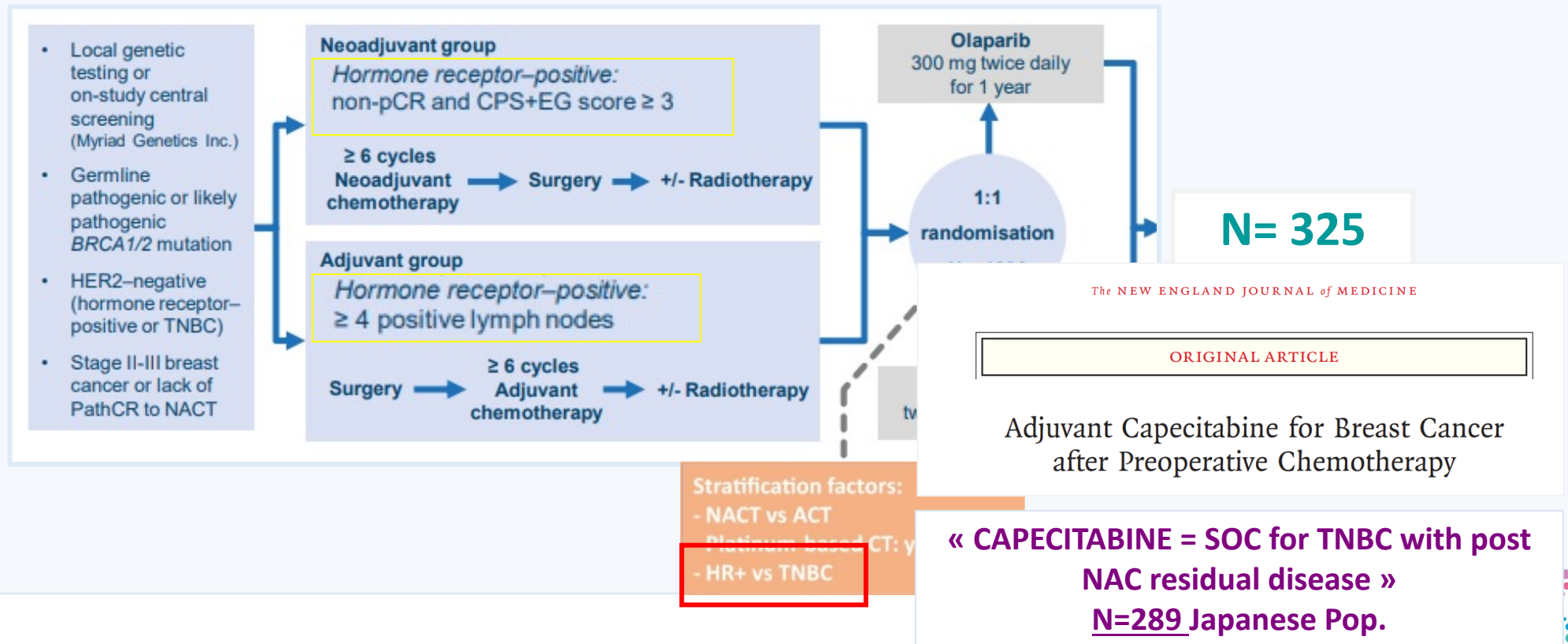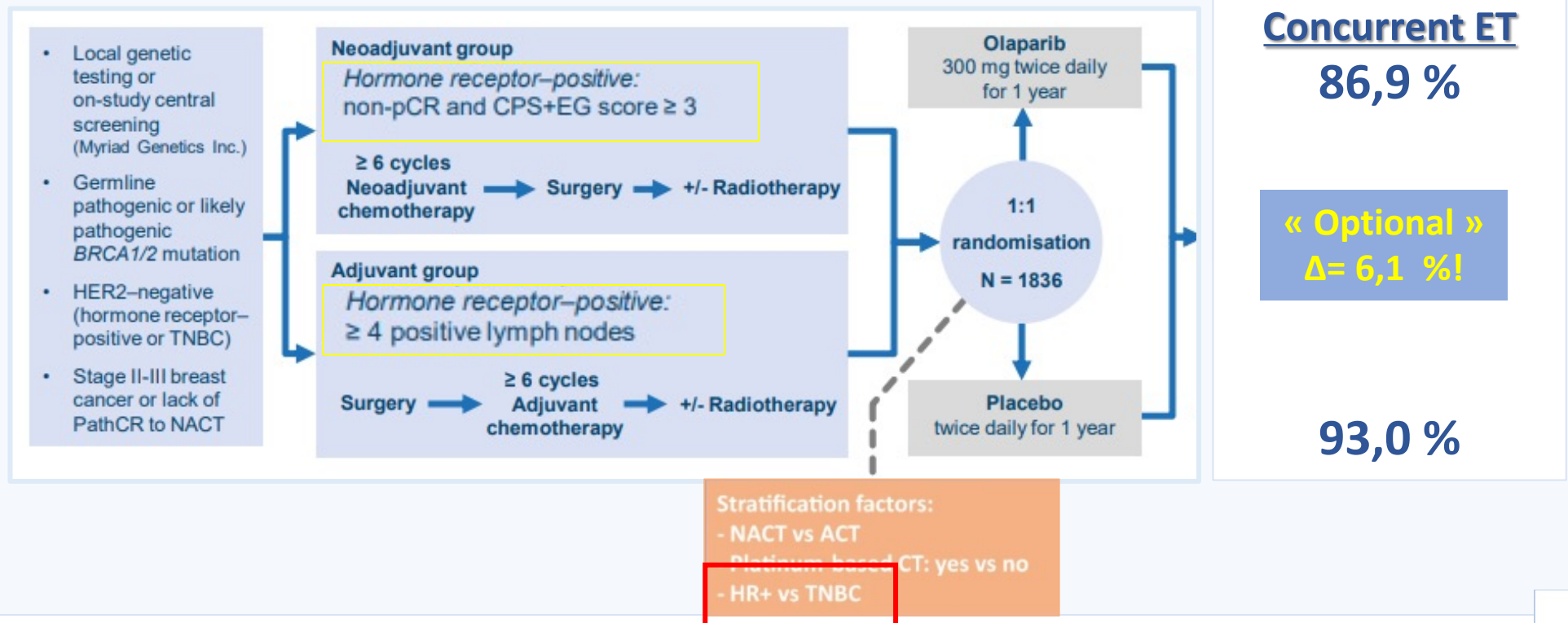**N=289 Japanese Pop.**

High Risk gBRCA mutant RH + Breast cancer

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ORIGINAL ARTICLE

Adjuvant Olaparib for Patients with *BRCA1*- or *BRCA2*-Mutated Breast Cancer

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Neoadjuvant group
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Adjuvant group
Hormone receptor–positive: ≥ 4 positive lymph nodes

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

1:1 randomisation
N = 1836

Olaparib 300 mg twice daily for 1 year

Placebo twice daily for 1 year

Stratification factors:
- NACT vs ACT
- Platinum-based CT: yes vs no
- HR+ vs TNBC

Concurrent ET
86,9 %

« Optional »
Δ= 6,1 %!

93,0 %

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Geyer C et al , Ann Oncol 2022

4 –year IDFS rate

≈ 4 –year DDFS rate

Relative Risk ↘ = 42 %

In MonarchE : Distant met. = 71 % of Invasive relapses

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Geyer C et al , Ann Oncol 2022

MonarchE : 4 published updates
NATALEE : ??? (PALLAS & Penelope B…)

Abemaciclib Combined With Endocrine Therapy for the Adjuvant Treatment of HR+, HER2−, Node-Positive, High-Risk, Early Breast Cancer (monarchE)

Johnston S , JCO 2020
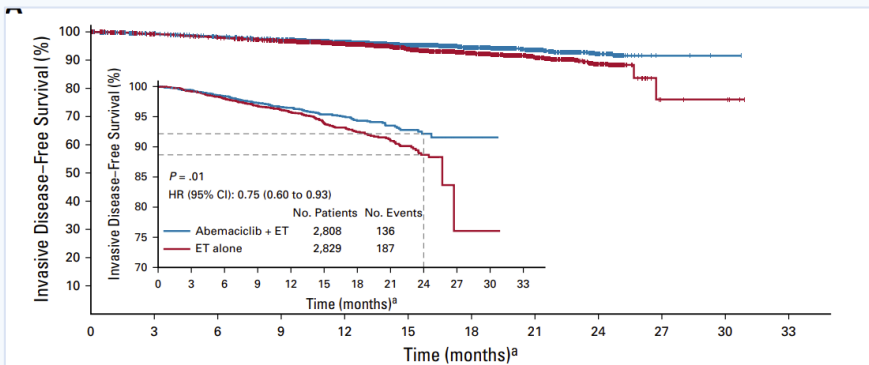
Adjuvant Abemaciclib Plus Endocrine Therapy for Hormone Receptor−Positive, Human Epidermal Growth Factor Receptor 2−Negative, High-Risk Early Breast Cancer: Results From a Preplanned monarchE Overall Survival Interim Analysis, Including 5-Year Efficacy Outcomes

Rastogi P, JCO 2024
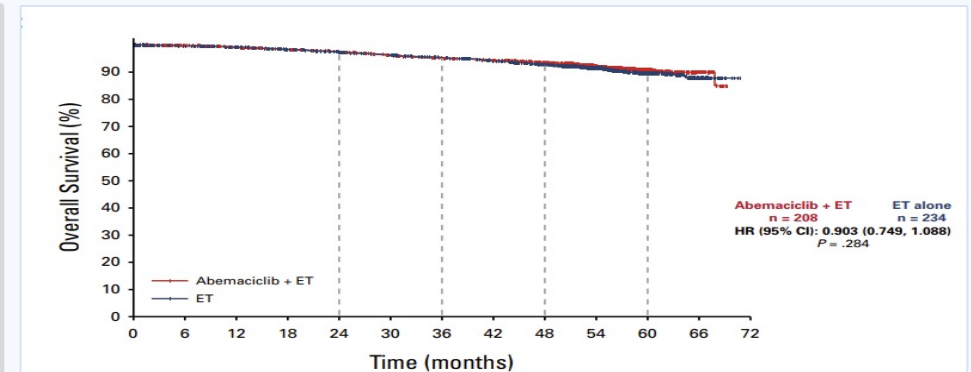
Review of the monarchE trial suggests no evidence to support use of adjuvant abemaciclib in women with breast cancer

Tomer Meirson • Daniel A Goldstein • Bishal Gyawali • Ian F Tannock ✉

THE LANCET Oncology June 2023

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If High Risk gBRCA mutant RH + Breast cancer → prefer Olaparib : ↗ Efficacity data

❖ Targeted therapy →biomarker defined population at poor prognosis

- **Δ IDF**S at 4 y : > in OLYMPIA , early separation of the curves **(13 Pt treated to avoid 1 relapse at 4y)**
- Convincing **OS** data in OLYMPIA ↔ not (yet) in monarchE (NATALEE)

❖ Same Benefit if **HR +** and **HR-** population

- Lack of mechanistic rationale for ≠ synthetic lethal effect of PARPis
- Clinical data by subgroups
  - ✓ Advanced setting : OLYMPIAD & EMBRACA ↔ similar PFS benefit
  - ✓ Early setting : OLYMPIA & Gepar-OLA (Neo adjuvant)

Tutt A, NEJM 2021, Geyer C Ann Oncol 2022, Robson M , NEJM 2017, Litton J , NEJM 2018, Fasching PA, Ann Oncol 2021

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ORIGINAL ARTICLE

Overall survival in the OlympiA phase III trial of adjuvant olaparib in patients with germline pathogenic variants in *BRCA1/2* and high-risk, early breast cancer

Geyer C et al , Ann Oncol 2022

SUBGROUP ANALYSIS DDFS

Subgroup	Olaparib	Placebo	Stratified hazard ratio for distant disease-free survival (95%CI)	P value for heterogeneity
	No. of patients with a distant disease event/total no.			
All patients	107 / 921	172 / 915		NA
Prior chemo				
Adjuvant	33 / 461	59 / 455		0.698
Neoadjuvant	74 / 460	113 / 460		
Prior platinum				
Yes	36 / 247	43 / 238		0.132
No	71 / 674	129 / 677		
HR status				
HR+/HER2-	23 / 168	31 / 157		0.608
TNBC	84 / 751	141 / 758		
BRCA				
BRCA1	66 / 579	118 / 588		0.927
BRCA2	28 / 235	41 / 216		
BRCA1/2 both	0 / 2	0 / 3		

Favours olaparib · Favours placebo

Geyer C et al , Ann Oncol 2022

SUBGROUP ANALYSIS OF OS

Subgroup	Olaparib	Placebo	Stratified hazard ratio for overall survival (95% CI)	P value for heterogeneity
	No. of patients who died /total no.			
All patients	75 / 921	109 / 915		NA
Prior chemo				0.543
Adjuvant	22 / 461	28 / 455		
Neoadjuvant	53 / 460	81 / 460		
Prior platinum				0.236
Yes	27 / 247	29 / 238		
No	48 / 674	80 / 677		
HR status				0.381
HR+/HER2-	16 / 168	17 / 157		
TNBC	59 / 751	92 / 758		
BRCA				0.845
BRCA1	49 / 579	75 / 588		
BRCA2	16 / 235	28 / 216		
BRCA1/2 both	0 / 2	0 / 3		

Favours olaparib   Favours placebo

If High Risk gBRCA mutant RH + Breast cancer → relative resistance to cdk4/6is ?

- **No direct evidence** (pivotal ph III , Meta analysis,..) → gBRCA mut = specific subgroup ?

- ctDNA exploratory analysis on ML series **André F et al , Ann Oncol 2023** → Unconvaincing for BRCA 1/2

If High Risk gBRCA mutant RH + Breast cancer → relative resistance to cdk4/6is ?

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- Subgroup analyses from **RWE** → worse outcome of gBRCA mutated Pts in 1L advanced setting (**retrospective** data)

Author	Results/Conclusions
Frenel et al.	BRCA/PALB2 mutated patients with shorter PFS (14.3 vs. 26.7m)
Collins et al.	BRCA mutated patients with shorter OS (26 vs. 51m)
Bruno et al.	BRCA/CHECK/ATM mutated patients with worse outcomes
Safonov et al.	BRCA2 mutations with worse PFS
Fuentes Antras, et al.	BRCA1/2 and PALB2 mutations with shorter PFS (9.9 vs. 26.8m)

Frenel J, et al. Ann Oncol 2020.
Bruno L, et al. JCO Precision Oncol, 2022.
Safonov A, et al. Cancer Res 2022.

