RAGMA 23

16ª Revisión Anual GEICAM de Avances en Cáncer de Mama

Realidades y esperanzas

Avances en cáncer de mama hereditario

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Organizado por:

GEICAM investigación en cáncer de mama

Disclosure information

- Employment: Hospital QuironSalud Zaragoza
- Consultant or Advisory Role: Gilead, Daichii, Astra Zeneca, Seagen
- Speaking: Roche, Eisai, Daichii, Pfizer, Lilly, Novartis, Astra-Zeneca, MSD, Myriad

Hereditary breast cancer

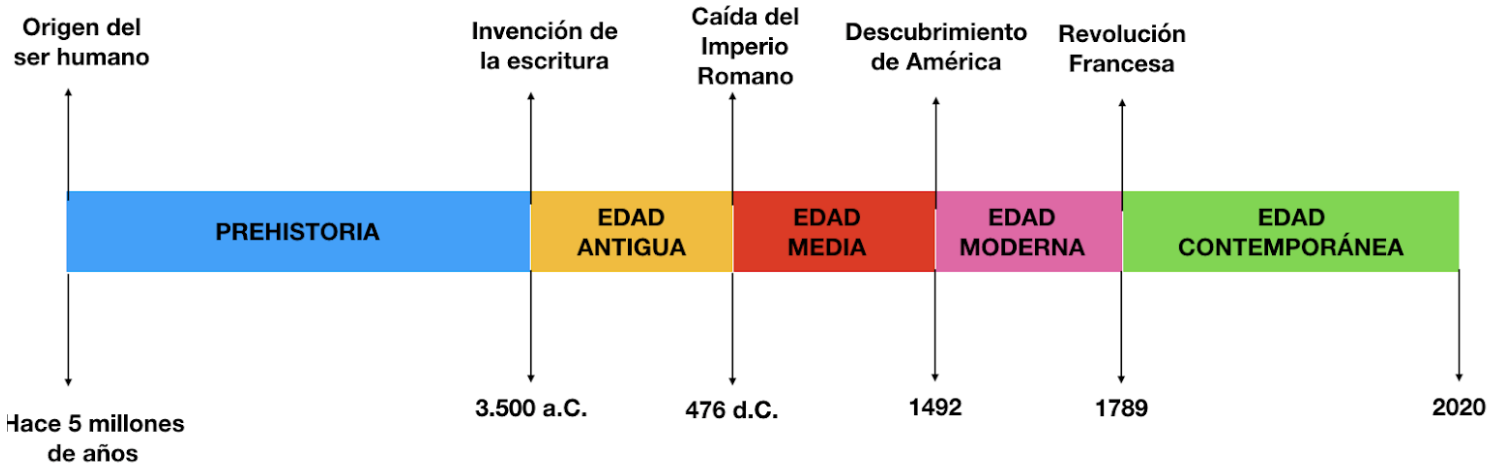
Are we (really) making any progress?

Yes, of course

- Genetic counselling approach: Mainstreaming
- Current advances in BC risk assessement: Canrisk
- Treatment intention: iPARP
- New issues in a new social era
- Other topics

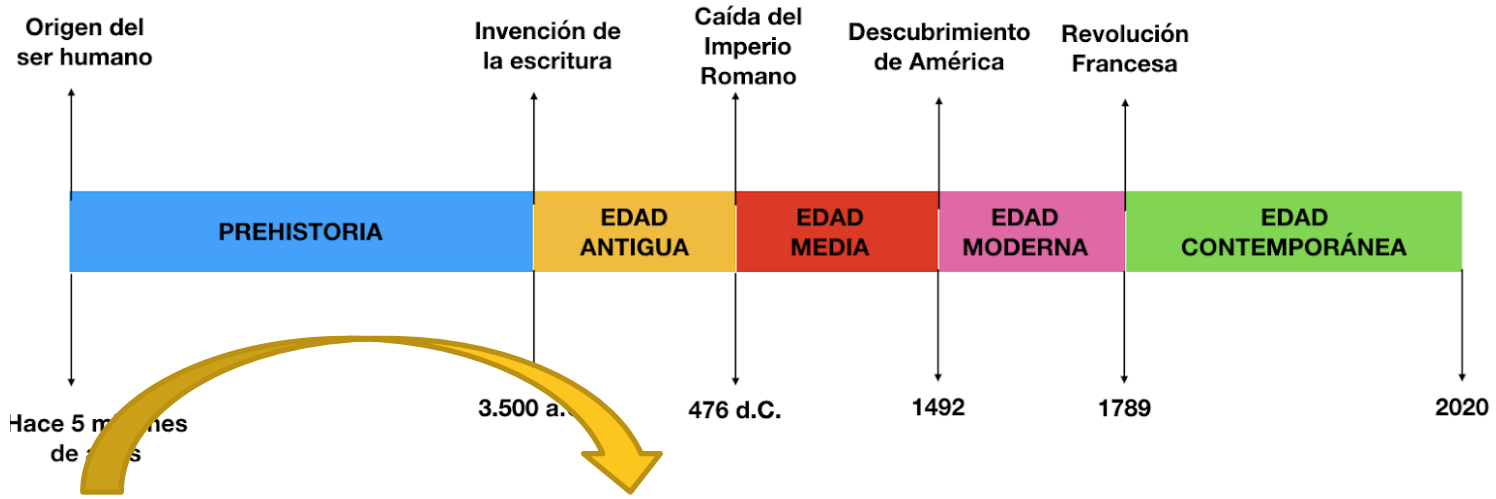
Genetic counselling approach

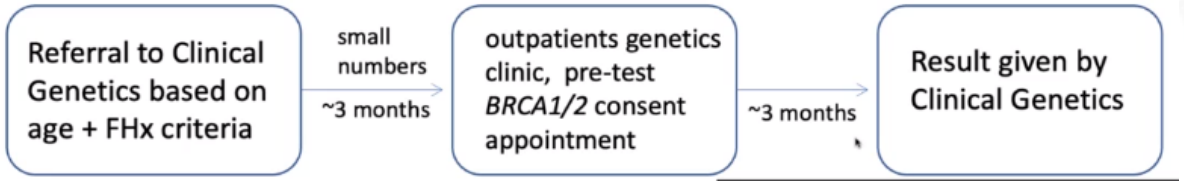
Mainstreaming model



Genetic counselling approach

Mainstreaming model

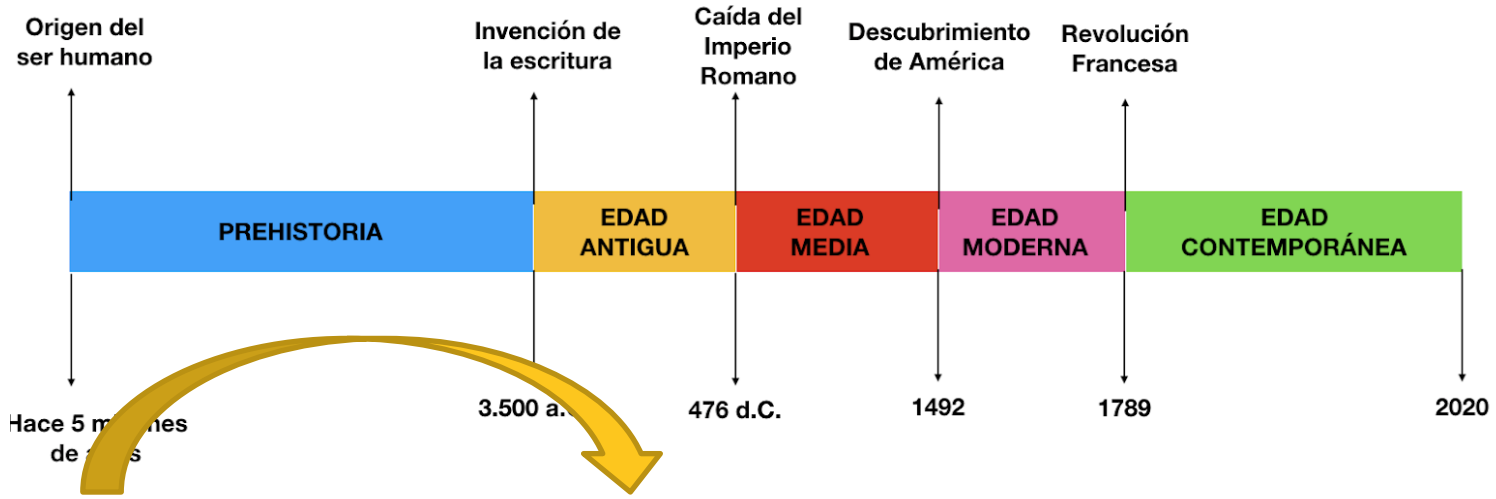




Mainstreaming in GC

Genetic counselling approach

Mainstreaming model

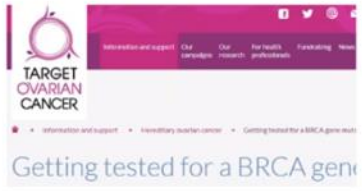


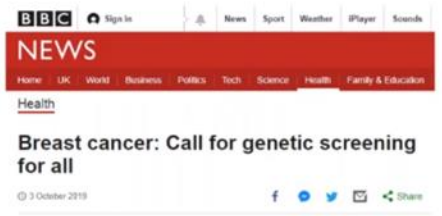
Referral to Clinical Genetics based on age + FHx criteria → small numbers, ~3 months → outpatients genetics clinic, pre-test *BRCA1/2* consent appointment → ~3 months → Result given by Clinical Genetics

