bjclub

breast Journal club

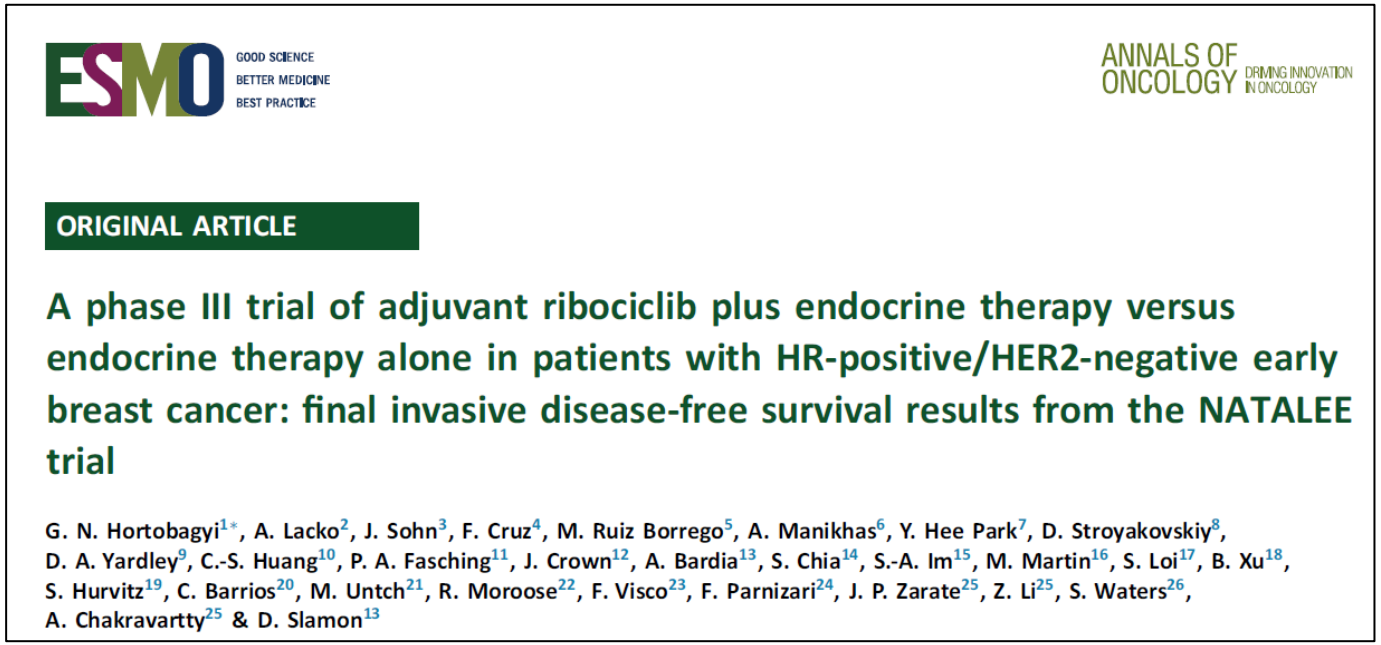
L'IMPORTANZA DELLA RICERCA IN ONCOLOGIA

7-8 MARZO 2025
NAPOLI
Hotel Royal Continental
Via Partenope, 38

BJClub AWARDS
Best paper internazionale

Intro e place in therapy

best paper internazionale



ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY DRIVING INNOVATION IN ONCOLOGY

ORIGINAL ARTICLE

A phase III trial of adjuvant ribociclib plus endocrine therapy versus endocrine therapy alone in patients with HR-positive/HER2-negative early breast cancer: final invasive disease-free survival results from the NATALEE trial