Collins J, et al. Oncol Therapy,
2021. Fuentes Antras J, et al.
ASCO 2023.

	Somatic alterations
gBRCA2	Rb1 loss
gBRCA1(2)	MYC Ampl(53 %)*

Xu et al , 2020

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Molecular Alterations associated with response to Abemaciclib in MonarchE

Turner N , SABCS 2023

Molecular Alterations associated with response to Abemaciclib in MonarchE

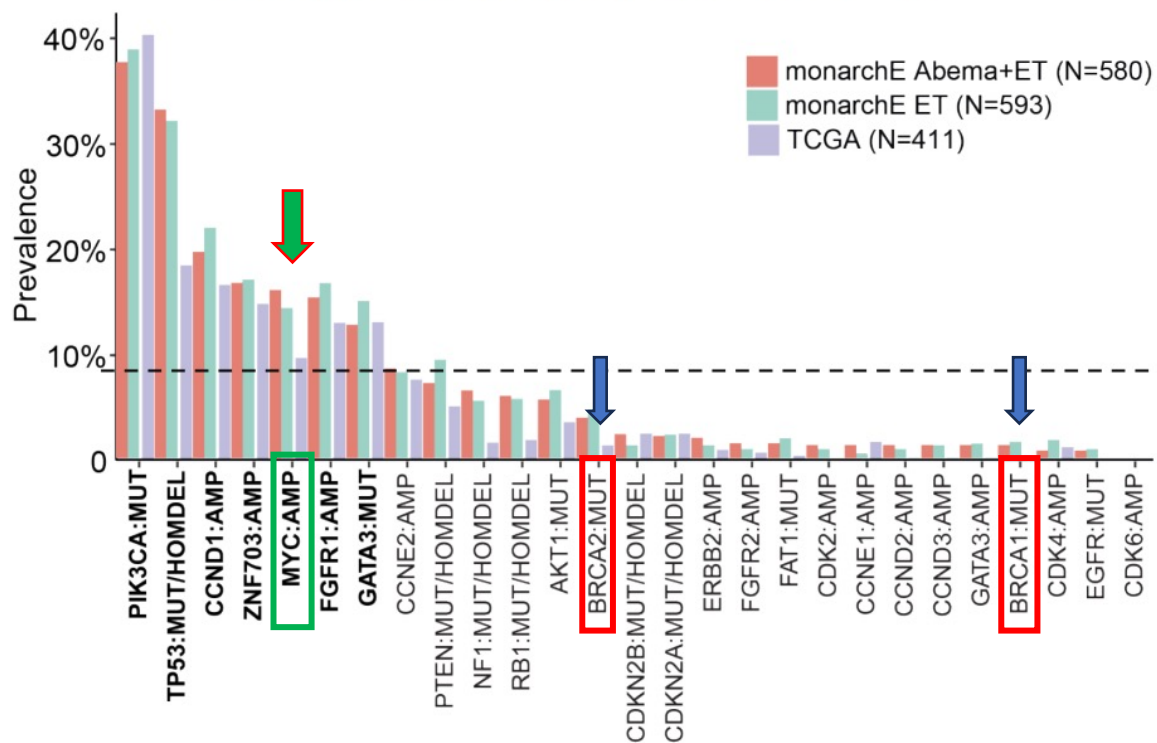Turner N , SABCS 2023

Oncogenic Mutations/Alterations + CNV

Legend:
- monarchE Abema+ET (N=580)
- monarchE ET (N=593)
- TCGA (N=411)

	Prevalence	Abemaciclib + ET Events/n (%)	ET Alone Events/n (%)	HR (95% CI)	Interaction p-value
All patients		123/580 (22%)	169/593 (28%)	0.72(0.57,0.91)	
PIK3CA mut	38%	**55/217 (26%)**	**73/229 (32%)**	**0.75(0.53,1.1)**	0.758
PIK3CA wt		68/363 (18%)	96/364 (26%)	0.70(0.51,0.95)	
TP53 mut/homdel	32%	**55/189 (30%)**	**82/184 (44%)**	**0.60(0.42,0.84)**	0.184
TP53 wt		68/391 (18%)	87/409 (22%)	0.81(0.59,1.1)	
CCND1 amp	20%	**36/113 (32%)**	**42/129 (32%)**	**0.94(0.6,1.5)**	0.177
CCND1 wt		87/467 (18%)	127/464 (28%)	0.66(0.5,0.87)	
ZNF703 amp	16%	**28/96 (30%)**	**37/100 (36%)**	**0.77(0.47,1.3)**	0.776
ZNF703 wt		95/484 (20%)	132/493 (26%)	0.71(0.54,0.92)	
MYC amp	16%	**34/92 (36%)**	**25/84 (30%)**	**1.30(0.77,2.2)**	0.014
MYC wt		89/488 (18%)	144/509 (28%)	0.62(0.47,0.8)	
FGFR1 amp	16%	**26/88 (30%)**	**35/98 (36%)**	**0.80(0.48,1.3)**	0.641
FGFR1 wt		97/492 (20%)	134/495 (28%)	0.70(0.54,0.91)	
GATA3 mut	14%	**13/73 (18%)**	**17/88 (20%)**	**0.86(0.42,1.8)**	0.513
GATA3 wt		110/507 (22%)	152/505 (30%)	0.69(0.54,0.89)	

Rb1 =negative regulator of CDK4/6 pathway
↓
loss of Rb1 leads to CDK4/6 inhibiton Resistance

…"Therefore, among ER-positive patients treated with adjuvant therapy or advanced therapy, CDK4/6 inhibitors __may be ineffective__ for those with BRCA2 germline mutations. PARP inhibitors can be used as the __first choice__ for these patients".

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If High Risk gBRCA mutant RH + Breast cancer : prefer Olaparib ?
Toxicity + Compliance issues : Side effects and Duration

Better Tolerance to Olaparib ? ↔ Better Compliance ?

Geyer C et al , Ann Oncol 2022

Johnston S , Lancet Oncol 2023

If High Risk gBRCA mutant RH + Breast cancer : prefer Olaparib ? Toxicity + Compliance issues : Side effects and Duration

Better Tolerance to Olaparib ? ↔ Better Compliance ?

Geyer C et al , Ann Oncol 2022

No majoration of TVE events

Discontinuation rate for AEs
- ➤ 9,9 % in Olaparib arm (vs 4,2 % in placebo arm)
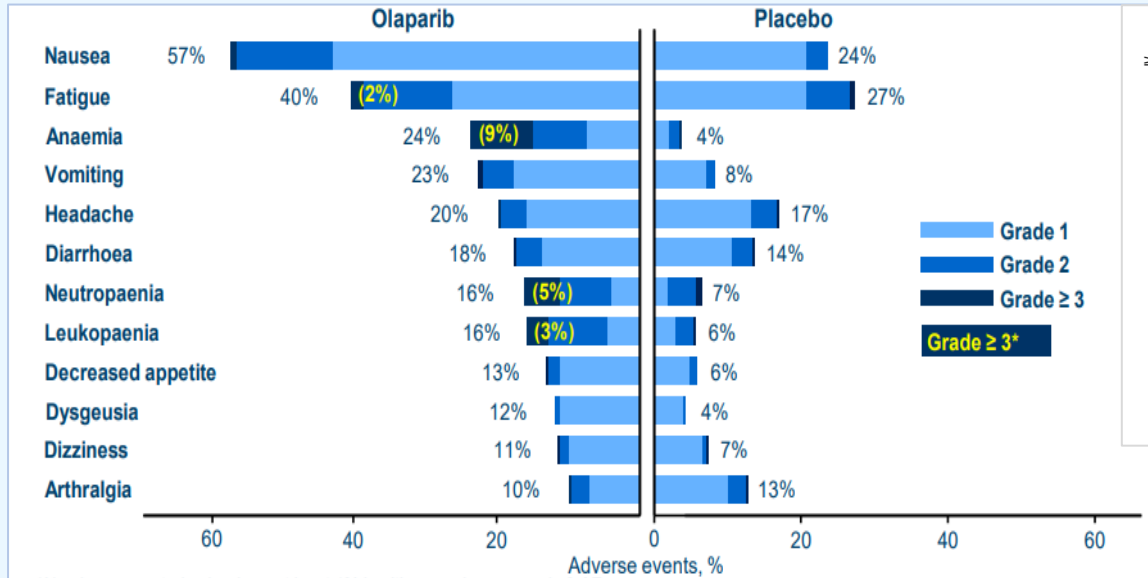- ➤ 18,5 % in MonarchE (open label Trial)

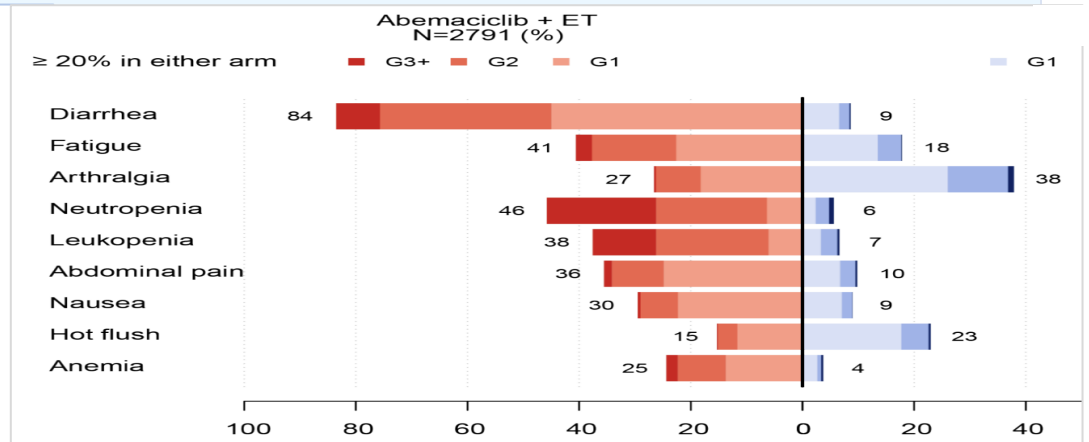# If High Risk gBRCA mutant RH + Breast cancer : prefer Olaparib ?
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Geyer C et al , Ann Oncol 2022

No majoration of TVE events

Discontinuation rate for AEs
➤ 9,9 % in Olaparib arm (vs 4,2 % in placebo arm)
➤ 18,5 % in MonarchE (open label Trial)
→ 6,5% : both Abema + ET vs 1,1% Stopped ET in control arm

AML/MDS   0,2 %   vs   0,3%

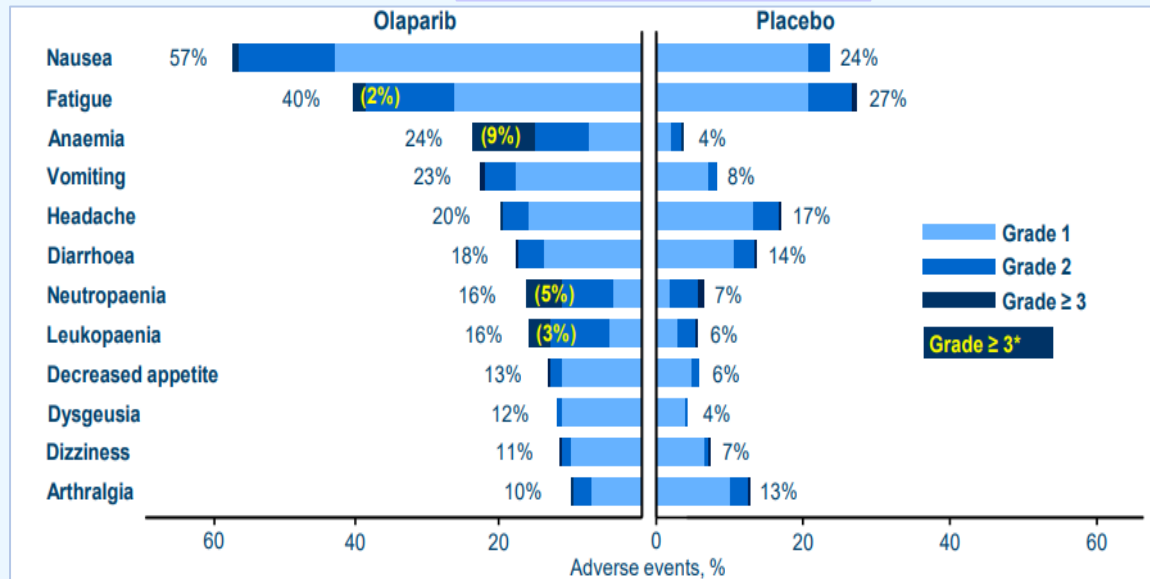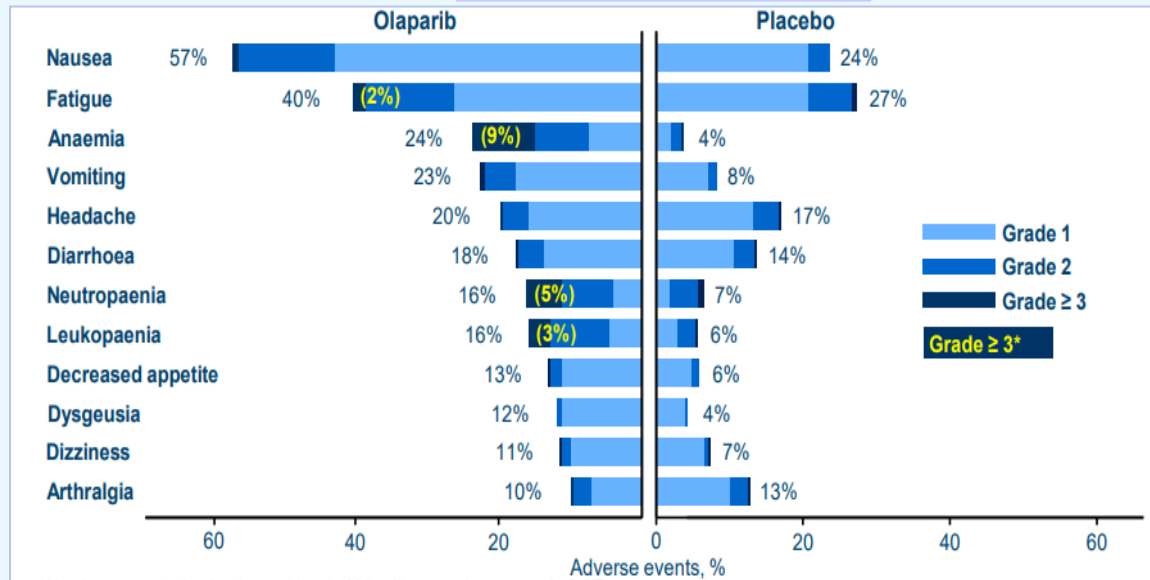**Numerical ↘ of second maligancies 1,5 vs 2,5 %**

Chemopreventive effect ?