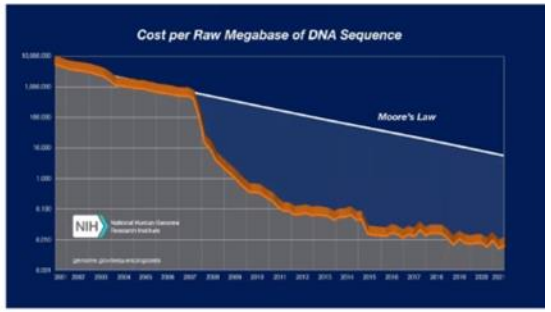
Mainstreaming in GC

Increasing Public awareness

Cheaper, faster testing







The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

A.N.J. Tutt, J.E. Garber, B. Kaufman, G. Viale, D. Fumagalli, P. Rastogi, R.D. Gelber, E. de Azambuja, A. Fielding, J. Balmaña, S.M. Domchek, K.A. Gelmon, S.J. Hollingsworth, L.A. Korde, B. Linderholm, H. Bandos, E. Senkus, J.M. Suga, Z. Shao, A.W. Pippas, Z. Nowecki, T. Huzarski, P.A. Ganz, P.C. Lucas, N. Baker, S. Loibl, R. McConnell, M. Piccart, R. Schmutzler, G.G. Steger, J.P. Costantino, A. Arahmani, N. Wolmark, E. McFadden, V. Karantza, S.R. Lakhani, G. Yothers, C. Campbell, and C.E. Geyer, Jr., for the OlympiA Clinical Trial Steering Committee and Investigators*

Brokkers K et al.Cancer 2022

Mainstreaming

Impact on patients

Positives

- Quicker result
- Can guide treatment
- More certainty about other cancer risks
- Personalised management (surgery)
- Access to targeted resources sooner (iPARP)

Negatives

- Less information pre-test
- Getting result just after diagnosis
- Less time to consider consequences of test
- Fear of other cancer risks
- Burden of telling family in early treatment

Mainstreaming in breast

A story that is currently changing

- Fast track units
- Design a structured pathway
- Multidisciplinary approach
- Who order the test: oncologist? Single vs panel?
- Clinical criteria: Clinical guidelines vs universal screening
- Maintain quality indicators

Mainstreaming in breast

A story that is currently changing

- Fast track units
- Design a structured pathway
- Multidisciplinary approach
- Who order the test: oncologist? Single vs panel?
- Clinical criteria: Clinical guidelines vs universal screening
- Maintain quality indicators

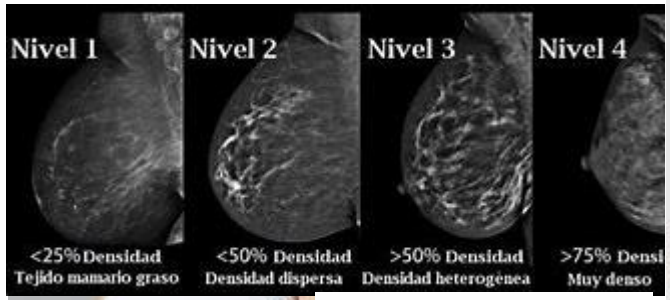
Technology is here and it has come to stay

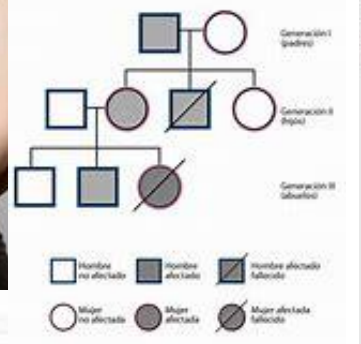
Current advances in BC risk assessement: Personalised approach