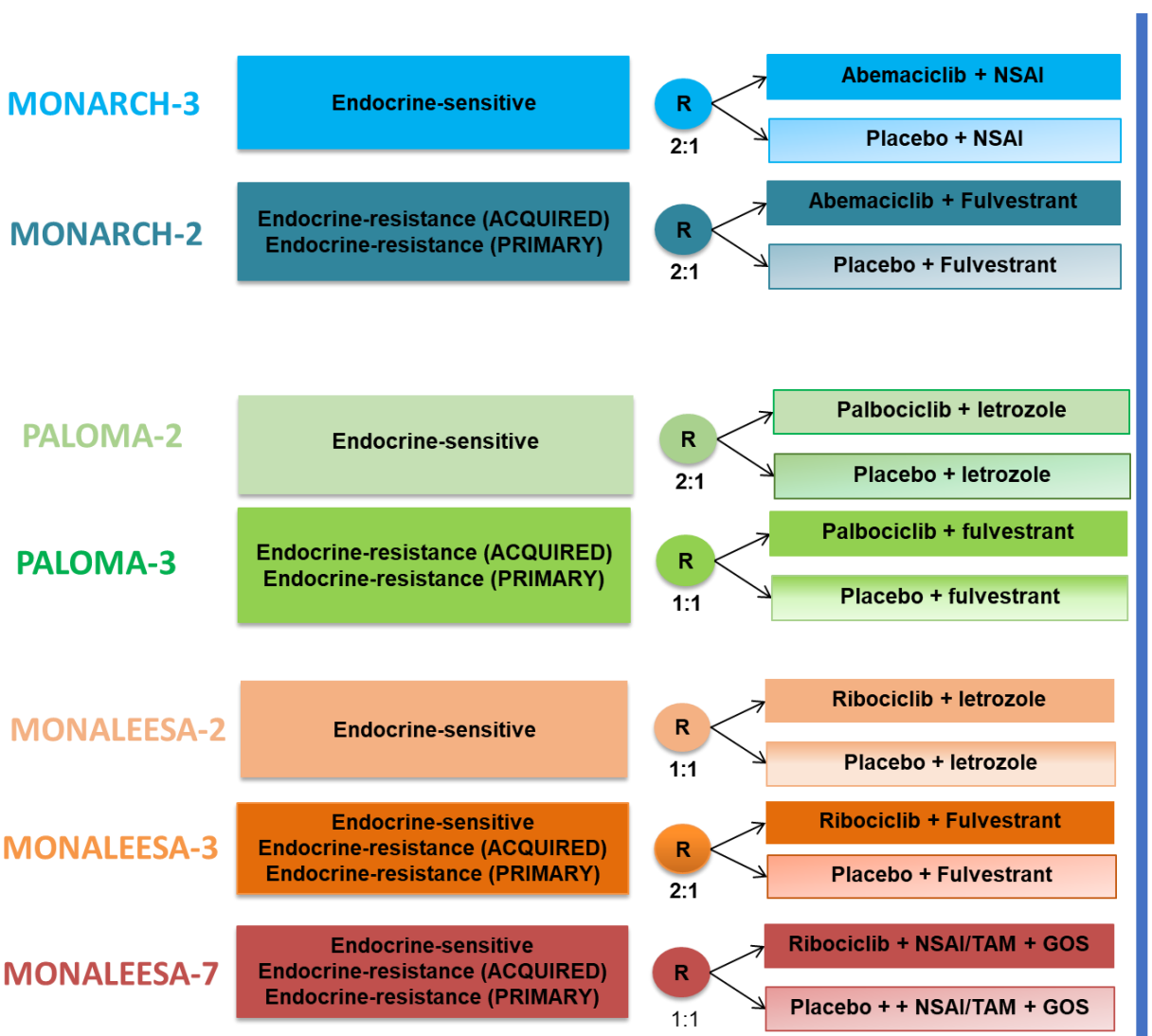
G. N. Hortobagyi[1*], A. Lacko[2], J. Sohn[3], F. Cruz[4], M. Ruiz Borrego[5], A. Manikhas[6], Y. Hee Park[7], D. Stroyakovskiy[8], D. A. Yardley[9], C.-S. Huang[10], P. A. Fasching[11], J. Crown[12], A. Bardia[13], S. Chia[14], S.-A. Im[15], M. Martin[16], S. Loi[17], B. Xu[18], S. Hurvitz[19], C. Barrios[20], M. Untch[21], R. Moroose[22], F. Visco[23], F. Parnizari[24], J. P. Zarate[25], Z. Li[25], S. Waters[26], A. Chakravartty[25] & D. Slamon[13]