If High Risk gBRCA mutant RH + Breast cancer : prefer Olaparib ?
Toxicity + Compliance issues : Side effects and Duration

Duration : 1 y vs 2-3 Y

➢ Longer duration of Adjuvant Tt = Factor for **lower adherence** (↗ If Aes , monitoring ,…)

➢ **Desire for pregnancy**
  - ✓ In POSITIVE trial → 52 % St II-III, inclusion after 18 To 30 mo of ET
  - ✓ Young gBRCA Pts : ↘ Fertility, RRSO ,…
  - ✓ Ovarian toxicity of cdk4/6is ? **Scavone G et al , Cancers 2023**

  Olaparib: more debated **FDA ressources 2022, Winship AT et al , Hum Reprod 2020**

➢ **Costs**

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If High Risk gBRCA mutant RH + Breast cancer : prefer Olaparib ?
Cost Effectiveness

Cost-Effectiveness of Adjuvant Olaparib for Patients With Breast Cancer and Germline _BRCA1/2_ Mutations

Christina M. Zettler, MPH; Dilanka L. De Silva, MD; Victoria S. Blinder, MD; Mark E. Robson, MD; Elena B. Elkin, PhD, MPA

Cost-Effectiveness of Abemaciclib in Early Breast Cancer Patients: One Size Fits All or Tailoring to Patients' Needs?

Elisabeth M Jongbloed[1], Hedwig M Blommestein[2], Hannah M van Schoubroeck[2], John WM Martens[1], Saskia M Wilting [1], Carin A Uyl-de Groot[2], Agnes Jager[1]

Ccl : Adjuvant olaparib was a cost-effective option for patients with high-risk, early-stage breast cancer and a germline BRCA1/2 mutation.

Ccl : The addition of abemaciclib to adjuvant endocrine therapy in all high-risk ER+, HER2- EBC patients is not cost-effective.

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St III Luminal BC in BRCA Mutated Pt who did not reach pCR
Beyong OLAPARIB or Cdk4/6 i ?

Phase III clinical trials of immunotherapy for high-risk HR+/HER2- EBC
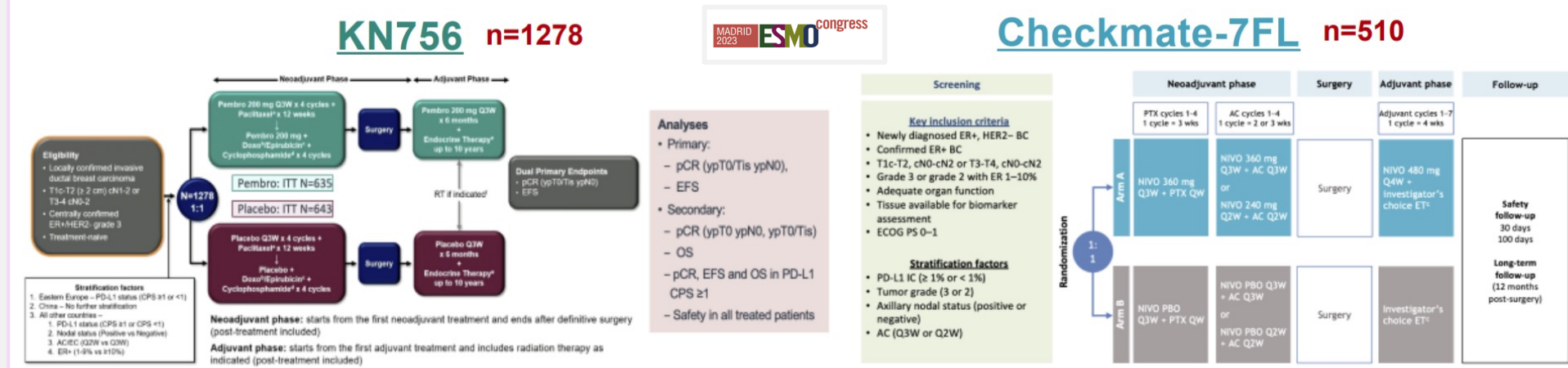
Combination with CPIs : Feasible with Olaparib

…. not feasible with cdk4/6is

St III Luminal BC in gBRCA Pt non pCR : <u>OLAPARIB</u> or Cdk4/6 i ?

In favor of Olaparib

1) **Population**

2) **Efficacity - Sensitivity to treatment**

3) **Toxicity - Compliance**

4) **Cost-effectiveness**

- ➤ Targeted treatment in high risk Pts

- ➤ More effective (IDFS , early signal for OS)

- ➤ Cdk4/6 less effective in this population

- ➤ To combine to ET ! Combinable with IOs…

- ➤ Better compliance , Shorter Tt, Fertility friendly

- ➤ Cost effective approach

- ➤ The Choice in ESMO guidelines, St Gallen Consensus,..

- ➤ …..

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St III Luminal BC in gBRCA Pt non pCR : <u>OLAPARIB</u> or Cdk4/6 i ?

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- ➤ .....

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St III Luminal BC in BRCA Mut.Pt non pCR : OLAPARIB or Cdk4/6 i Remaining debate ?

➤ **Olaparib** <u>OR</u> cdk4/6 i ✓ **OK**

➤ **Olaparib** <u>IF</u> cdk4/6 i(ongoing) ✓ **OK**

St III Luminal BC in BRCA Mut.Pt non pCR : OLAPARIB or Cdk4/6 i Remaining debate ?

➢ **Olaparib** OR cdk4/6 i   ✓ **OK**

➢ **Olaparib** IF cdk4/6 i(ongoing)   ✓ **OK**

➢ Olaparib **AND** cdk4/6 i

- ▪ Combo   **?**

- ▪ Sequence   **?/OK**

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St III Luminal BC in BRCA Mut.Pt non pCR : OLAPARIB → Cdk4/6 i

OLYMPIA: TRIAL SCHEMA

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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 randomisation N = 1836

Olaparib 300 mg twice daily for 1 year

Min 2 w-Max 12 w after all local Tt

NeoAdjuvant ChemoT	OP	± RT	12 mo

OlympiA
OLaparib in Adjuvant BRCAm breast cancer

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Monarch-E Design

HR+, HER2-, node positive high-risk EBC
- Women or men
- Pre-/postmenopausal
- With or without prior neo- and/or adjuvant chemotherapy
- No metastatic disease
- Maximum of 16 months from surgery to randomization and 12 weeks of ET following the last non-ET

Cohort 1: High risk based on clinical pathological features
- ≥4 ALN OR
- 1-3 ALN and at least 1 of the below:
  - Grade 3 disease
  - Tumor size ≥5 cm

Cohort 2: High risk based on Ki-67
- 1-3 ALN and
- Ki-67 ≥20% and
- Grade 1-2 and tumor size <5 cm

R 1:1 N = 5637

On-study treatment period 2 years

Abemaciclib (150mg twice daily) + Endocrine Therapy: AI or tamoxifen

Endocrine Therapy: AI or tamoxifen

NeoAdjuvant ChemoT	OP	± RT	12 mo	12-16 Mo Post-OP, 2 Years

✓ **49% of 2023 St Gallen pannelists « In very Selected cases «**

✓ **But why if poorly effective ?**

Friday January 26, 2024

BREAST CANCER DEBATE OF THE YEAR 2023

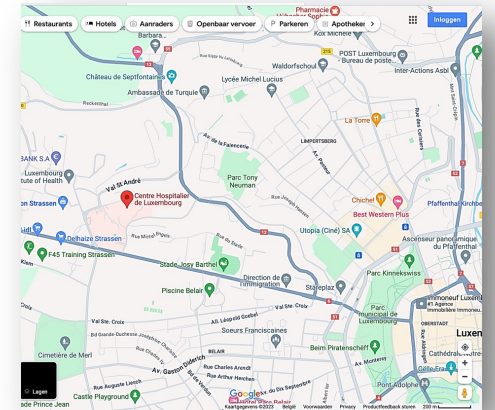# Stage III Luminal BC in BRCA mutated patient who did not reach pCR : Olaparib !

Cdk4/6 Inhibitor ??
H. Denys -UGent

BEST OF THE BEST
WINNER · AWARD

À VAINCRE SANS PÉRIL, ON TRIOMPHE SANS GLOIRE

Pierre CORNEILLE

CONGRATULATIONS

- **Consulting or Advisory Role:** Pfizer (Inst), Roche (Inst), PharmaMar (Inst), AstraZeneca (Inst), Eli Lilly (Inst), Novartis (Inst), Amgen (Inst), GSK (Inst), Seagen (Inst), MSD (Inst), Gilead (Inst)

- **Travel, Accommodations:** Pfizer (Inst), Roche (Inst), PharmaMar (Inst), Teva (Inst), AstraZeneca (Inst), MSD (Inst), Gilead (Inst), GSK (Inst)
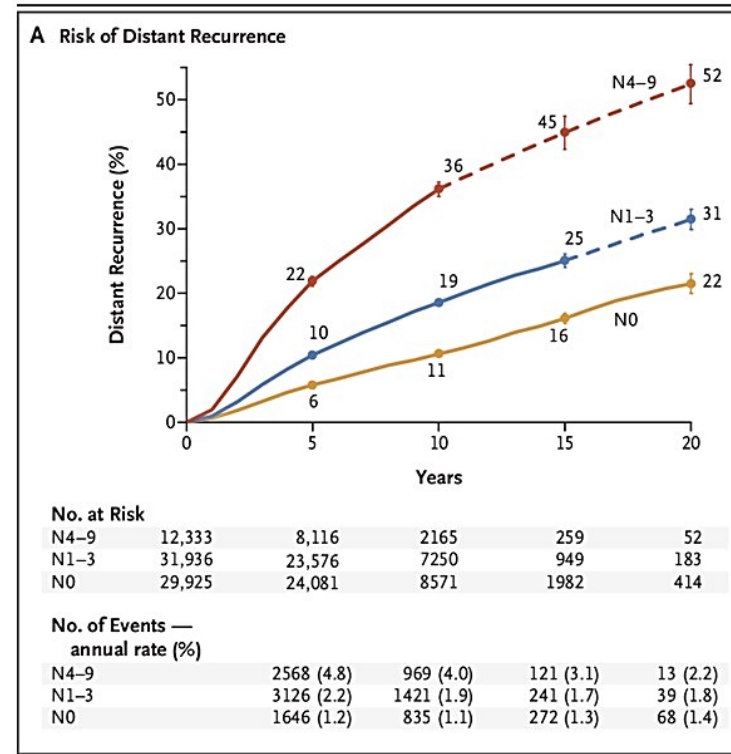
Stage III luminal BC in BRCA mutant patient who did not reach pCR: CDK4/6i
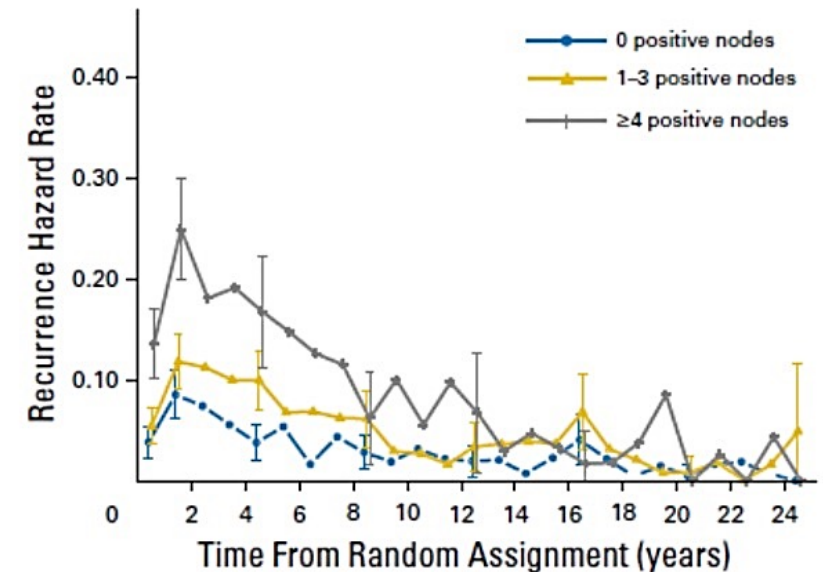
Stage III BC: high risk patients

- stage 3A breast (4-9+LN)
- T0 N2 M0
- T1 N2 M0
- T2 N2 M0
- T3 N1 M0
- T3 N2 M0
- Stage 3B (>5cm with 1-3 +LN, Skin or chest wall invasion)
- T4 N0 M0
- T4 N1 M0
- T4 N2 M0
- Stage 3C :
- Any T N3 M0 (>10+ LN, LN collar bone)

EBCTCG --- 20-year risk after stopping endocrine therapy at 5 years

Hazard of Recurrence over 25 Years:

IBCSG Trials I to V
testing chemo-endocrine therapies,
premenopausal (I,II,V) & postmenopausal (III,IV,V)

Stage and tumor burden are important indicators of distant recurrence (46% to 57%)

Pan H et al, N Eng Med 2017; Pistilli B et al ASCO educational boo 2022; Iqbal J et al JAMA 2015