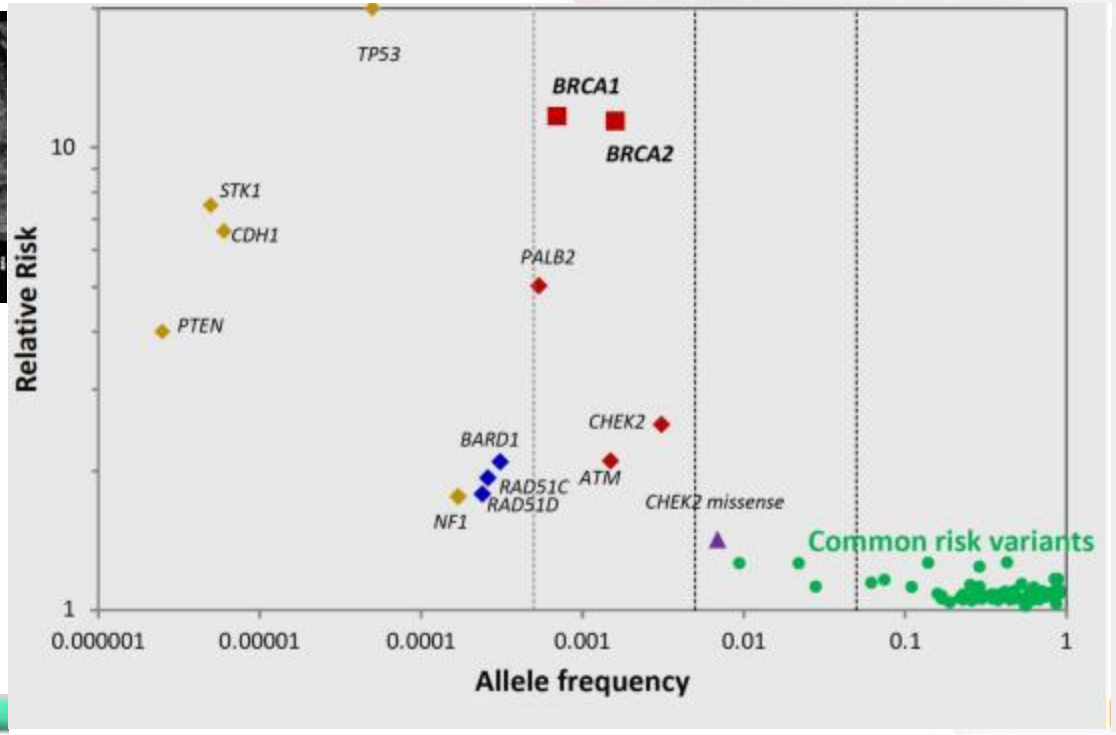
Poligenic risk and clinical utility

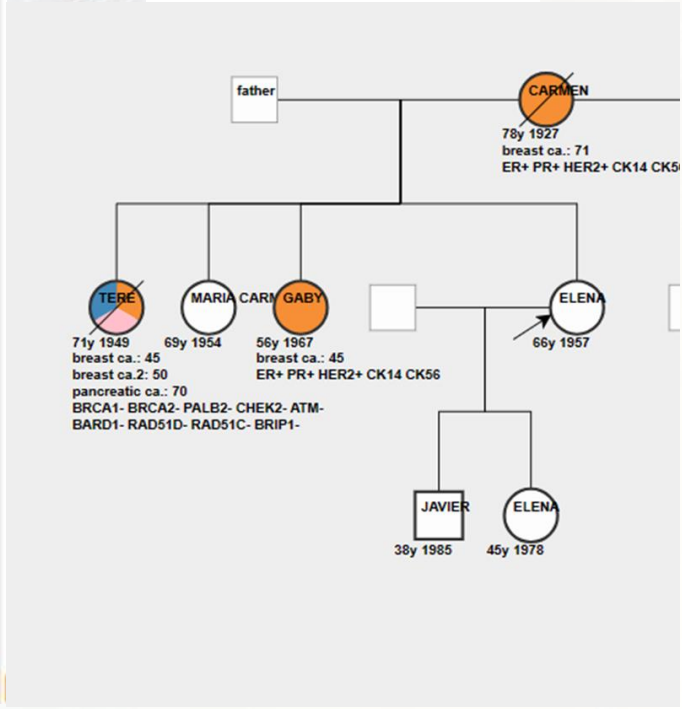
From Gail to new improved tools

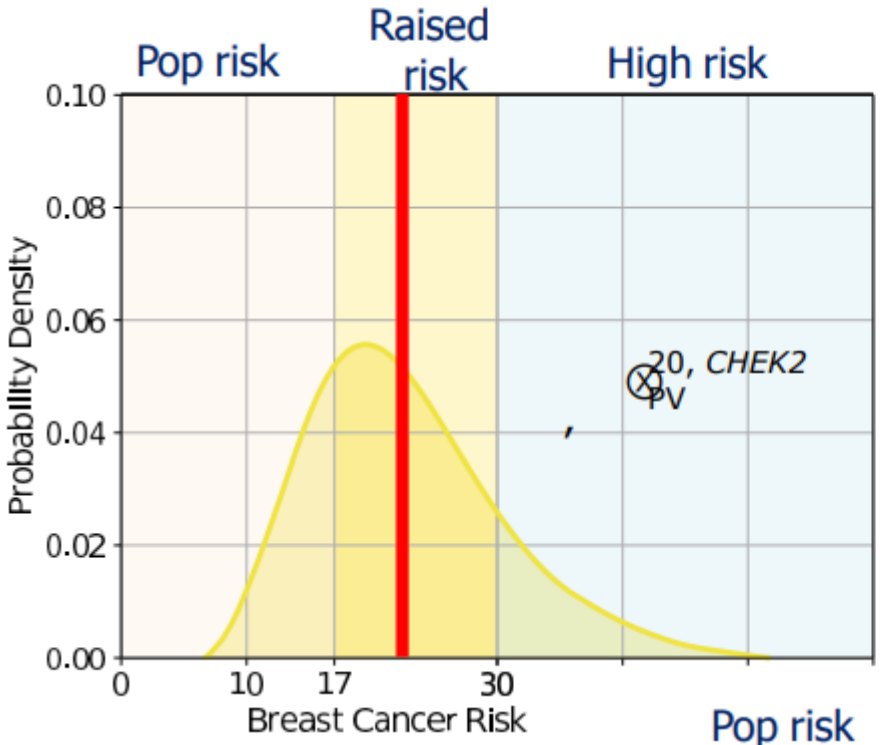
CanRisk
www.canrisk.org





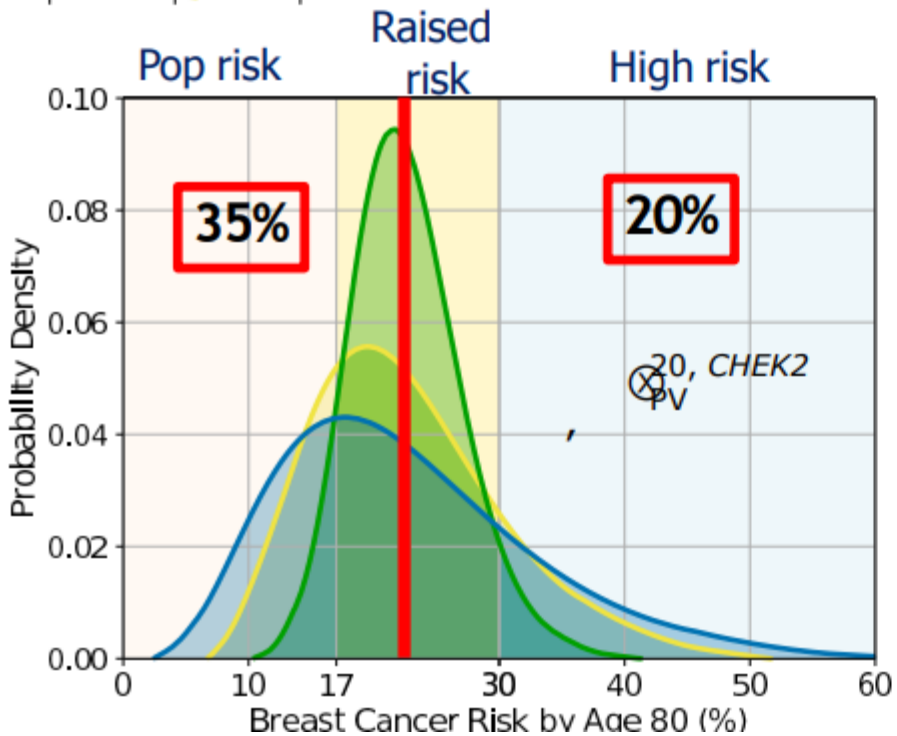






Average *CHEK2* Risk

Polygenic Risk Score



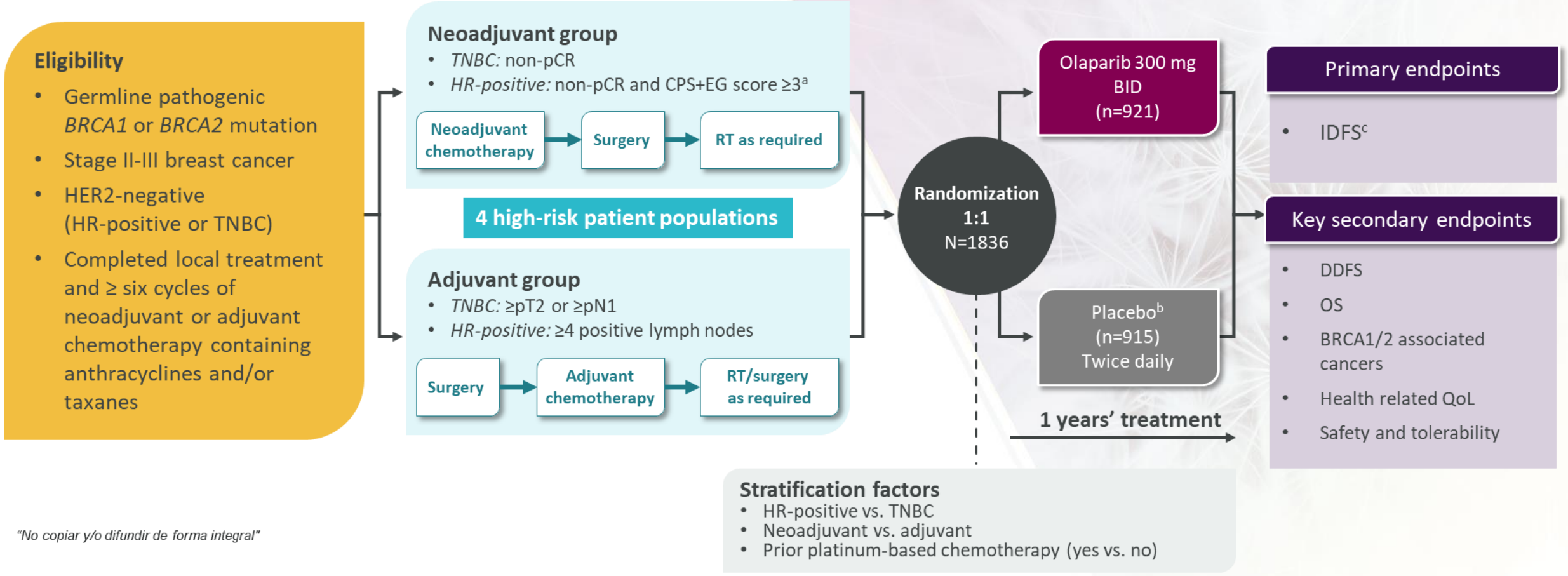
Average *CHEK2* Risk

Polygenic Risk Score

Lifestyle/hormonal risk factors

Full model

Why? Therapeutic evidence:
OlympiA trial: phase III study of olaparib versus placebo as adjuvant treatment for high risk gBRCA-mutated, HER2-negative BC