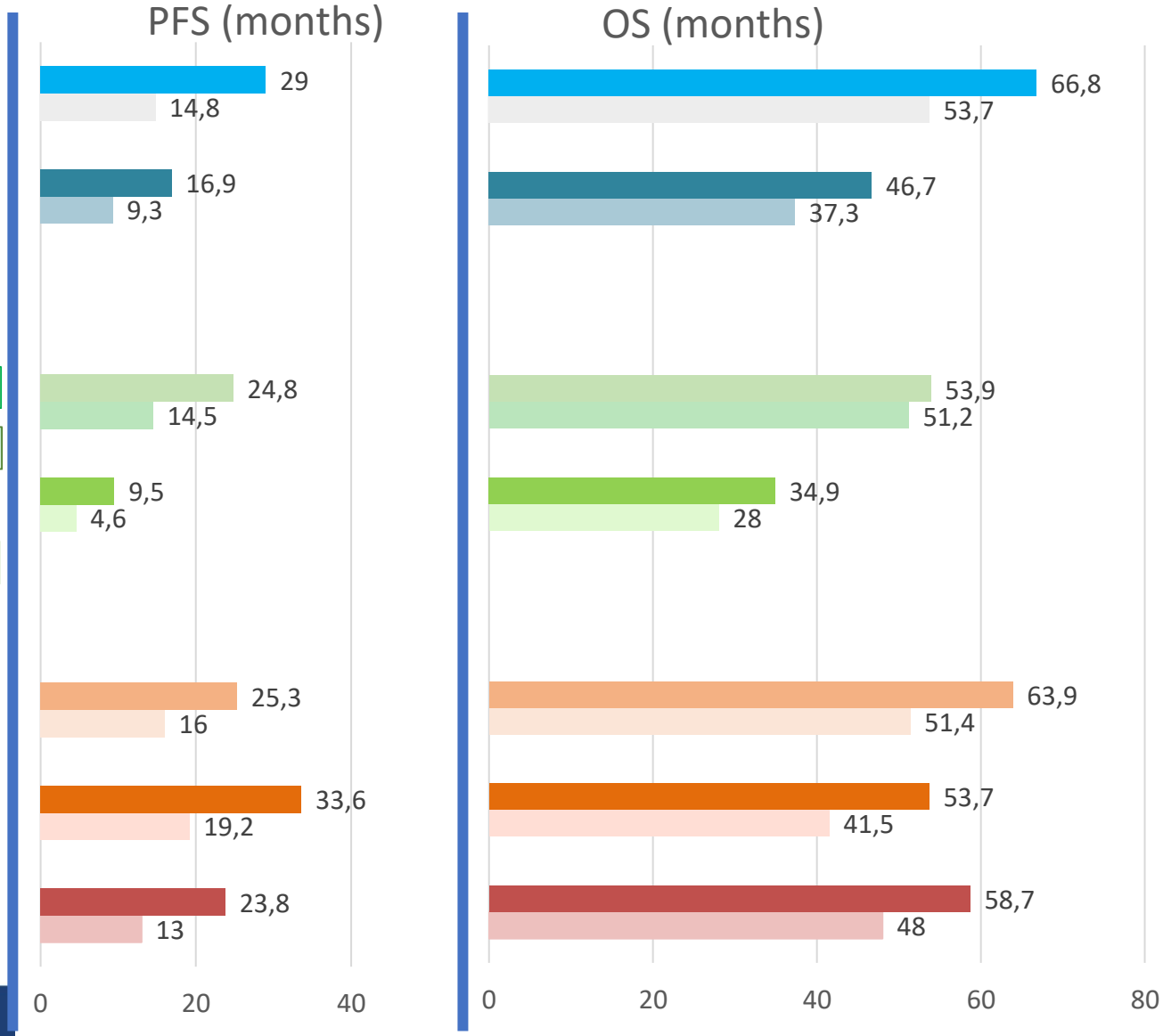
Disclosures

Consultancy/Advisory Board:

Novartis, Eli Lilly, Pfizer, AstraZeneca, Roche, Daiichi Sankyo, Seagen, EISAI, MSD, Gilead, Menarini/Stemline, Exact Science, Agendia, Takeda, Helsinn

CDK4/6i in metastatic setting: transformative





Finn et al. *Lancet Oncol.* 2015; Finn et al. NEJM 2016; Hortobagyi et al, NEJM 2016; Goetz et al. JCO 2017; Slamon et al, JCO 2018; Tripathy et al. Lancet Oncol. 2018, Goetz MP et al, ESMO 2023

CDK4/6 inhibitors in high-risk HR+/HER2- EBC

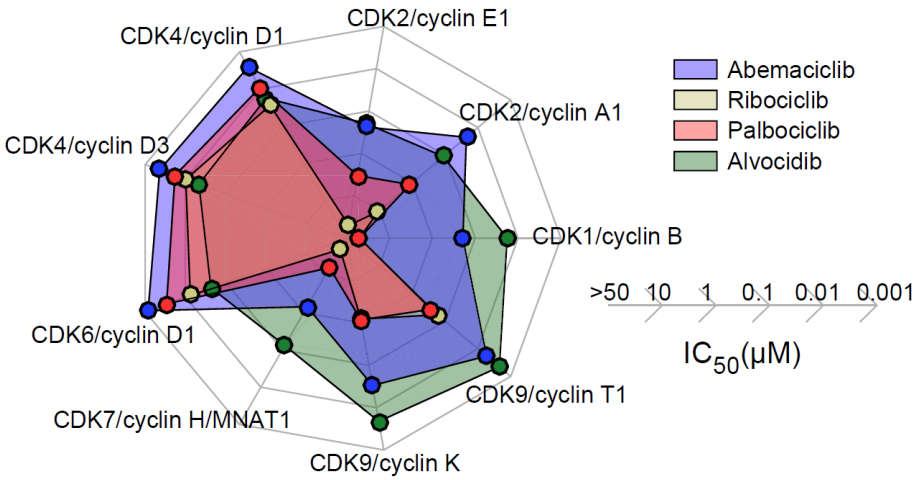
	PENELOPE-B	PALLAS	MonarchE	NATALEE
Sponsor/Collaborator	GBG	ABCSG/AFT	Eli Lilly/NSABP	TRIO/Novartis
CDK 4/6 Inhibitor	Palbociclib	Palbociclib	Abemaciclib	Ribociclib
Sample Size	1250	5600	5637	5000
Design	Phase 3 randomized placebo-controlled	Phase 3 randomized open label	Phase 3 randomized open label	Phase 3 (non) randomized open label
Patient population	High-risk	Stage II-III	High-risk	Stage II-III
Duration of Combination Therapy	1 year **125mg/m² d 1-21 q28** (13 cycles) ET at least 5 years	2 years **125mg/m² d 1-21 q28** (26 cycles) at least 5 years ET total	2 years **150mg cont.** (26 cycles) at least 5 years ET total	**400mg day 1-21 q28** 3 years; At least 5 years ET
Primary Endpoint	iDFS	iDFS	iDFS	iDFS
First results reported	December 2020	September 2020	September 2020	December 2025