Strategies to improve prognosis

-

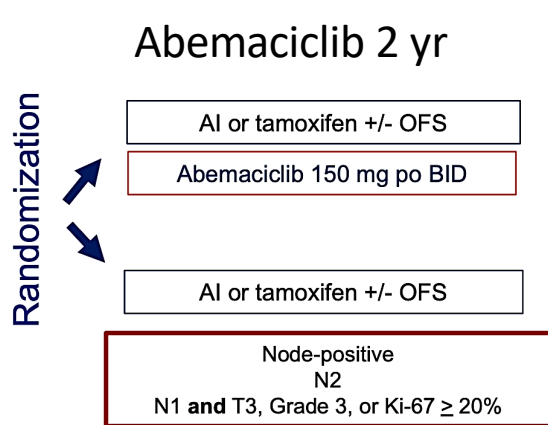|	PALLAS (N=5760) Palbociclib	PENELOPE-B (N=1250) Palbociclib	monarchE (N=5637) Abemaciclib	NATALEE (N=5101) Ribociclib
Population median age	Pre/postmeno, men 52 yr	Pre/postmeno 49 yr	Pre/postmeno, men 51 yr	Pre/postmeno, men
Stage IIA / IIB / III	18% / 33% / 49%	(No pCR after NACT; CPS-EG≥3; or 2 & ypN+)	12% / 14% / 74%	IIA, IIB, III (limited ~40% II)
Primary endpoint met	No	No	Yes	Yes

Mayer et al 2021; Loibl et al 2021, Johnston et al 2022, Slamon D et al ASCO 2023
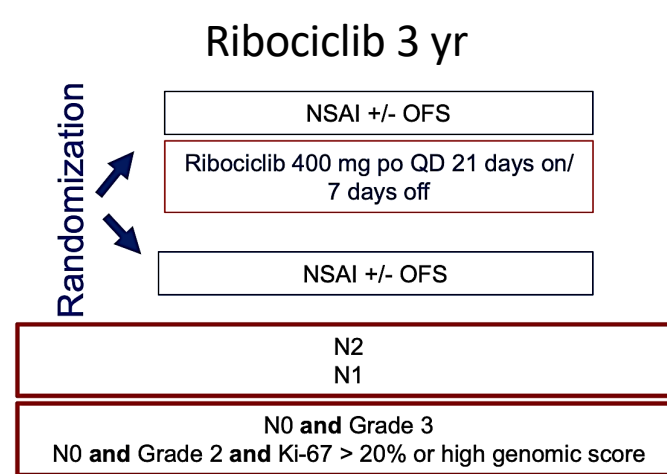
- PARPi for gBRCA: OlympiA

Adjuvant CDK4/6i

Study population

Abemaciclib 2 yr

Randomization

- AI or tamoxifen +/- OFS
- Abemaciclib 150 mg po BID
- AI or tamoxifen +/- OFS

Node-positive
N2
N1 **and** T3, Grade 3, or Ki-67 $\geq$ 20%

Ribociclib 3 yr

Randomization

- NSAI +/- OFS
- Ribociclib 400 mg po QD 21 days on/ 7 days off
- NSAI +/- OFS

N2
N1

N0 **and** Grade 3
N0 **and** Grade 2 **and** Ki-67 > 20% or high genomic score

~30% pts early-stage tumors eligible for NATALEE and not MonarchE

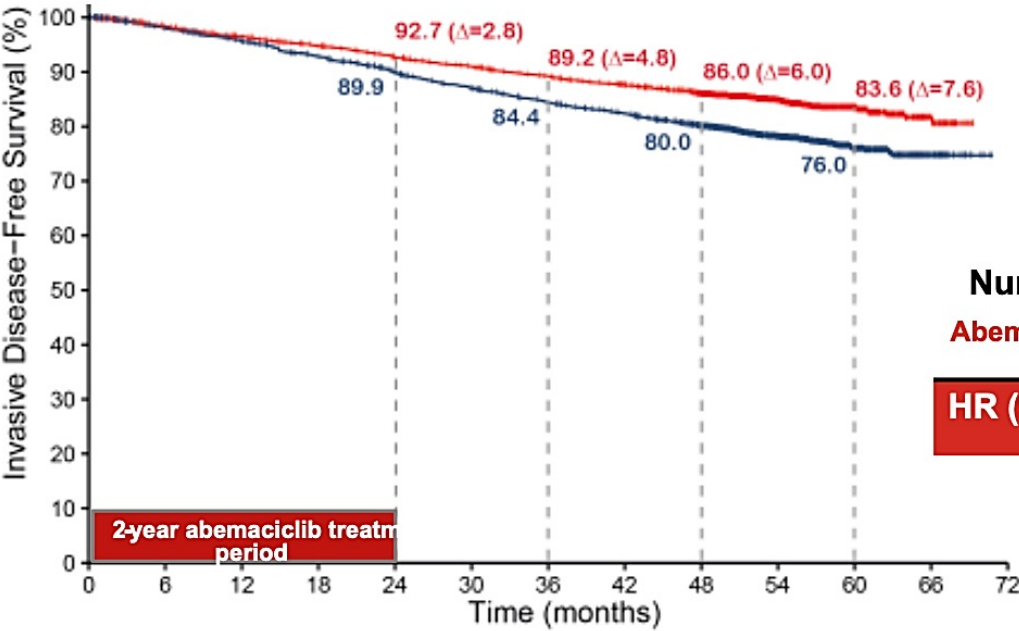NSAI = Non-Steroidal Aromatase Inhibitor; OFS = Ovarian Function Suppression

Johnston S et al ESMO 2023; Slamon D et al ASCO 2023

AJCC anatomical staging[1]	TN (M0)	NATALEE[2,3]	monarchE[4]
Stage IA	T1N0		
Stage IB	T0N1mi		
	T1N1mi		G3 or Ki67 $\geq$ 20%
Stage IIA	T0N1		
	T1N1		G3 or Ki67 $\geq$ 20%
	T2N0	G3, or G2 with Ki-67 $\geq$ 20% or high genomic risk[c]	
Stage IIB	T2N1		G3 or Ki67 $\geq$ 20%
	T3N0		
Stage IIIA	T0N2		
	T1N2		
	T2N2		
	T3N1		
	T3N2		
Stage IIIB	T4N0		
	T4N1		
	T4N2		
Stage IIIC	Any TN3		

Adjuvant CDK4/6i in HR+ EBC

monarchE

(median FU 54 mo)

Number of IDFS events

Abemaciclib + ET	ET Alone
407	**585**

HR (95% CI): 0.680 (0.599,
Nominal p <0.001

2-year abemaciclib treatm
period

Number at risk

| ET | 2808 | 2621 | 2549 | 2479 | 2408 | 2347 | 2284 | 2220 | 2095 | 1175 | 490 | 74 | 0 |
| lone | 2829 | 2653 | 2573 | 2474 | 2374 | 2281 | 2195 | 2125 | 1974 | 1124 | 473 | 67 | 0 |

NATALEE

(median FU 33,3 mo)
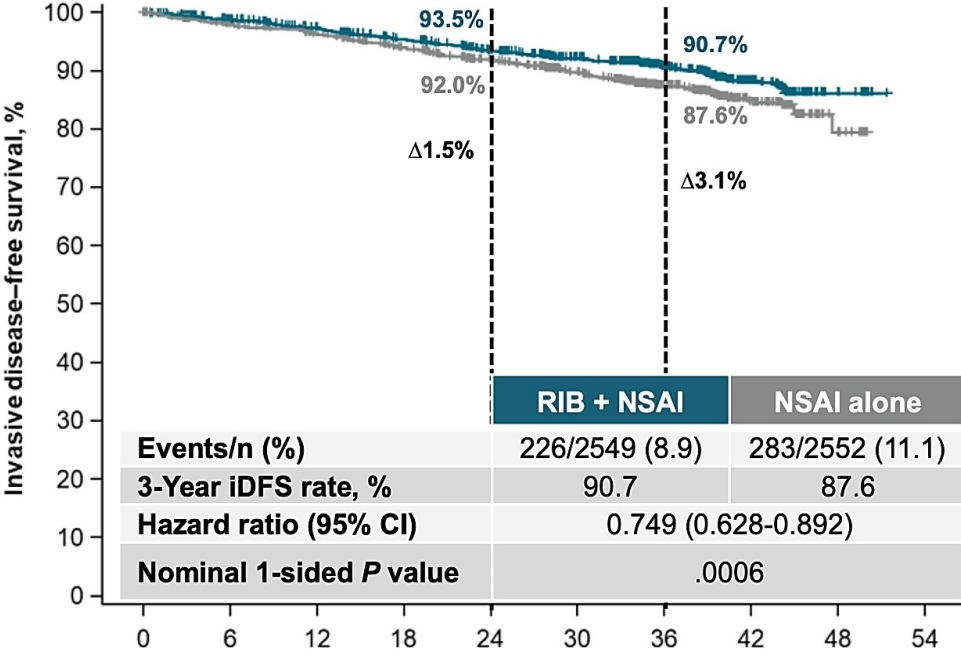
	RIB + NSAI	NSAI alone
Events/n (%)	226/2549 (8.9)	283/2552 (11.1)
3-Year iDFS rate, %	90.7	87.6
Hazard ratio (95% CI)	0.749 (0.628-0.892)	
Nominal 1-sided *P* value	.0006	

No. at risk

| RIB + NSAI | 2549 | 2350 | 2273 | 2204 | 2100 | 1694 | 1111 | 368 | 21 | 0 |
| NSAI alone | 2552 | 2241 | 2169 | 2080 | 1975 | 1597 | 1067 | 354 | 26 | 0 |

Harbeck N ESMO 2023

Hortobagyi et al SABCS 2023

Overall Survival

monarchE

Number of OS events

Abemaciclib + ET	ET Alone
208	234

HR (95% CI): 0.903 (0.749, 1.088)
p=0.284

2-year abemaciclib treatment period

Number at risk
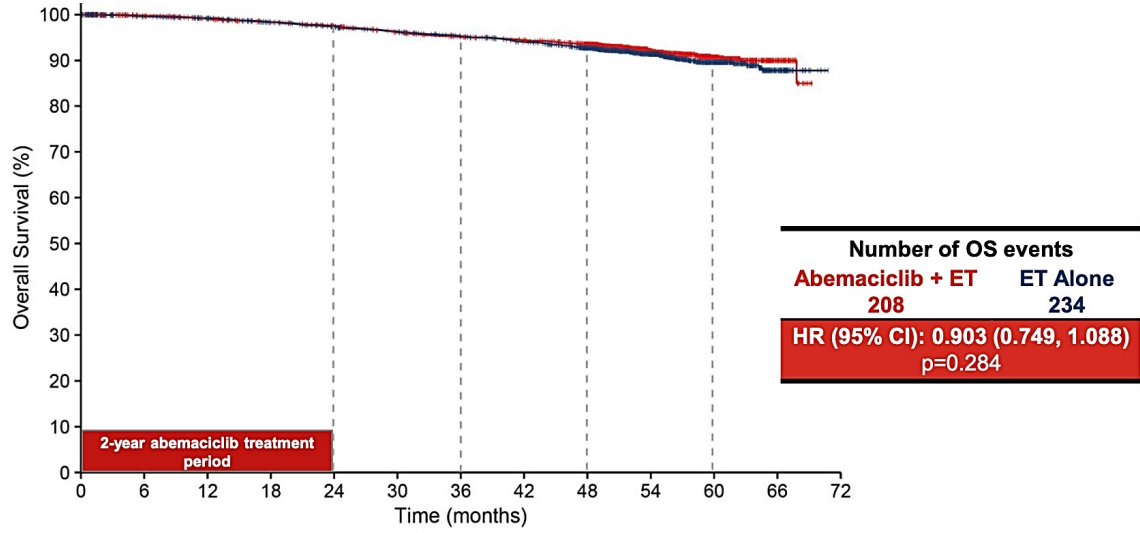
ciclib + ET	2808	2666	2614	2566	2518	2455	2407	2373	2260	1271	528	80	0
ET alone	2829	2705	2664	2599	2545	2496	2440	2382	2243	1279	538	77	0