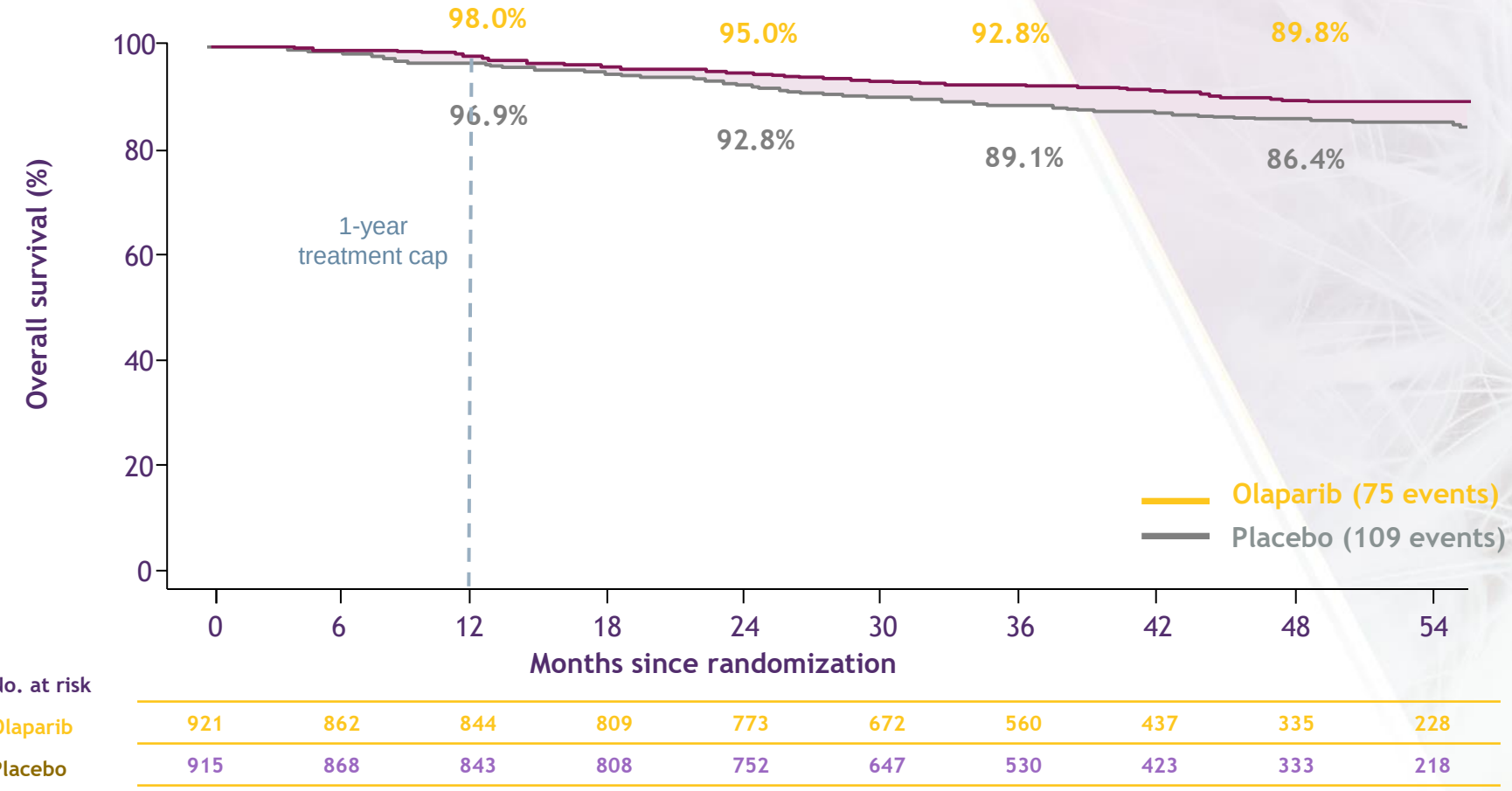


[a] CPS+EG score incorporates pretreatment clinical stage, oestrogen receptor status, nuclear grade and pathological stage after neoadjuvant chemotherapy
[b] Data to support adjuvant capecitabine was not available when the OlympiA study was initiated in 2014
[c] by STEEP system[2]

1. NEJM OlympiA; 2.Hudis CA. J Clin Oncol 2007;25:2127–32

Results: Secondary endpoint: OS

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



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

Olaparib approval in early breast cancer

EMA

- monotherapy or in combination with endocrine therapy for the adjuvant treatment of adult patients with germline BRCA1/2-mutations who have HER2-negative, high risk early breast cancer previously treated with neoadjuvant or adjuvant chemotherapy (see sections 4.2 and 5.1).

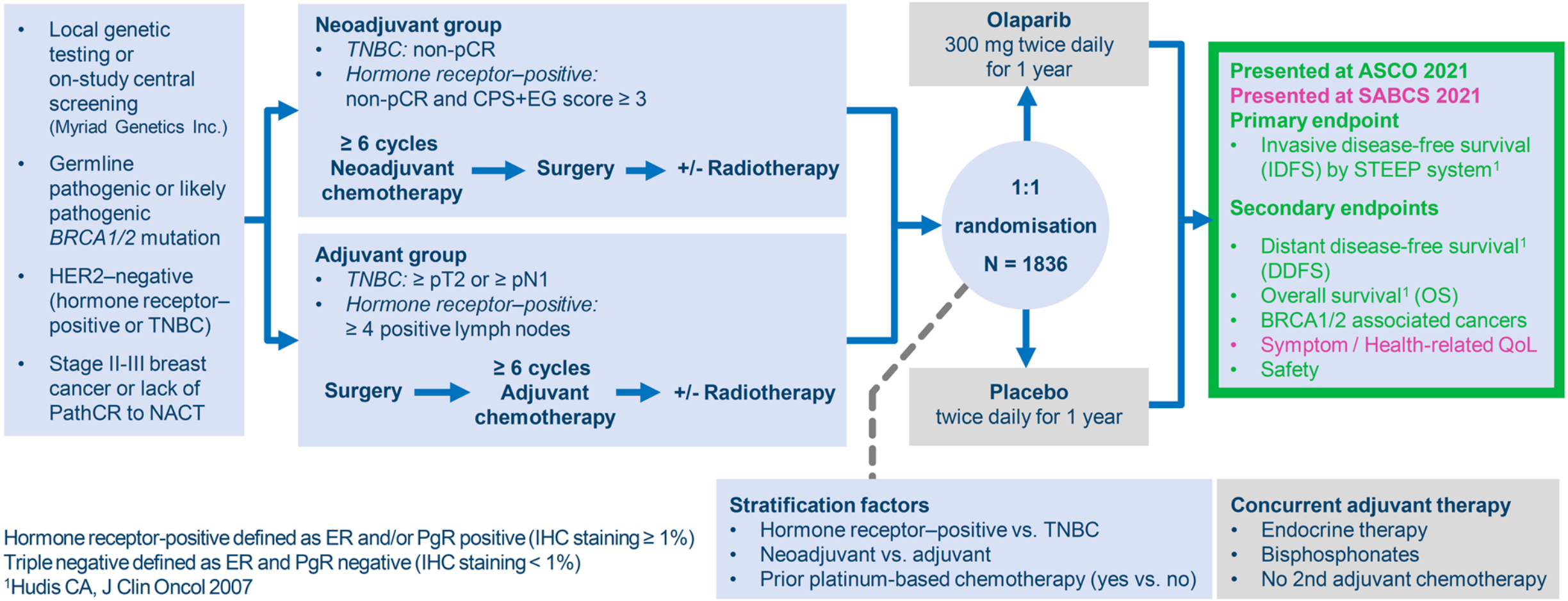
Triple-negative breast cancer (82% of patients):
▪ If treated with adjuvant chemotherapy, were required to have axillary node-positive disease or an invasive primary tumor measuring at least 2 cm on pathologic analysis.
▪ If treated with neoadjuvant chemotherapy, were required to have residual invasive breast cancer in the breast or resected lymph nodes (ie, no pCR from neoadjuvant therapy).
Hormone receptor-positive breast cancer (18% of patients):
▪ If treated with adjuvant chemotherapy, were required to have at least 4 pathologically confirmed positive lymph nodes.
▪ If treated with neoadjuvant chemotherapy, were required to have not had a pCR with a CPS+EG score of 3 or higher.[2,3] The CPS+EG scoring system estimates relapse probability on the basis of clinical and pathologic stage (CPS) and estrogen receptor status and histologic grade (EG); scores range from 0 to 6, with higher scores indicating worse prognosis.

https://www.ema.europa.eu/en/medicines/human/EPAR/lynparza#authorisation-details-section

Tutt A, NEJM 2021

Clinical problems with the OlympiA trial

Who to test?



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

Clinical guidelines

Guidelines are changing

- Loss of diagnoses when using restrictive clinical guidelines
- Most guidelines are based on personal/FH. FH has limitations
  - Requires healthy individuals to be aware of their FH (three generations)
  - Small/adopted families or families dispersed
  - De novo germline mutation

- New genomic sequencing techniques (testing more accessible): reducing the cost and time taken for results to become available
- Guidelines made for high penetrance genes
- Social factor
- Therapeutic evidence

Ledermann J, N Engl J Med.2012. Moore K et al. N Engl J Med.2018. Robson M et al. NEnglJMed. 2017. Mateo J et al. NEnglJMed. 2015. Golan T et al. NEnglJMed.2019. Kamps R et al. Int J Mol Sci. 2017

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- Social factor
- Therapeutic evidence

"Life comes with many challenges. The ones that should not scare us are the ones we can take on and take control of"

Should we test every single patient meeting OlympiA criteria irrespectiveless of personal or family history??

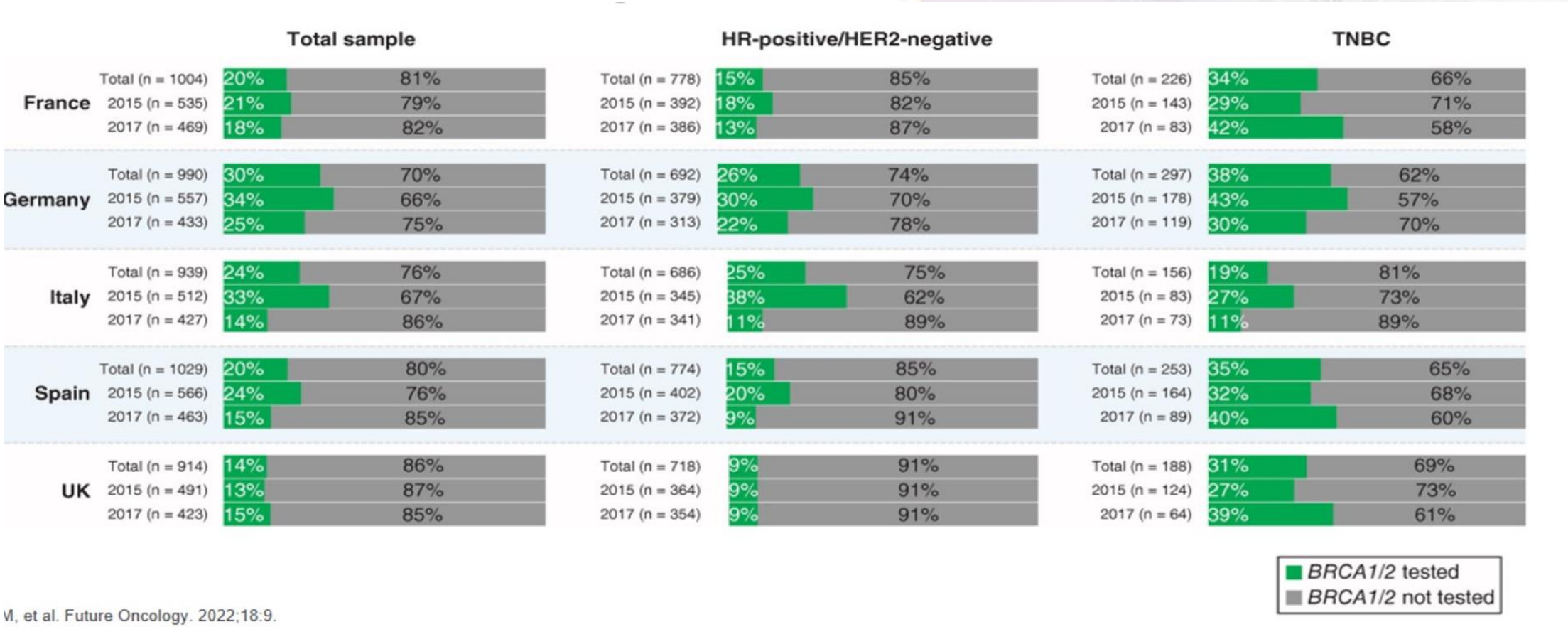
Ledermann J, N Engl J Med.2012. Moore K et al. N Engl J Med.2018. Robson M et al. NEnglJMed. 2017. Mateo J et al. NEnglJMed. 2015. Golan T et al. NEnglJMed.2019. Kamps R et al. Int J Mol Sci. 2017

Requirement for increased of BRCA testing for patients with BC

In the past, only patients with strong FH were recommended to urdergo testing

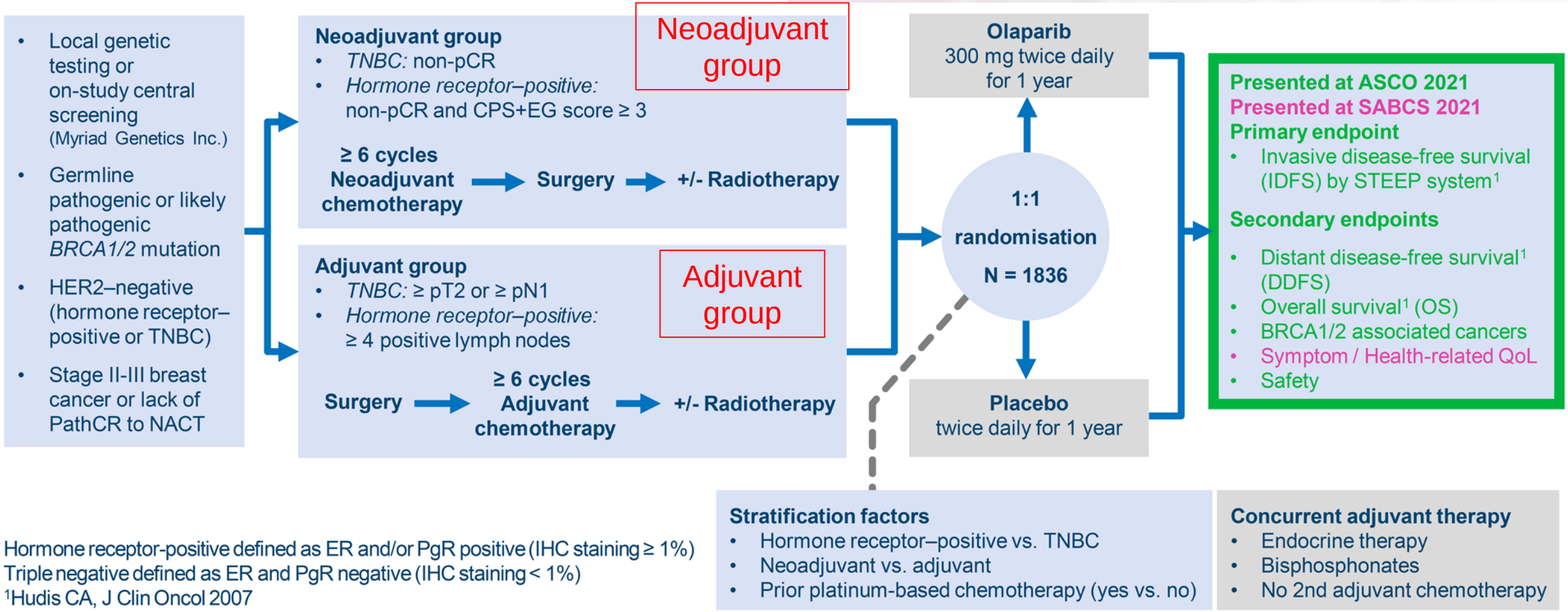
Given recent approvals, BRCA mutation testing should be performed at diagnosis in a broader population

- Low BRCA mutation testing rates across Europe



M, et al. Future Oncology. 2022;18:9.

Clinical problems with the OlympiA trial



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

Adjuvant group

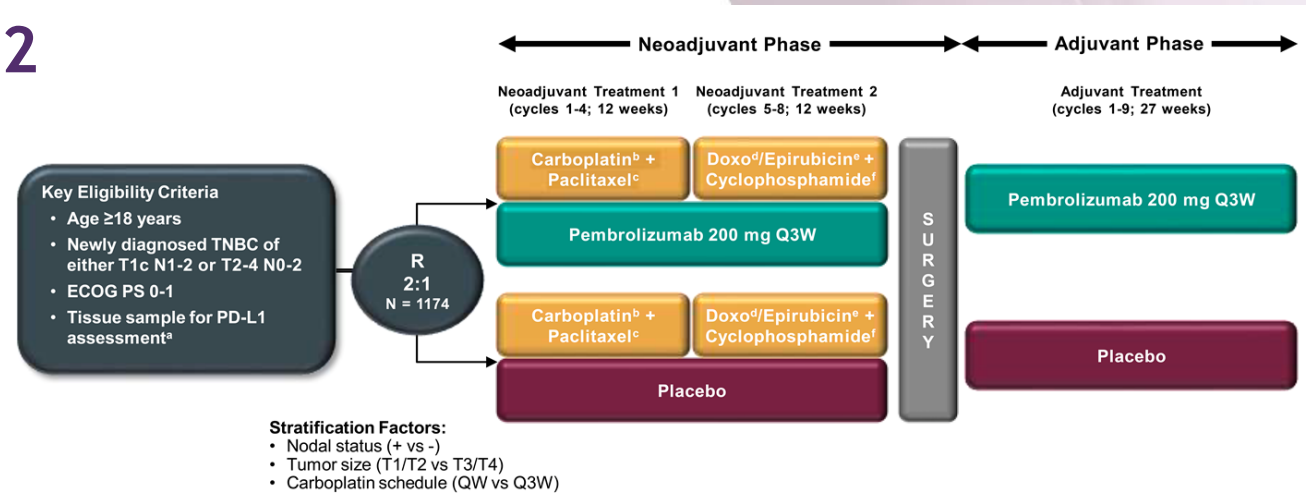
- TN: T2 and or N1
  - Up front surgery??? Nearly ≈0%?
  - Other approved treatments??? Metronomic cape for one year? (Wang Xi ASCO 2020)
- Luminal: >N2
  - Not very “frequent”
  - Other approved agents? iCDK