At OS IA3 statistical significance was not reached for OS

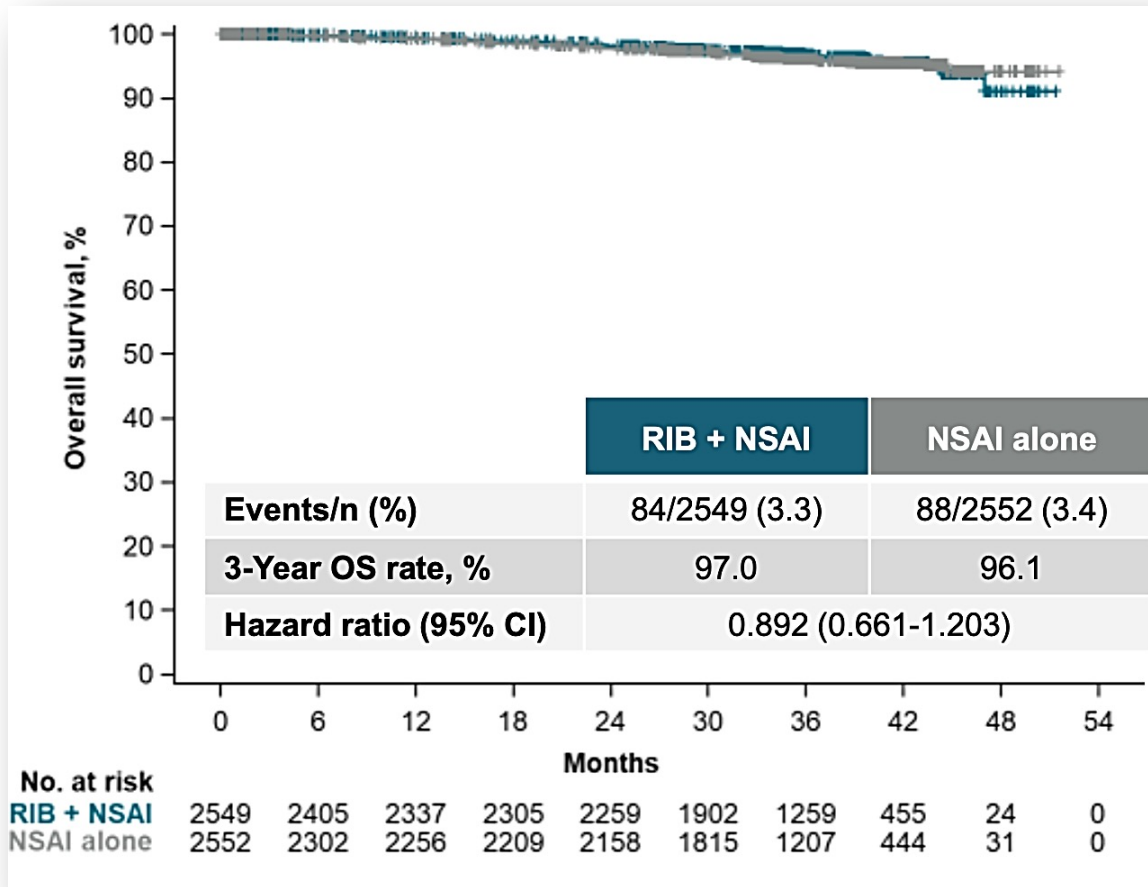## Fewer Patients with Metastatic Disease in the Abemaciclib Arm
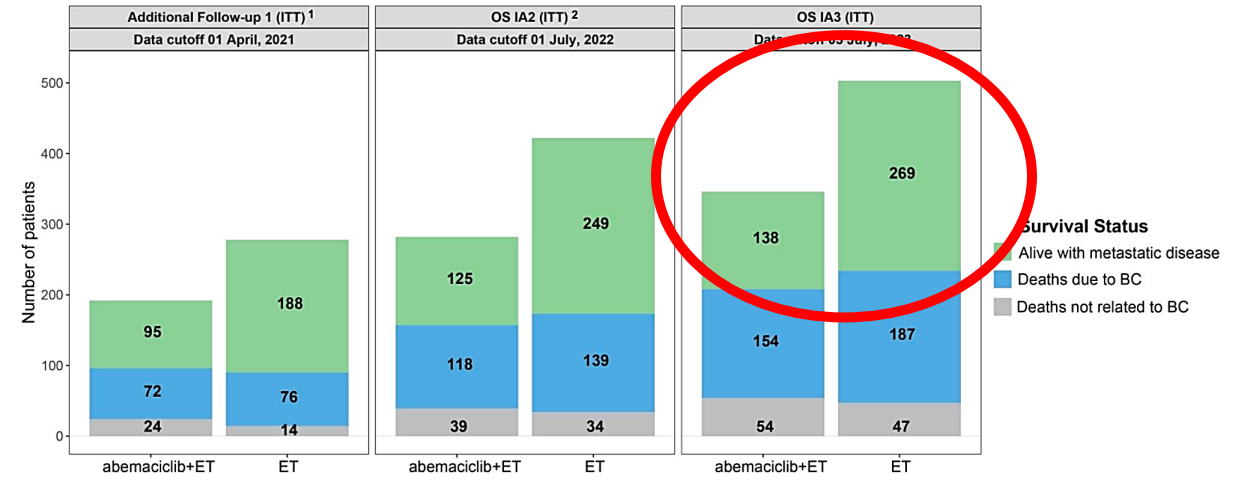
The imbalance of incurable metastatic recurrence continues to be substantial at OS IA3

[1]Harbeck* N, Rastogi* P, et al. Ann Oncol. 2021;32(12):1571-1581 *co-first authors
[2]Johnston SRD, et al. Lancet Oncol. 2023;24:77-90

Harbeck N et al; ESMO 2023

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Overall Survival

NATALEE

	RIB + NSAI	NSAI alone
Events/n (%)	84/2549 (3.3)	88/2552 (3.4)
3-Year OS rate, %	97.0	96.1
Hazard ratio (95% CI)	0.892 (0.661-1.203)	

No. at risk

RIB + NSAI	2549	2405	2337	2305	2259	1902	1259	455	24	0
NSAI alone	2552	2302	2256	2209	2158	1815	1207	444	31	0

Immature, fewer than 4% of events in both treatment arms

Hortobagyi et al SABCS 2023
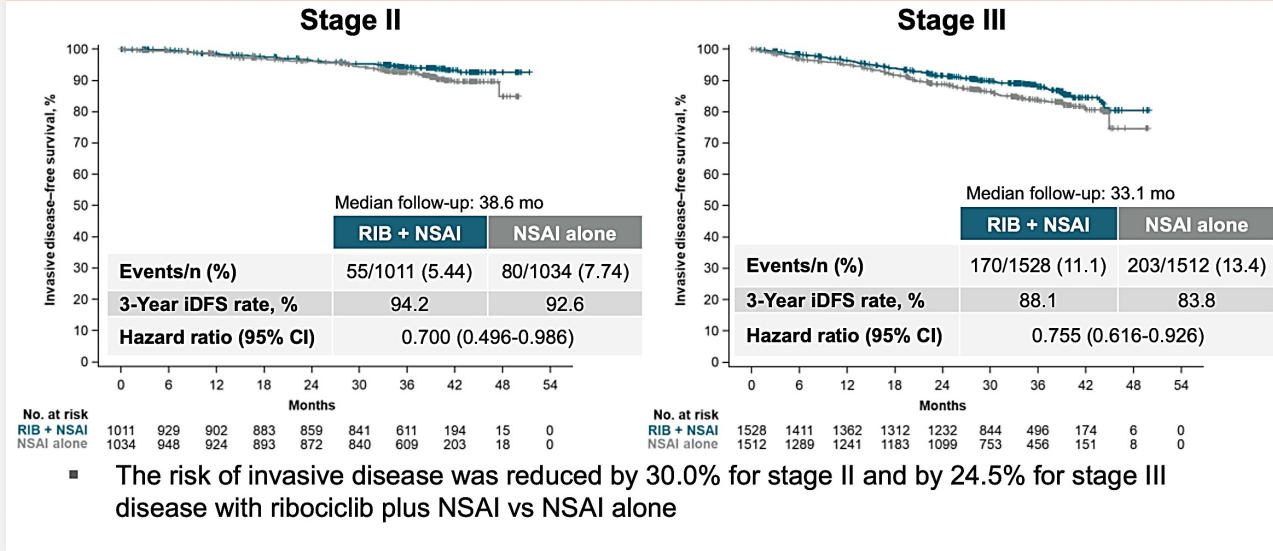
CDK4/6i and stage III EBC

monarchE

NATALEE

Consistent IDFS Benefit Observed in Selected Subgroups*

	Abemaciclib + ET		ET		← Favors Abemaciclib + ET Favors ET alone →	HR (95% CI)	Interaction p-value
	No.	Events	No.	Events			
Overall	2808	407	2829	585		0.680 (0.599, 0.772)	
Pooled Age Group 1							0.229
<65 years	2371	325	2416	485		0.658 (0.571, 0.757)	
≥65 years	437	82	413	100		0.797 (0.595, 1.067)	
IWRS Menopausal Status							0.095
Premenopausal	1221	150	1232	237		0.597 (0.487, 0.733)	
Postmenopausal	1587	257	1597	348		0.746 (0.635, 0.876)	
IWRS Prior Treatment							0.596
Neoadjuvant chemotherapy	1039	202	1048	297		0.649 (0.543, 0.776)	
Adjuvant chemotherapy	1642	183	1647	260		0.694 (0.574, 0.838)	
Baseline ECOG PS							0.097
0	2405	337	2369	489		0.654 (0.569, 0.751)	
1	401	70	455	95		0.869 (0.638, 1.184)	
Primary Tumor Size							0.053
<20 mm	781	82	767	150		0.517 (0.395, 0.677)	
≥20 mm but <50 mm	1371	214	1419	284		0.771 (0.646, 0.920)	
≥50 mm	607	102	610	144		0.676 (0.525, 0.871)	
Number of positive lymph nodes							0.438
1-3	1118	136	1142	182		0.750 (0.601, 0.937)	
4-9	1107	142	1126	231		0.614 (0.498, 0.757)	
10 or more	575	127	554	172		0.661 (0.526, 0.832)	
Tumor Grade							0.769
G1 - Favorable	209	24	216	35		0.698 (0.415, 1.174)	
G2 - Mod Favorable	1377	181	1395	268		0.665 (0.551, 0.803)	
G3 - Unfavorable	1086	195	1064	249		0.737 (0.608, 0.893)	
Tumor Stage							0.382
Stage II	716	79	740	106		0.764 (0.571, 1.022)	
Stage III	2078	326	2077	476		0.661 (0.574, 0.761)	
First ET							0.054
Tamoxifen	857	111	898	196		0.561 (0.445, 0.708)	
Aromatase Inhibitor	1931	293	1887	386		0.738 (0.634, 0.859)	

*Region of enrollment and Progesterone status data not shown

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MADRID 2023 ESMO congress

iDFS by Anatomical Stage

Stage II

Median follow-up: 38.6 mo

	RIB + NSAI	NSAI alone
Events/n (%)	55/1011 (5.44)	80/1034 (7.74)
3-Year iDFS rate, %	94.2	92.6
Hazard ratio (95% CI)	0.700 (0.496-0.986)	

No. at risk
	0	6	12	18	24	30	36	42	48	54
RIB + NSAI	1011	929	902	883	859	841	611	194	15	0
NSAI alone	1034	948	924	893	872	840	609	203	18	0

Stage III

Median follow-up: 33.1 mo

	RIB + NSAI	NSAI alone
Events/n (%)	170/1528 (11.1)	203/1512 (13.4)
3-Year iDFS rate, %	88.1	83.8
Hazard ratio (95% CI)	0.755 (0.616-0.926)	

No. at risk
	0	6	12	18	24	30	36	42	48	54
RIB + NSAI	1528	1411	1362	1312	1232	844	496	174	6	0
NSAI alone	1512	1289	1241	1183	1099	753	456	151	8	0

- The risk of invasive disease was reduced by 30.0% for stage II and by 24.5% for stage III disease with ribociclib plus NSAI vs NSAI alone
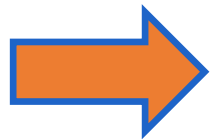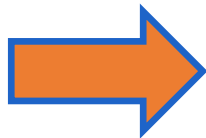
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Conclusion CDK4/6i in EBC

- Consistent and substantial treatment benefits with CDK4/6 inhibitors in adjuvant setting
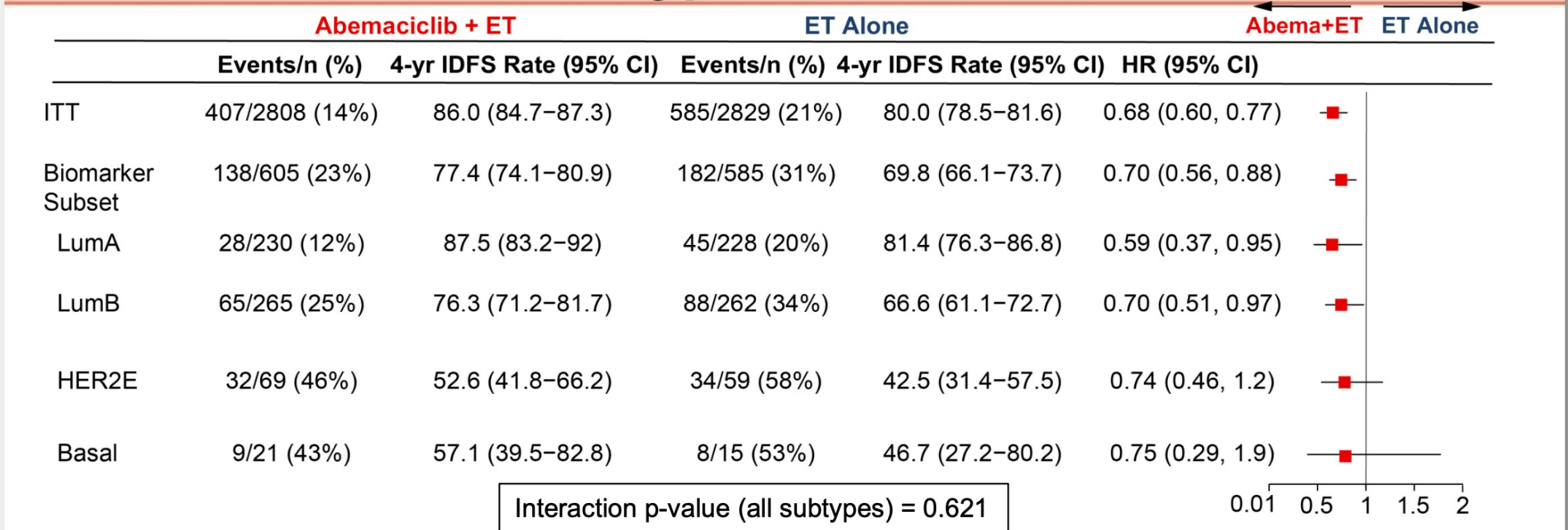- OS data are immature

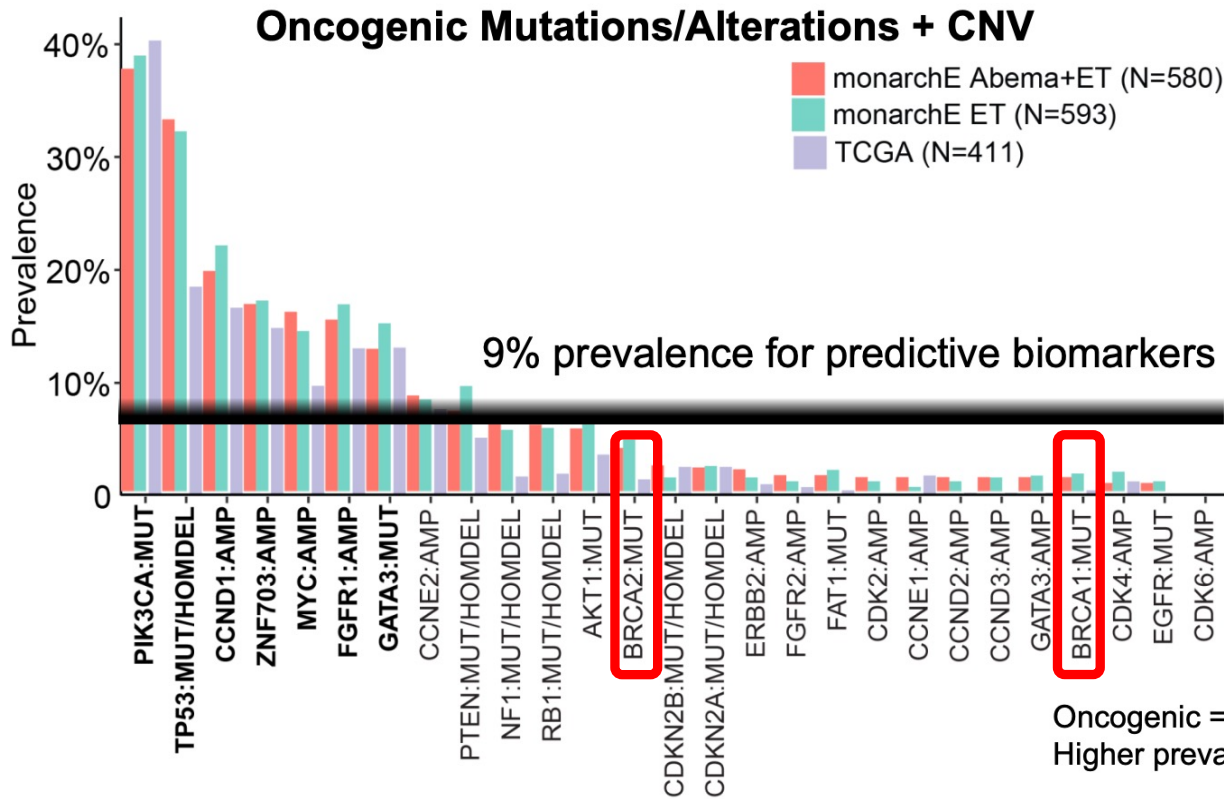**Longterm FU for magnitude of benefits and survival outcomes**

Predictive biomarker?