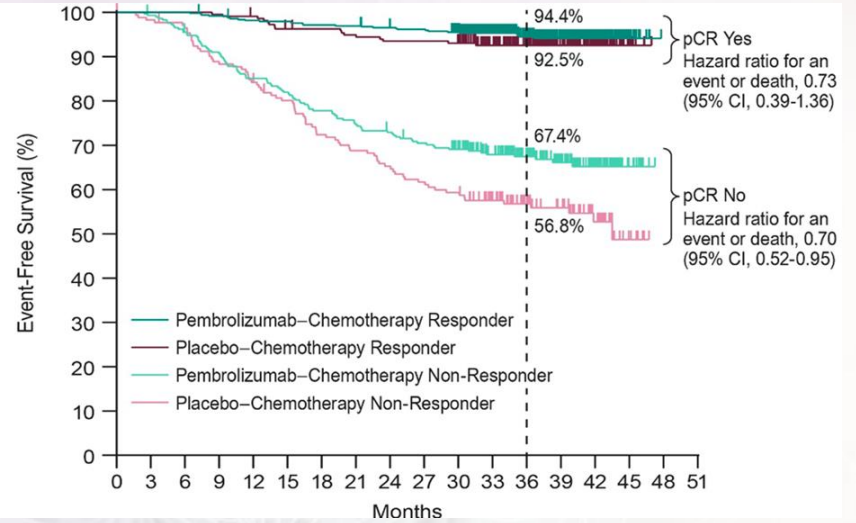
*Myers S. Poster 374. ASCO 2023

Neoadjuvant group

- TNBC and no pCR
  - TNBC > 15mm (multidisciplinay team) candidates to neoadjuvant
  - pCR: almost 50% RCp. Platine salts commonly used (only 30% OlympiA) even more in *gBRCAm**
  - New agents: Pembro nearly 65% (olympiA 0%)
  - Adjuvant pembro is used in the Keynote 522 trial (no data in the adjuvant scenario with PARPi +IO)
  - Adjuvant cape? (CREATE-X)
- Luminal: no pCR + CPS + EG score ≥ 3
  - Luminal tumors candidate for neoadjuvant therapy
  - CPS EG scores is not currently used
  - iCDK could be also used

Keynote 522





Strengths

- Optimal control arm
- Platine salts 100%
- Improvement in pCR/EFS

Weak points

- DD anthracyclines
- No impact in OS
- No data on BRCAm status 80% not testing/missing
- No biomarker (PDL1)
- AE (inmuno-e)
- No use of adjuvant cape if no pCR
- Mandatory pembro use even if pCR
- Adjuvant olapa not allowed

No pCR and gBRCAm: if we are thinking in iPARP + pembro?

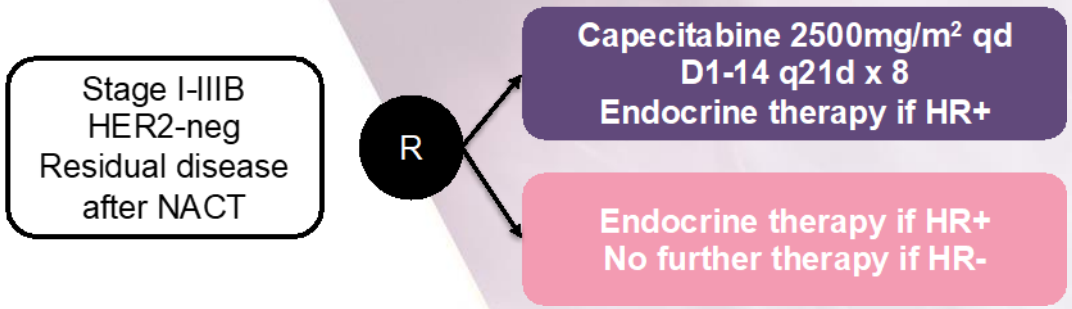
- Biological rational to combine iPARP + IA
- Comparable AE profiles PARPi + IO vs monotherapy
- ETCTN10020: olaparib +/- atezolizumab in gBRCAm-associated HER- advanced BC has completed enrollment and results are pending (NCT02849496)

Table 1. Safety profile of immune-checkpoint inhibitors plus PARPi in patients with metastatic breast cancer.

Characteristic	TOPACIO[20] (n=55)	MEDIOLA[21] (n=34)	KEYLYNK-007[22] (n=168)	JAVELIN PARP Medley[23] (n=34)
Treatment	Pembrolizumab + Niraparib	Durvalumab + Olaparib	Pembrolizumab + Olaparib	Avelumab + Talazoparib
TNBC	47 (100%)	18 (53%)	N/A (multiple tumor types included)	22 (100%)
gBRCAm carriers	15 (32%)	100%	N/A	N/A
ORR	21%	63%	6.3%-28.6%	8%
DoR	NR	9.2 months	N/A	N/A
PFS	2.3 months (8.3 months in gBRCAm carriers)	8.2 months	N/A	N/A
Grades 3-4	58%	32%	35.7%	47.4%
Discontinuation for AE	N/A	9%	2.4%	N/A
Most common AE	Nausea (55%), Fatigue (44%), Anemia (35%), Thrombocytopenia (25%), Constipation (24%)	Fatigue (65%), Nausea (59%), Anemia (41%), Diarrhea (35%)	Nausea (39.3%), Anemia (30.4%), Fatigue (15.5%)	Anemia (57.9%), Nausea (26.3%), Fatigue (21.1%), Thrombocytopenia (21.1%)

Maio M et al Cancer Res 2021
Domcheck SM Lancet Oncol 2020

CREATE-X



Strengths

- TN: Improvement EFS and OS
- Front a clinical practice point of view
  - Easy to use
  - Manejable EA
  - Available, cheap
  - DPYD disponibility
- Combination chemo (Cape) plus pembro seems feasible

Weak points

- Study population: No TN (32%; N 286)
- No results according to mutation status
- Benefit of adjuvant cape may be restricted to certain molecular subtypes (basal)
- Do not seem feasible to combine with olapa
- Metastatic scenario (OlimpiAD) cape is inferior to olaparib
- Metastatic scenario (Keynote 355) cape plus pembro was not an option

Masuda N et al. N Engl J Med 2017;376:2147-59
Lluch A et al. J Clin Oncol.
Cancer Genome Atlas Network. Nature. 2012

Olaparib after platinum chemo

Platine salts

- Only ¼ patients in the OlympiA trial were treated with platine salts
- All patients in the KN522 were treated with platinum
- Little is known about the efficacy of PARPi in g*BRCA*m patients with poor response to platinum
- Available data suggesting potential cross-resistance mechanisms
- OlympiAD /EMBRACA not allow enrollment of platinum-refractory patients
- In the BrighNess trial the pCR did not differ according to BRCA status
- All patients receiving neoadjuvant chemo in the OlympiA trail had residual disease including those treated with platinum (≈26%)
  - The absence of pCR might be interpreted as a suboptimal response to platinum
  - In the subgroup analysis the benefit of olaparib was maintained in platinum pre-treated patients.
  - Still an area of research

Adjuvant iCKD: MONARCH-E and NATALEE

If you have to choose between iCDK or iPARP in the adjuvant….

Strengths

- N1 patients could benefit from iCDK adjuvant (Even N0 in NATALEE)
- Difference in IDFS, still not OS data
- Factors increasing rate of discontinuation therapy have been described for iCDK in the monarch-e trial
  - Postmenopausal
  - > 65 years
  - 1-3 nodes +
  - < morbilities

Tolaney JCO 2022 / Tung JCO 2020 /Slamon ASCO 2023

Weak points

- No results according to mutation status
- No OS
- Do not seem feasible to combine
- Some data in the metastatic scenario suggesting gBRCA less responses to iCDK
- iPARP activity in MBC gBRCA mutation carriers
- Sequential used?

Fuentes Antras F. Poster 298. ASCO 2023

Other problems with the eligible population. Any other patient to treat?

What about less than T2N0 TN BC?