Molecular subtype

Consistent abemaciclib treatment benefit across all intrinsic molecular subtypes

	Abemaciclib + ET		ET Alone			
	Events/n (%)	4-yr IDFS Rate (95% CI)	Events/n (%)	4-yr IDFS Rate (95% CI)	HR (95% CI)	Abema+ET / ET Alone
ITT	407/2808 (14%)	86.0 (84.7–87.3)	585/2829 (21%)	80.0 (78.5–81.6)	0.68 (0.60, 0.77)	
Biomarker Subset	138/605 (23%)	77.4 (74.1–80.9)	182/585 (31%)	69.8 (66.1–73.7)	0.70 (0.56, 0.88)	
LumA	28/230 (12%)	87.5 (83.2–92)	45/228 (20%)	81.4 (76.3–86.8)	0.59 (0.37, 0.95)	
LumB	65/265 (25%)	76.3 (71.2–81.7)	88/262 (34%)	66.6 (61.1–72.7)	0.70 (0.51, 0.97)	
HER2E	32/69 (46%)	52.6 (41.8–66.2)	34/59 (58%)	42.5 (31.4–57.5)	0.74 (0.46, 1.2)	
Basal	9/21 (43%)	57.1 (39.5–82.8)	8/15 (53%)	46.7 (27.2–80.2)	0.75 (0.29, 1.9)	

Interaction p-value (all subtypes) = 0.621

0.01 0.5 1 1.5 2

- The selected biomarker subset is enriched for IDFS events using case-cohort design
- IDFS rates are presented as indicative of relative prognosis across subtypes but do not inform the actual risk of recurrence within each subtype because of IDFS enrichment

LumA = luminal A, LumB = luminal B, HER2E = Human Epidermal Growth Factor Receptor 2 – Enriched

Prevalence oncogenic mutations and copy number variation

Oncogenic Mutations/Alterations + CNV

Legend:
- monarchE Abema+ET (N=580)
- monarchE ET (N=593)
- TCGA (N=411)

9% prevalence for predictive biomarkers

- Overall similar prevalence of biomarker alterations in monarchE and TCGA cohorts

- Oncogenic mutations and copy number alterations (≥ 9%) were selected for the predictive biomarker analysis

Oncogenic = Known activating or loss-of-function variants
Higher prevalence rates observed in TP53, NF1, and RB1

MUT = mutation **HOMDEL** = homozygous deletion **AMP** = amplification
TCGA BRCA WES cohort: T0,1,2; Primary; ER+ HER2- cases; n=411

9% prevalence was used to reach 80% statistical power for each predictive biomarker for the respective DNA biomarker sample size

Consistent treatment benefit across most prevalent genomic alterations

	Prevalence	Abemaciclib + ET Events/n (%)	ET Alone Events/n (%)	HR (95% CI)		Interaction p-value
All patients		123/580 (22%)	169/593 (28%)	0.72(0.57,0.91)		
PIK3CA mut	38%	**55/217 (26%)**	**73/229 (32%)**	**0.75(0.53,1.1)**		0.758
PIK3CA wt		68/363 (18%)	96/364 (26%)	0.70(0.51,0.95)		
TP53 mut/homdel	32%	**55/189 (30%)**	**82/184 (44%)**	**0.60(0.42,0.84)**		0.184
TP53 wt		68/391 (18%)	87/409 (22%)	0.81(0.59,1.1)		
CCND1 amp	20%	**36/113 (32%)**	**42/129 (32%)**	**0.94(0.6,1.5)**		0.177
CCND1 wt		87/467 (18%)	127/464 (28%)	0.66(0.5,0.87)		
ZNF703 amp	16%	**28/96 (30%)**	**37/100 (36%)**	**0.77(0.47,1.3)**		0.776
ZNF703 wt		95/484 (20%)	132/493 (26%)	0.71(0.54,0.92)		
MYC amp	16%	**34/92 (36%)**	**25/84 (30%)**	**1.30(0.77,2.2)**		0.014
MYC wt		89/488 (18%)	144/509 (28%)	0.62(0.47,0.8)		
FGFR1 amp	16%	**26/88 (30%)**	**35/98 (36%)**	**0.80(0.48,1.3)**		0.641
FGFR1 wt		97/492 (20%)	134/495 (28%)	0.70(0.54,0.91)		
GATA3 mut	14%	**13/73 (18%)**	**17/88 (20%)**	**0.86(0.42,1.8)**		0.513
GATA3 wt		110/507 (22%)	152/505 (30%)	0.69(0.54,0.89)		

Abema+ET ←   → ET alone

0.01 0.5 1 1.5 2

MUT = mutation

HOMDEL = homozygous deletion

AMP = amplification

MYC, GATA3, FGFR1, ZNF703: analyses limited by small sample size

MYC amplifications were associated with diminished benefit in this exploratory analysis

No data on BRCAm and abemacyclib in monarchE

CDK4/6i in gBRCA MBC

- *Mostly retrospective*
- *Subgroup analyses*
- *Small sample size of BRCAm patients*

Author	Results/Conclusions
Frenel et al.	BRCA/PALB2 mutated patients with shorter PFS (14.3 vs. 26.7m)
Collins et al.	BRCA mutated patients with shorter OS (26 vs. 51m)
Bruno et al.	BRCA/CHECK/ATM mutated patients with worse outcomes
Safonov et al.	BRCA2 mutations with worse PFS
Fuentes Antras, et al.	BRCA1/2 and PALB2 mutations with shorter PFS (9.9 vs. 26.8m)

PADA trial 1017 pts, 16 BRCA2m, 1 BRCA1m

Retrospective Flatiron database , 2968 pts, 85 BRCAM

Retrospective , 217 pts, 10 BRCA2m, mPFS 10,2m vs 15.6m in wt

Retrospective 2242 pts, 81 BRCA2m

Retrospective, 153 pts, 21pat BRCA/PalB2m

Frenel J et al, Ann Oncol 2020; Bruno L et al, JCO Precision oncol 2022; Safonov A et al, Cancer Res 2022; Collins L et al, Oncol Therapy 2021; Fuentes-Antras J et al, ASCO 2023.

BRCAm patients treated with CDK4/6i: Mechanisms for potential worse outcome?

Resistance to CDK4/6i is heterogenous
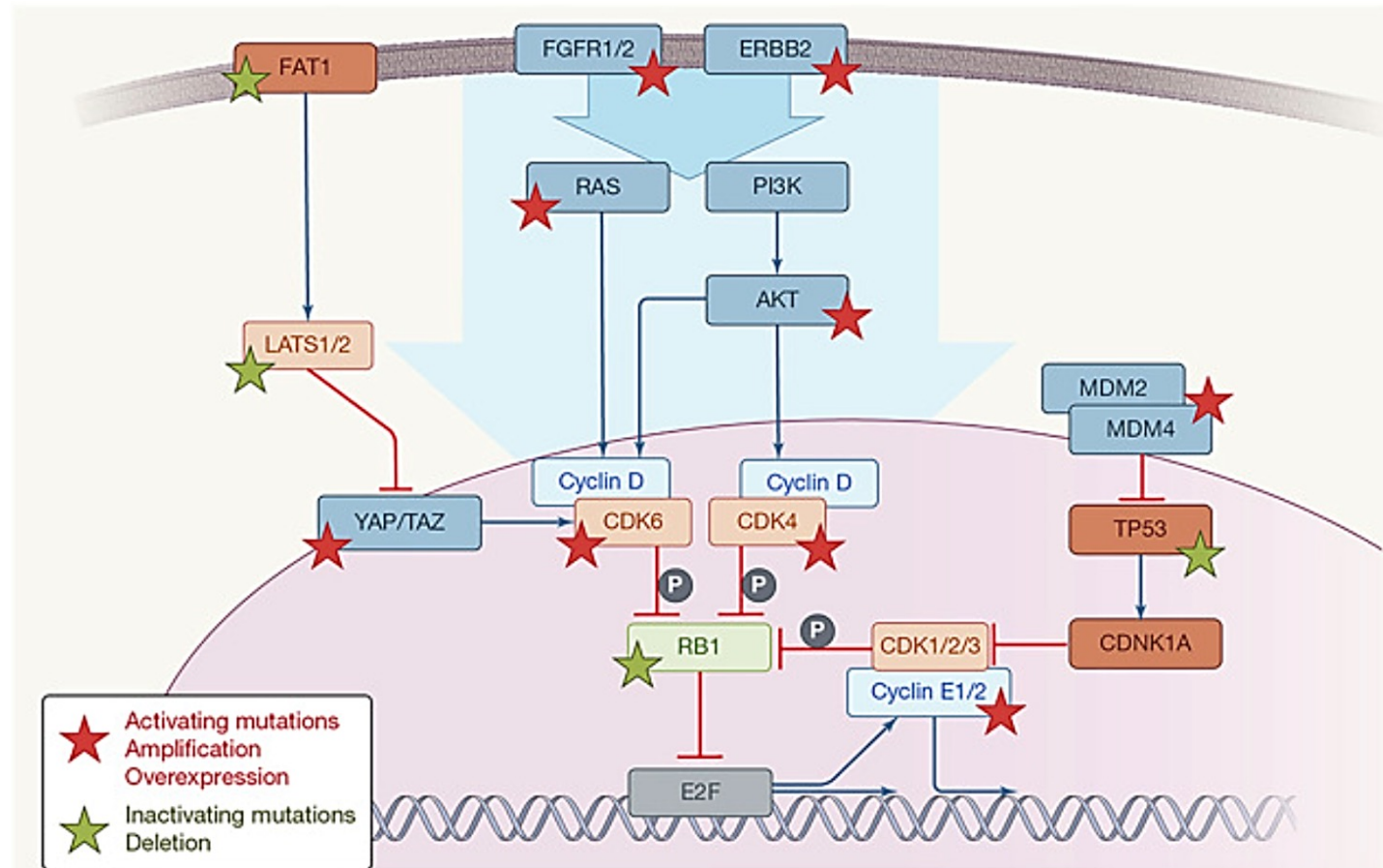
Álvarez-Fernández and Malumbres 2020 PMID: 32289274

- Cell cycle machinery
  - RB1, CCNE1/2, CDK6, p16, INK4, FAT1
- Growth factor signaling
  - FGFR, HER2, RAS/MAPK pathway, PTEN
- Epigenetic
  - Basal subtype, loss of ER/PR expression
- Microenvironment
  - Interferon signaling

Loss of Rb drives resistance to CDK4/6i

Approximately 10% of patients that progress on CDK4/6 inhibitors acquire loss-of-function *RB1* mutations
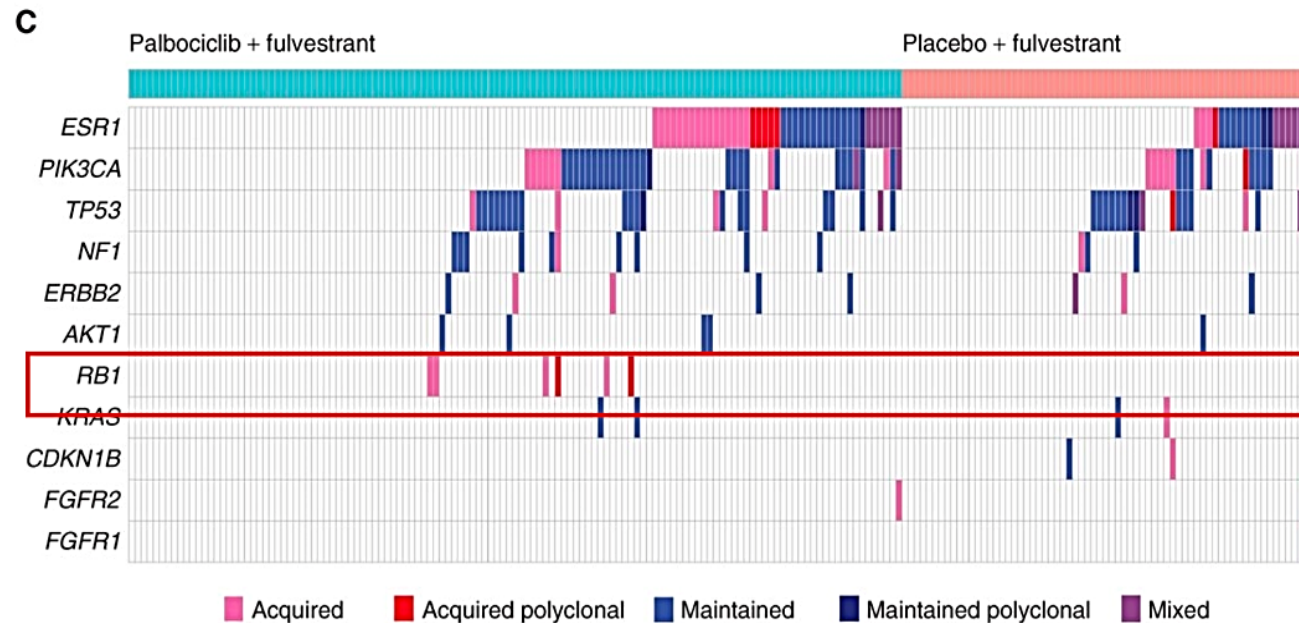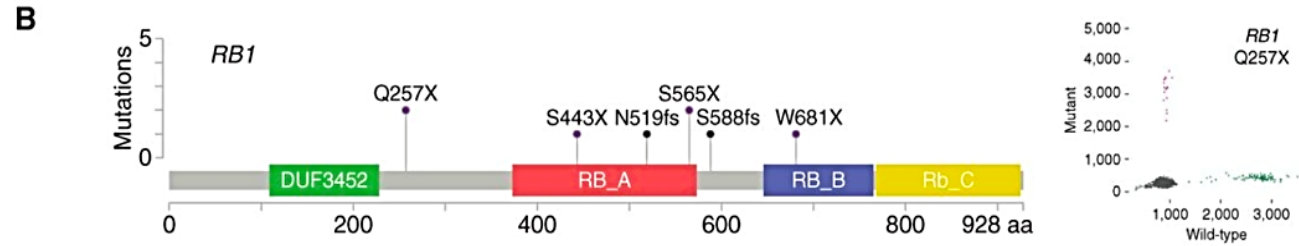
O'Leary B, et al. 2018. PMID: 30206110

Hanker A SABCS 2023

Rb1 alterations enriched in gBRCA2 carriers

Germline-somatic gene enrichment
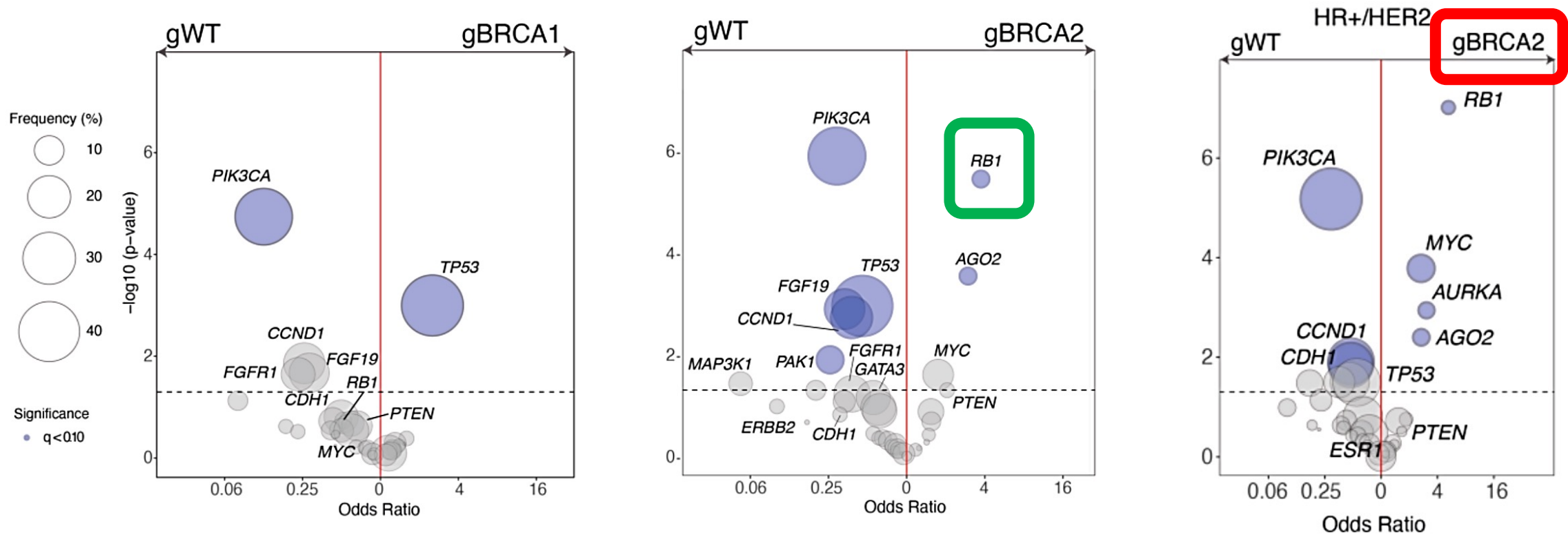
n= 4,640 patients

Rb1 LOH associated with worse outcome on CDK4/6i

Safonov et al SABCS 2023

Nicholas Turner and Ben O'Leary
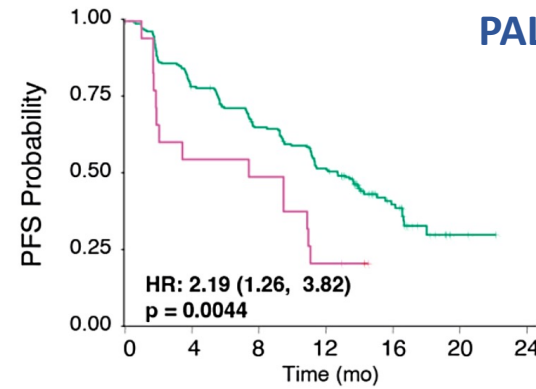
gBRCA2: worse PFS on CDK4/6i

Razavi et al SABCS 2023
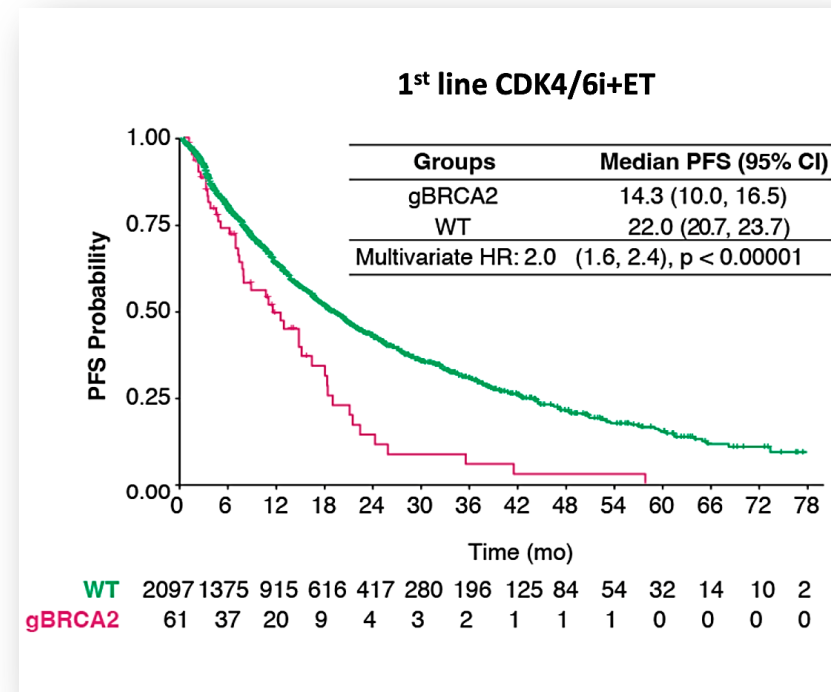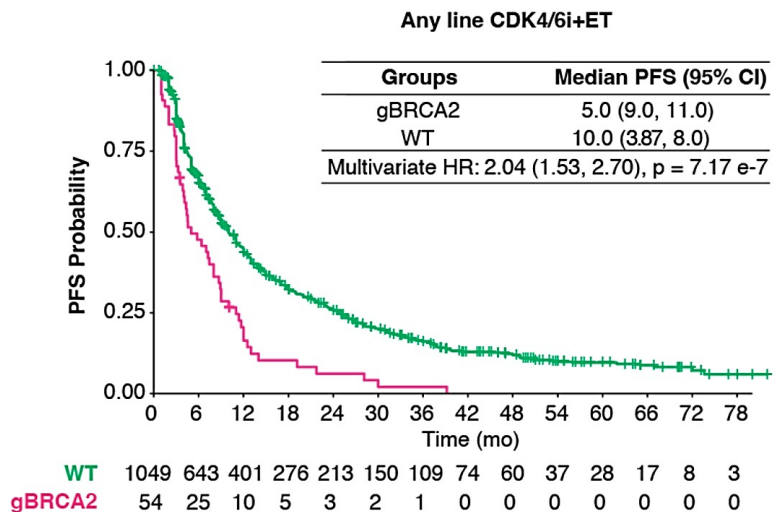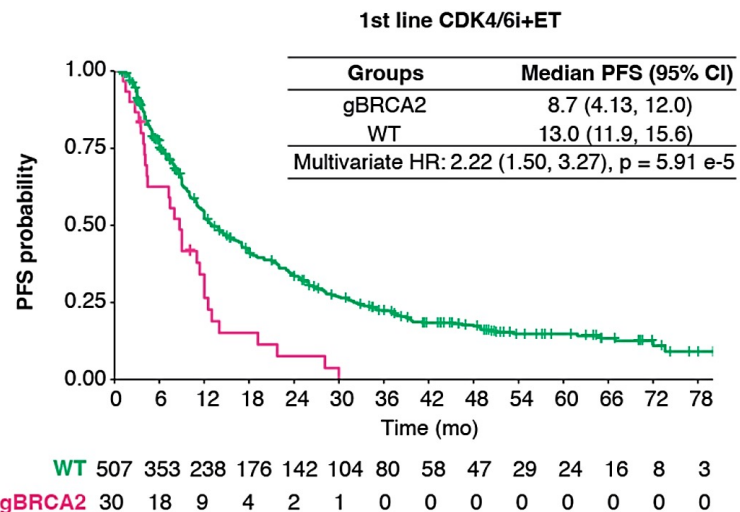
Rb1 and BRCA2 are co-located on Chromosome 13q
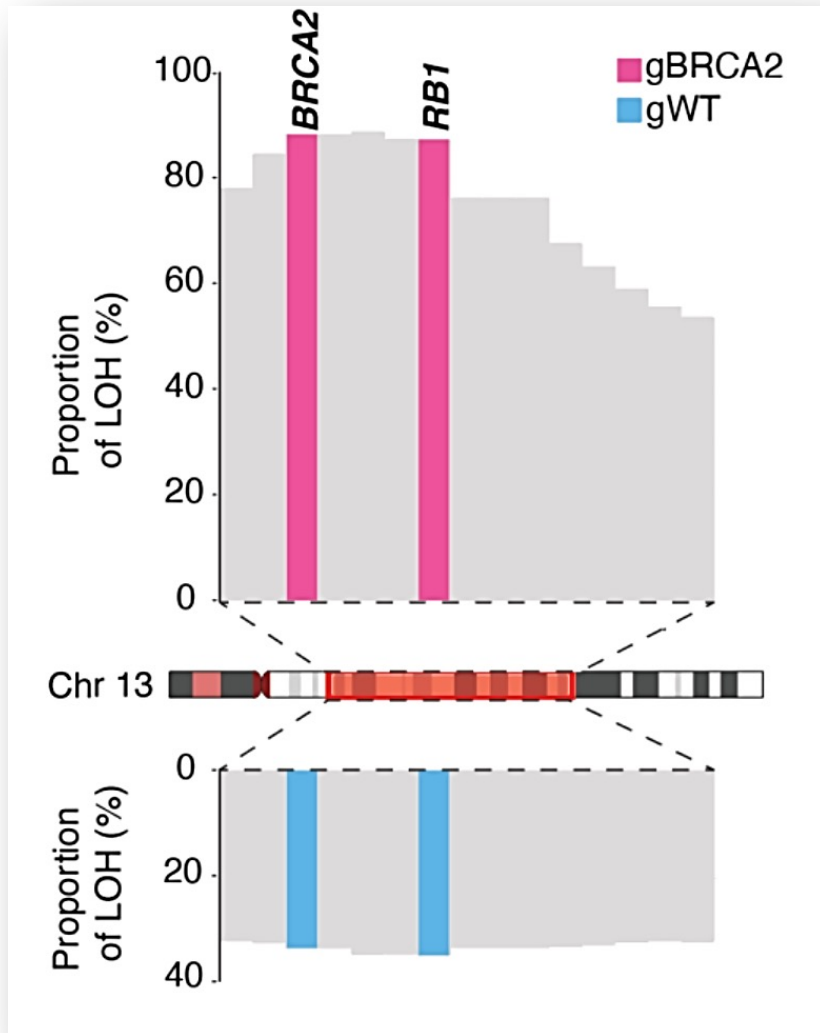
Loss of heterozygosity of *BRCA2* and *RB1*