- No data to recommend adjuvant olaparib for stage I patients.
- Stage I TNBC: 5-year iDFS >90% (Meta-A ASCO 2023). Overtreatment?
- Trend toward better outcomes for gBRCA1m-associated TNBC
- Could olaparib replace adjuvant chemotherapy?

What about ER low (ER between 1-10%)

- Recognized as a distinct reporting category by the 2020 ASCO/CAP
- Often basal-like and poorly differentiated
- Retrospective studies showed similar risk of recurrence/mortality than TNBC
- Many ER+ in gBRCAm carriers are ER-low, especially among gBRCA1m carriers.
- In the OlympiA study, patients with ER-low BC were included (number ???) in the ER+ group and were eligible according to those criteria)Outcomes???)

Fusco N et al. Histol Histopathol. 2021;36(12):1235-1245 // Schrodi S et al. Ann Oncol. 2021;32(11):1410- 1424.
Benefield HC J Natl Cancer Inst. 2020;112(7):728-736 // Sanford RA et al. Cancer. 2015;121(19):3422-3427// Tung NM et al. J Clin Oncol. 2020

Other problems with the eligible population

Expanding Eligibility to PALB2 Carriers

Sigle vs large panels?

PALB2 N=13	*sBRCA1/2* N=17^	*ATM & CHEK2*** N=17
Germline: 9/11 PR (82%) 10/11 had tumor regression; 1 SD > 1 yr **Somatic: 0/2 – both SD*** **(limited assessments)**	**8/16 PR (50%)**	**0/13 germline** **0/4 somatic**

TBCRC 056 preoperative niraparib and dostarlimab (anti PD-1) por BRCA1/2 or PALB2 deficient BC). Currently enrolling. NCT04584255

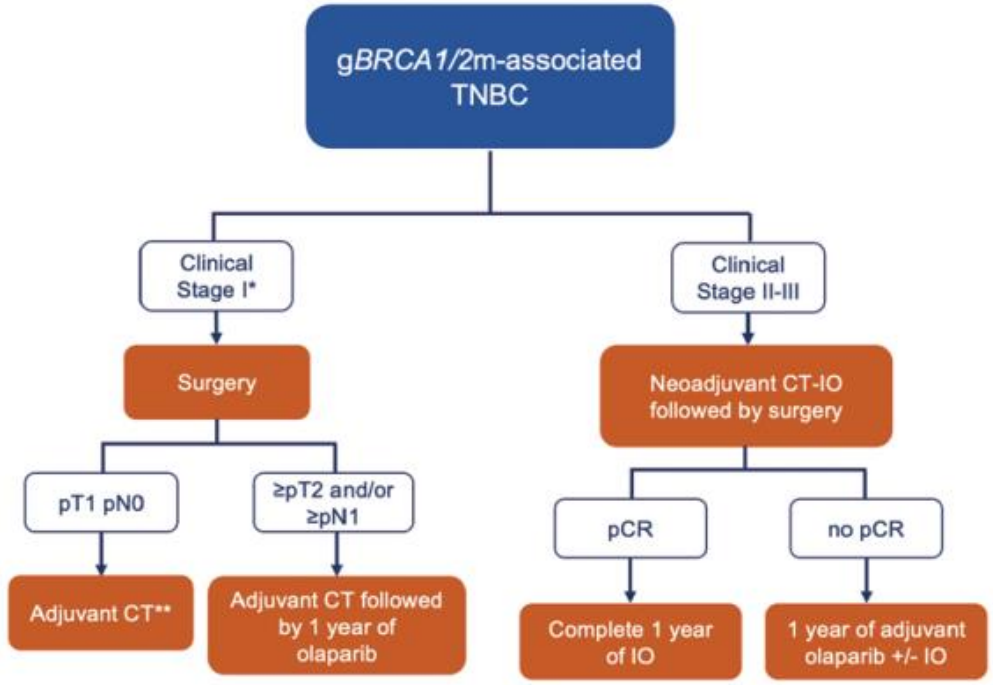
Gruber JJ, Nat Cancer.
Isaac D et al.JCO Precis. Oncol. 2018
Tung NM et al. J Clin Oncol. 2020

The Oncologist, 2023, **XX**, 1–10
https://doi.org/10.1093/oncolo/oyad123
Advance access publication 20 May 2023
Review Article

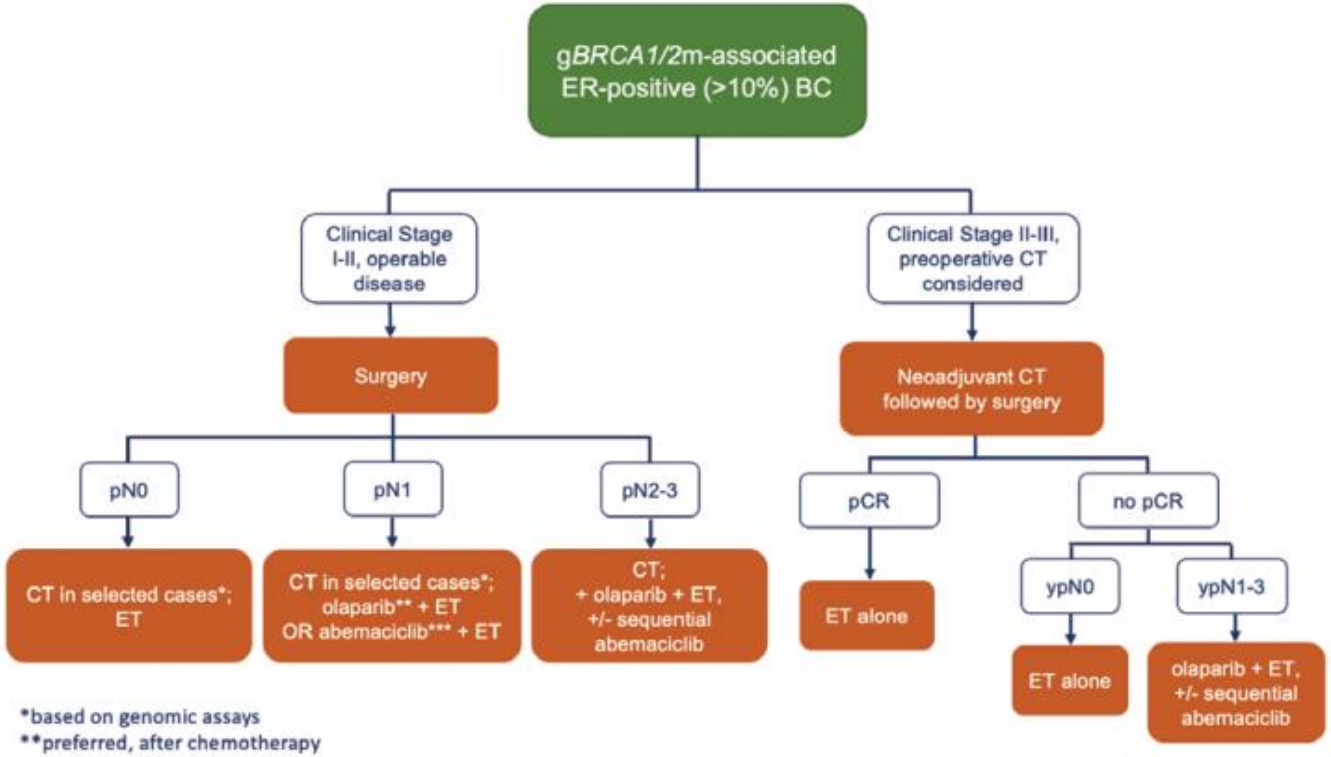
OXFORD

Adjuvant Olaparib for Germline BRCA Carriers With HER2-Negative Early Breast Cancer: Evidence and Controversies

Stefania Morganti[1,2,3,4,5,6], Brittany L. Bychkovsky[1,2,3,7], Philip D. Poorvu[1,2,3], Ana C. Garrido-Castro[1,2,3,4], Anna Weiss[8], Caroline C. Block[1,2,3], Ann H. Partridge[1,2,3], Giuseppe Curigliano[5,6], Nadine M. Tung[3,9], Nancy U. Lin[1,2,3], Judy E. Garber[1,2,3,7], Sara M. Tolaney[1,2,3], Filipa Lynce[*,1,2,3]



*axillary staging recommended to exclude nodal involvement in cT1 tumors
**case-by-case for pT1a



*based on genomic assays
**preferred, after chemotherapy
***when olaparib is contraindicated and only for tumor size>5 cm and/or grade 3

original reports

Contralateral Breast Cancer Risk Among Carriers of Germline Pathogenic Variants in *ATM*, *BRCA1*, *BRCA2*, *CHEK2*, and *PALB2*

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CARRIERS study
Conservative surgery
Premenopausal patients, CMC (inci 10y):

- 33% BRCA1
- 27% BRCA2
- 13% CHEK2
- 35% PALB2 (RH-)

Postmenopausal patients

- 12% BRCA1
- 9% BRCA1
- 4% CHEK2

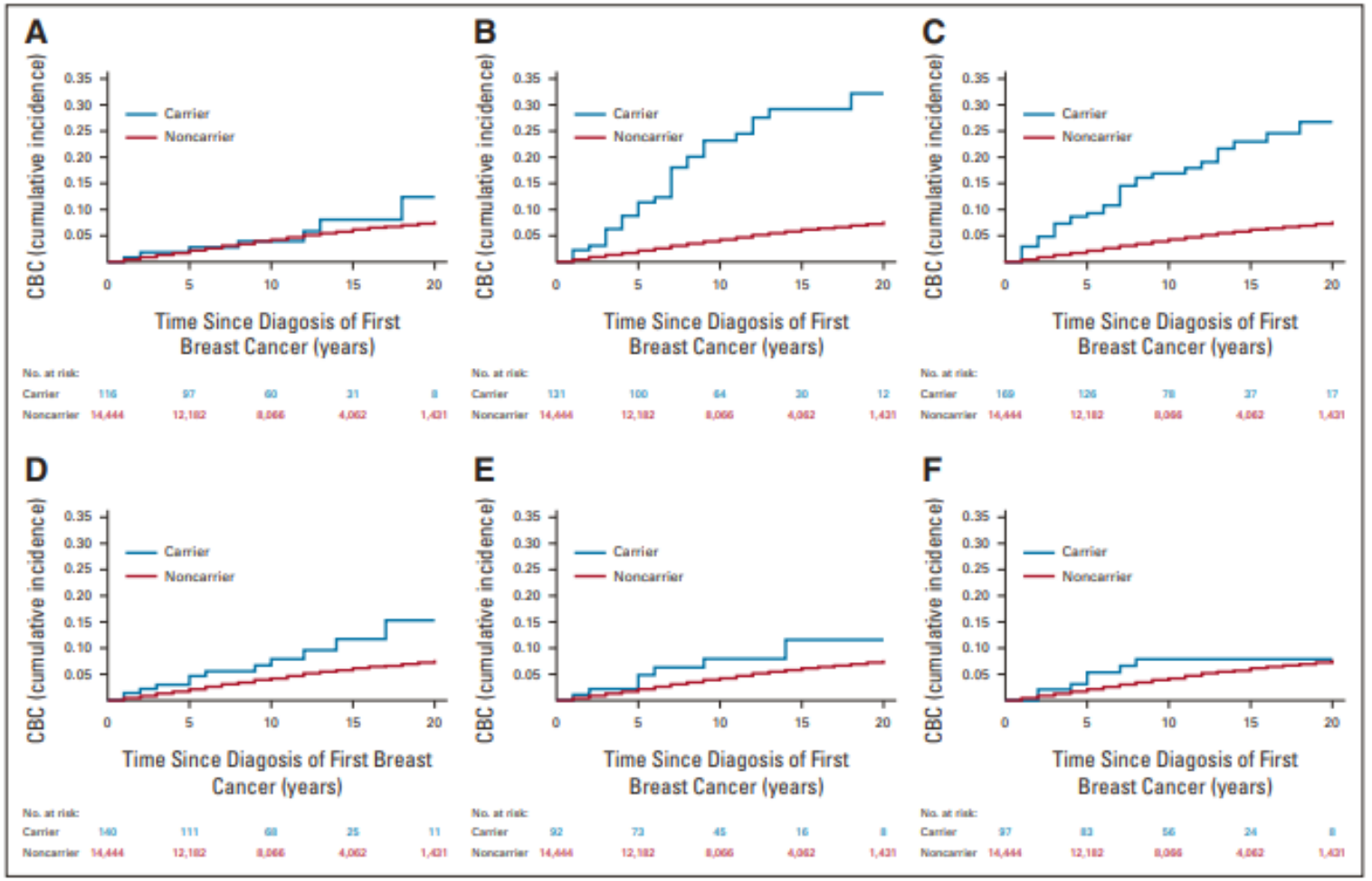


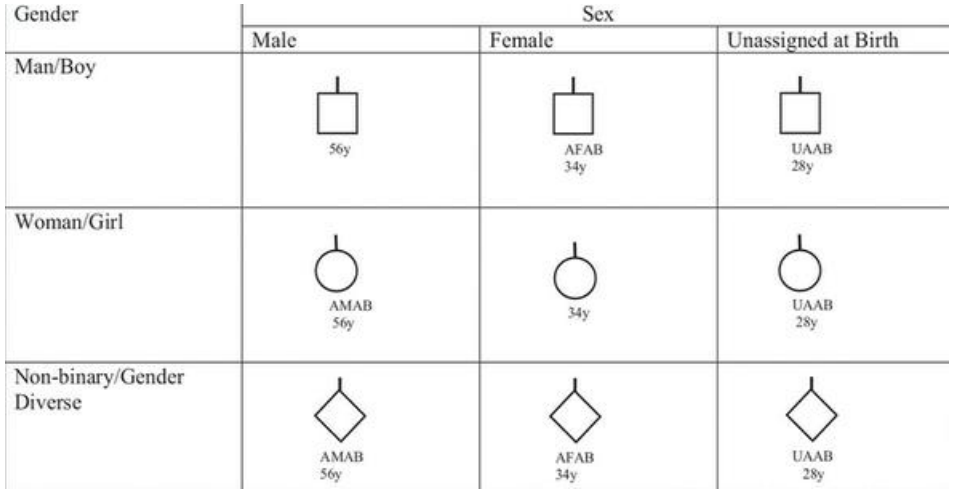
FIG 1. Cumulative incidence of CBC risk in PV carriers. Cumulative incidence plots for first contralateral breast cancers after primary breast cancer. Cumulative incidence is plotted against years since first breast cancer. Stepped plots for non-PV carriers (red), and carriers of variants are (A) *ATM*; (B) *BRCA1*; (C) *BRCA2*; (D) *CHEK2*, all pathogenic; (E) *CHEK2* c.1100delC; and (F) *PALB2*. Numbers of carriers and noncarriers at each time point are displayed below the individual graphs. CBC, contralateral breast cancer; PV, pathogenic variant.

Managing cancer Risk in Transgender patients with inherit cancer predisposition

2023 ASCO ANNUAL MEETING

Case based panel discussion

- 1,6% en EEUU (5,1% < 30y)
- Significant barriers to healthcare
- Concepts
  - Gender identity
  - Gender expression
  - Sex assigned as birth
  - Gender (Social construct)



NSGC Pedigree Standardization TASL Force update sept 2022

	Average Risk Cis Women	Average Risk Cis Men	*BRCA1+* Cis Women	*BRCA1+* Cis Men
Breast	12.9%	0.1%	70%	0.2-1.2%
Prostate	--	12.9%	--	7-26%
Pancreas	1.7%	1.7%	≤5%	≤5%
Ovary	1.1%	--	39-58%	--

	Average Risk Cis Women	Average Risk Cis Men	*BRCA2+* Cis Women	*BRCA2+* Cis Men
Breast	12.9%	0.1%	68%	2-7%
Prostate	--	12.9%	--	19-61%
Pancreas	1.7%	1.7%	5-10%	5-10%
Ovary	1.1%	--	13-29%	--

Conclusions

- Mainstreaming vs fast track models in genetic counselling
  - Efforts should be made to be adapted for new models
  - Training the educating the multidisciplinary team
- Available clinical tools that better inform the risk of cancer (in 5-10y or lifetime) incorporating not only high/moderate risk genes but also PRS
- Olaparib should be used in gBRCAm high risk BC during 1 year
  - Clinical guidelines should incorporate every high risk BC patients suitable for olaparib treatment
  - Universal screening is under the scope
- News in the near horizon. Be update
- Challenges and possible solutions

Type of Challenge	Possible Solutions
Referral	Developed standardized tools for assessing eligibility for testing Multidisciplinary team education
Indication	Focus on those at risk rather than coffee for everyone
Uptake	Culture-sensitive genetic counselling Streamline the process within oncology clinic visit Public policy to protect against genetic discrimination Awareness campaigns
Interpretation	Focus on those at risk Development and improvement of tools such as RNA sequencing and in silico analysis Promote collaboration across the world to facilitate sharing information from different populations
Genetic Counselling	Support expanding programs to train more genetic counsellors Multidisciplinary team education Utilization of telemedicine and artificial intelligence
Financial challenge to access	Collaboration between researchers and pharma Research to support cost efficacy in cancer care (prevention treatment) Support from insurers and govermments

ASCO Ed Book 2023

Save the Date

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Barcelona, 21 de **marzo** de **2024**