RB1   *BRCA2*

Mandigo et al 2020, *CCR*

ONCOGENESIS
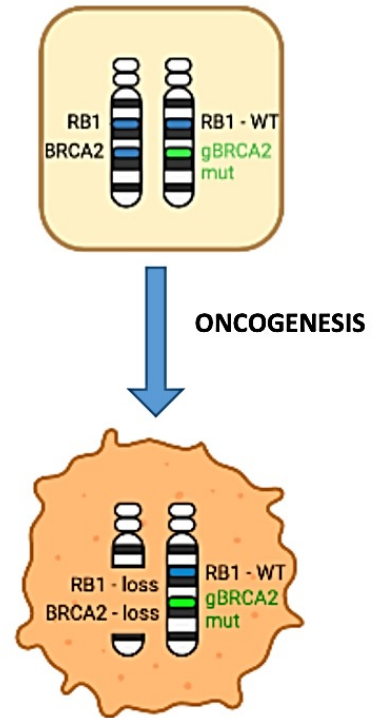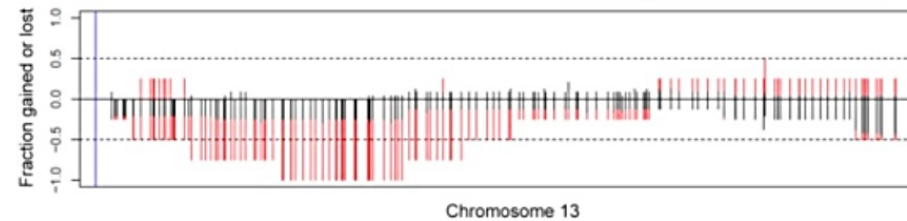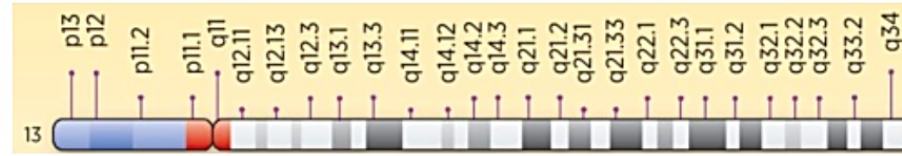
Mono-allelic loss of both
BRCA2 and RB1

wt RB1 allele vulnerable to on-treatment mutations

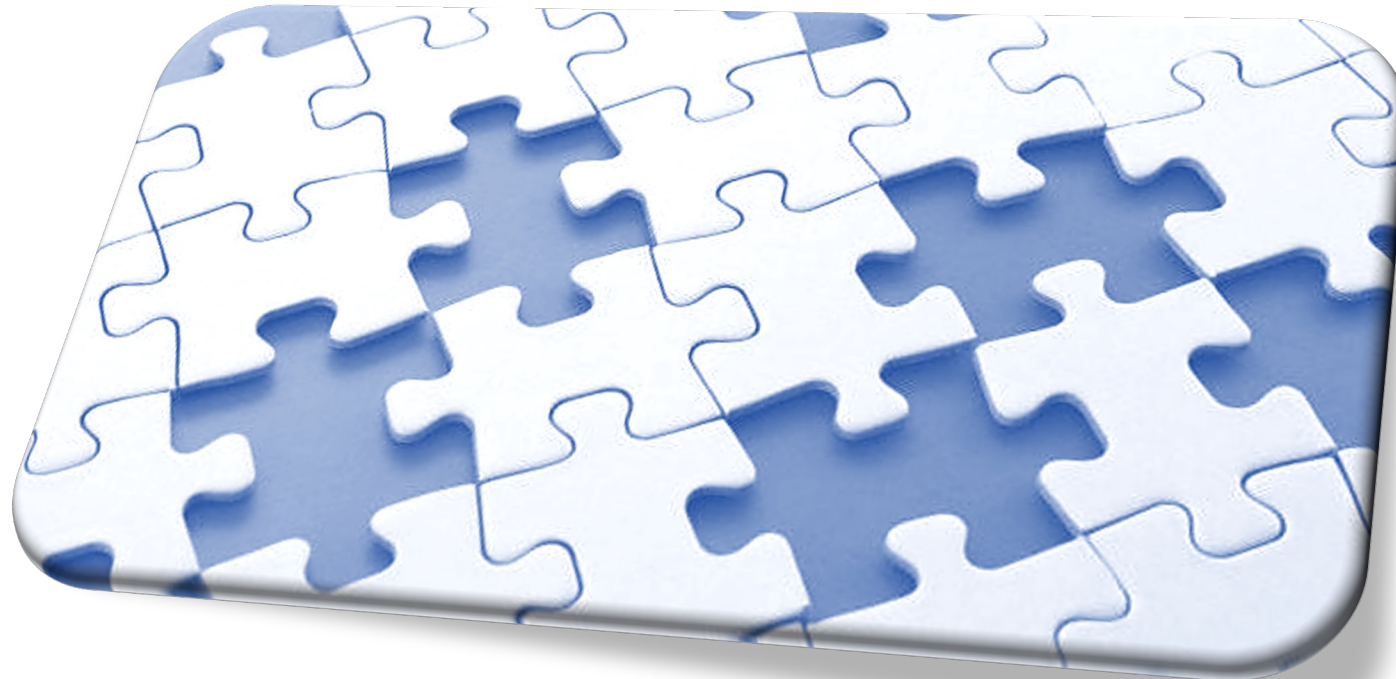**Hypothesis for worse outcome of BRCAm patients treated with CDK4/6i?**

Interesting data for the role of Rb1 in BRCA2m MBC

No data in EBC

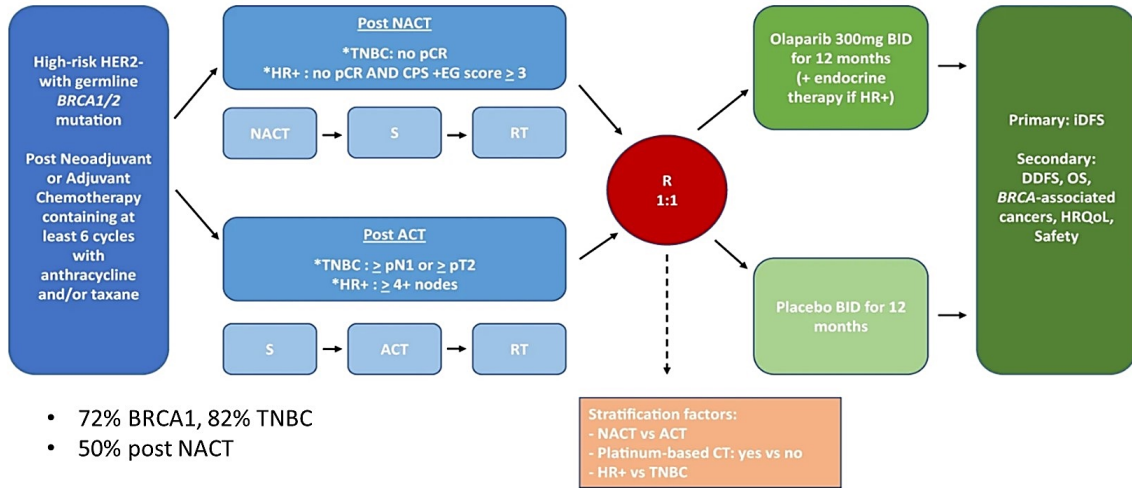# Prospective trials of CDK4/6i in gBRCA patients?

HOPE: Olaparib, Palbociclib and Fulvestrant in Patients With BRCA Mutation-associated, HR+, HER2-metastatic Breast Cancer
ClinicalTrials.gov ID NCT03685331

Trials in EBC?
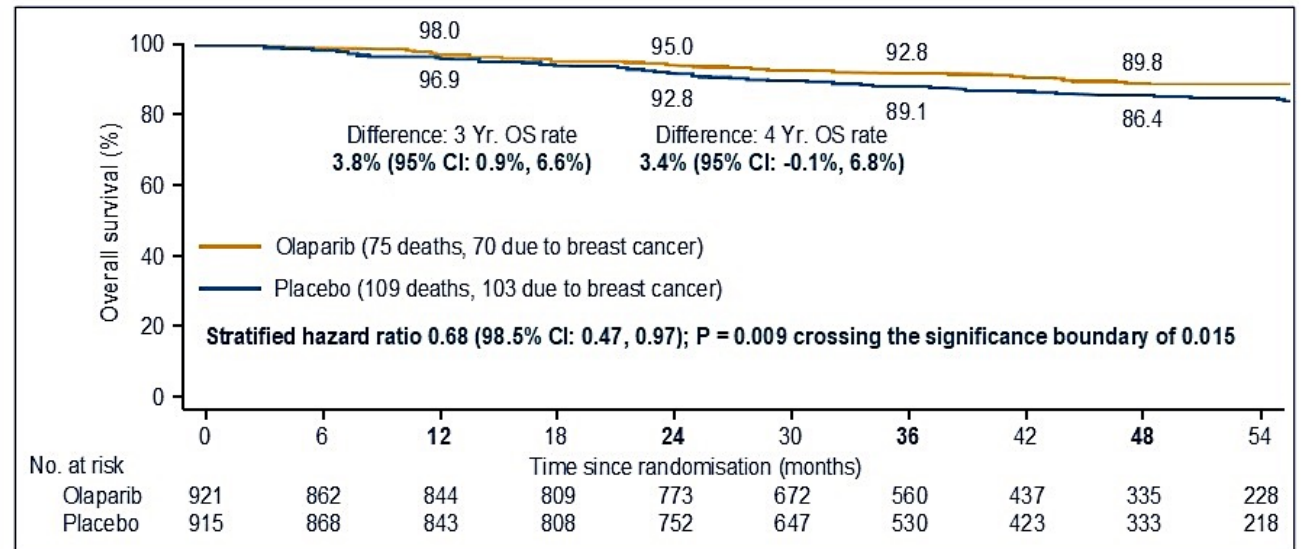
Adjuvant PARPi

OlympiA: adjuvant olaparib for gBRCA1/2

- 72% BRCA1, 82% TNBC
- 50% post NACT

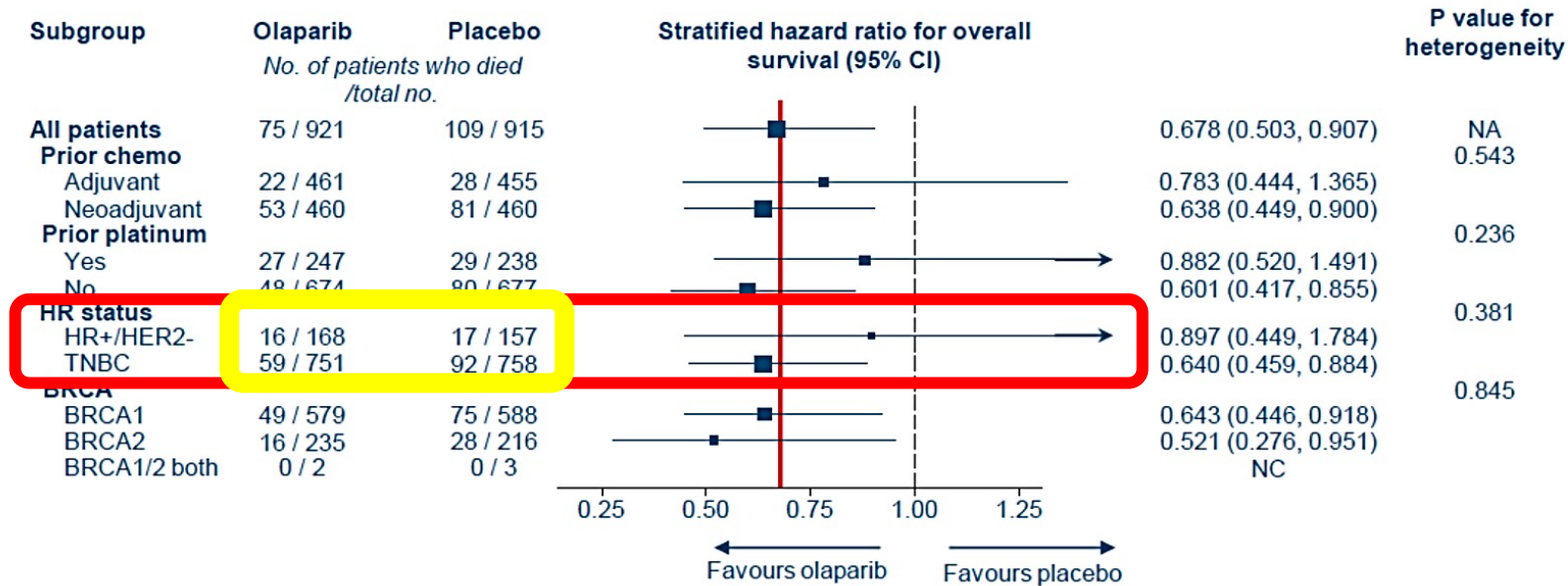Tutt et al. N Engl J Med. 2021;384(25):2394-2405, Tung N npj Breast Cancer 2022: 8(47)

Tutt et al, N Eng J Med 2021; Geyer CE et al, 2022

Are PARPi indicated for ER+ gBRCAm EBC?

SUBGROUP ANALYSIS OF OS

Subgroup	Olaparib	Placebo	Stratified hazard ratio for overall survival (95% CI)	P value for heterogeneity
	No. of patients who died /total no.			
All patients	75 / 921	109 / 915	0.678 (0.503, 0.907)	NA
Prior chemo				0.543
Adjuvant	22 / 461	28 / 455	0.783 (0.444, 1.365)	
Neoadjuvant	53 / 460	81 / 460	0.638 (0.449, 0.900)	
Prior platinum				0.236
Yes	27 / 247	29 / 238	0.882 (0.520, 1.491)	
No	48 / 674	80 / 677	0.601 (0.417, 0.855)	
HR status				0.381
HR+/HER2-	16 / 168	17 / 157	0.897 (0.449, 1.784)	
TNBC	59 / 751	92 / 758	0.640 (0.459, 0.884)	
BRCA				0.845
BRCA1	49 / 579	75 / 588	0.643 (0.446, 0.918)	
BRCA2	16 / 235	28 / 216	0.521 (0.276, 0.951)	
BRCA1/2 both	0 / 2	0 / 3	NC	

0.25 0.50 0.75 1.00 1.25

Favours olaparib ← → Favours placebo

All subgroup hazard ratio point estimates are < 1 and confidence intervals include the hazard ratio for olaparib treatment effect in the overall ITT population

We urgently need more data in ER+ gBRCAm EBC

Conclusion:

Olaparib and abemaciclib approved for high risk HR+ gBRCA

Significant questions remain for:

- ***Abemaciclib***: – can biomarkers identify patients most likely to (or not) benefit? C-myc? RB1?

  - prospective data in gBRCA patients are lacking

  - longer FU for OS

- ***Olaparib***: limited data in HR+ gBRCA

<p style="text-align:center; color:red;">***Patient selection will be the key to more success***</p>

- Dynamic biomarker changes?
- Small short-term neoadjuvant trials to predict successful therapies? (*eg ADAPTLate, POETIC A, ..*)

HOW to choose?

- IDFS benefit
- Immature OS data
- 2y Abema / 3y Ribo
- Costs
- Safety
- Adherence

- **Biomarker driven**
- DFS benefit
- **OS benefit** (also for ER+?)
- 1y Olaparib
- Costs
- Safety
- Adherence

HOW to choose?

- IDFS benefit
- Immature OS data
- 2y Abema / 3y Ribo
- Costs
- Safety
- Adherence

Fertility?

- **Biomarker driven**
- DFS benefit
- **OS benefit** (also for ER+?)
- 1y Olaparib
- Costs
- Safety
- Adherence