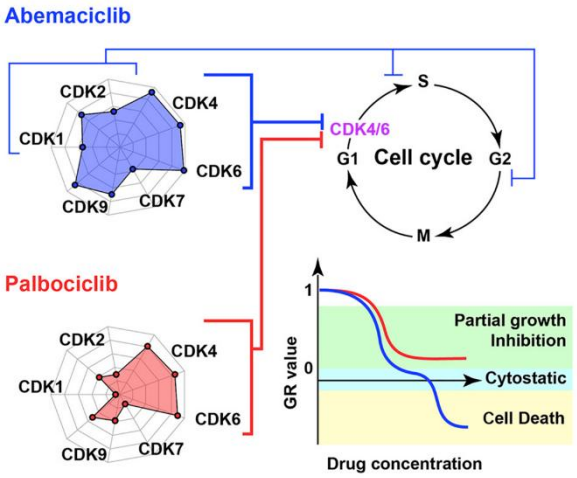
Gnant M, et al. JCO 2022 Jan 20; 40 (3); Loibl S, et al. JCO 2021 May 10; 39 (14); Johnston S, et al. Lancet 2023; 24 (77-90); Slamon D, et al. 2023 Jun; 41 (17)

CDK4/6i not an homogenous class of compounds

Abemaciclib ≠ Palbociclib ≠ Ribociclib

Different kinases targeted and potency of inhibition





Administration modality

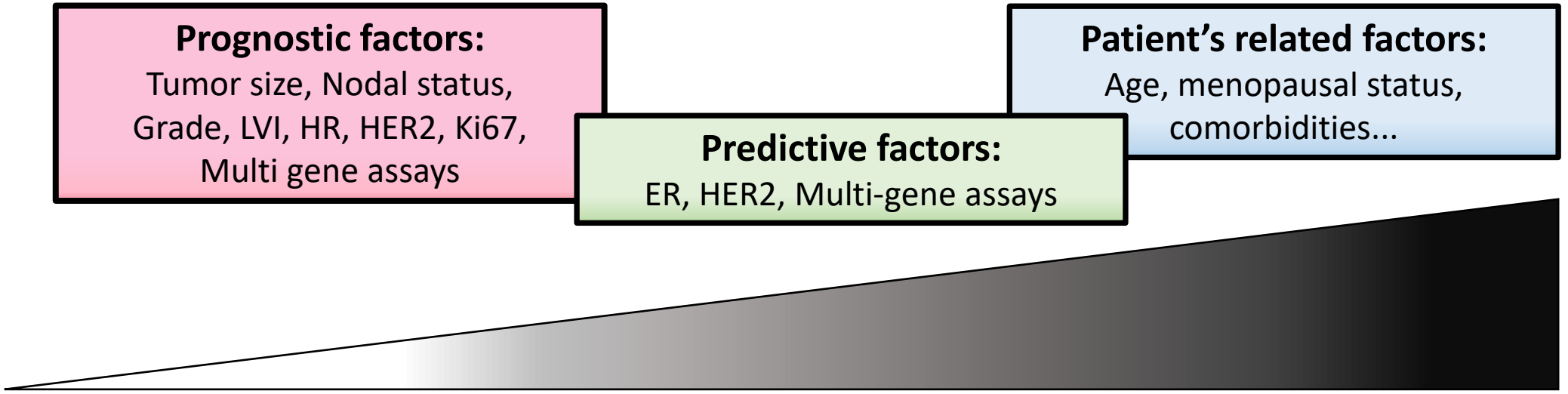
Continuous

vs

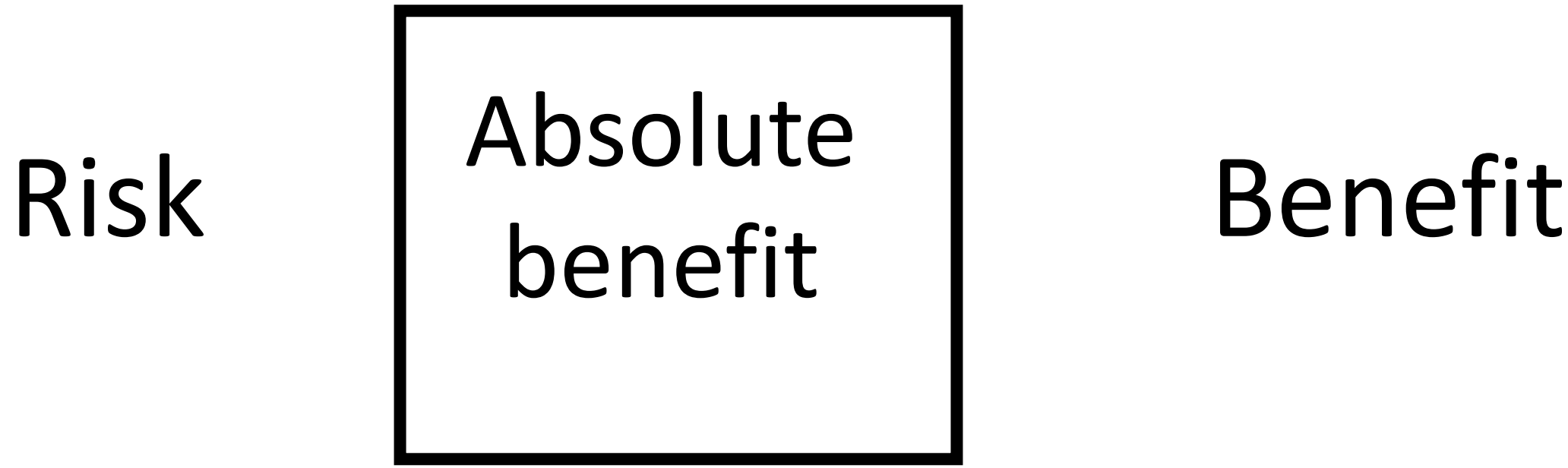
Intermittent

Hafner M Cell Chemical Biology 2019

The decision-making process for ER+/HER2- EBC



Risk, benefit and absolute benefit



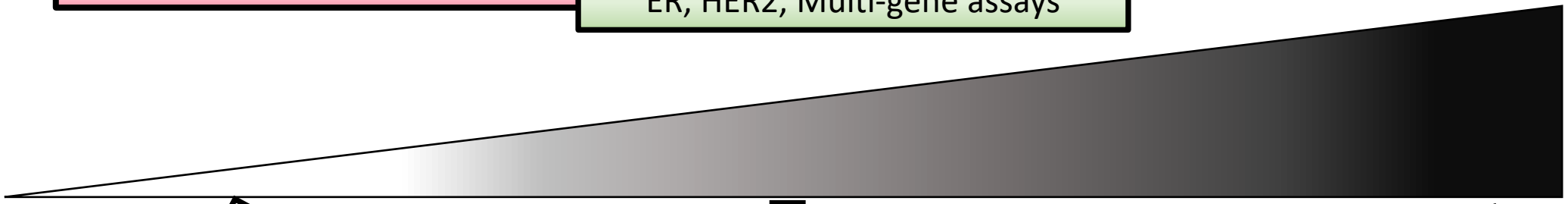
Bartlett et al. JNCI 2016

The decision-making process for ER+/HER2- EBC

Prognostic factors:
Tumor size, Nodal status, Grade, LVI, HR, HER2, Ki67, Multi gene assays

Predictive factors:
ER, HER2, Multi-gene assays

Patient's related factors:
Age, menopausal status, comorbidities...



Risk / Treatment Benefit

Very LOW RISK
De-escalation
- NO chemotherapy
- Duration 5 years ET
- TAM alone in premenopausal
- NO CDK4/6i

Intermediate RISK
Tailored approach
- De-escalated CT
- Duration 5 vs 7/8
- TAM + aLH-RH in premenopausal
- +/- CDK4/6i

Very HIGH RISK
Escalation
- Sequential CT (+/-dd)
- Extended ET
- EXE + a-LHRH in premenopausal
- CDK4/6i + ET

Unique therapeutic landscape

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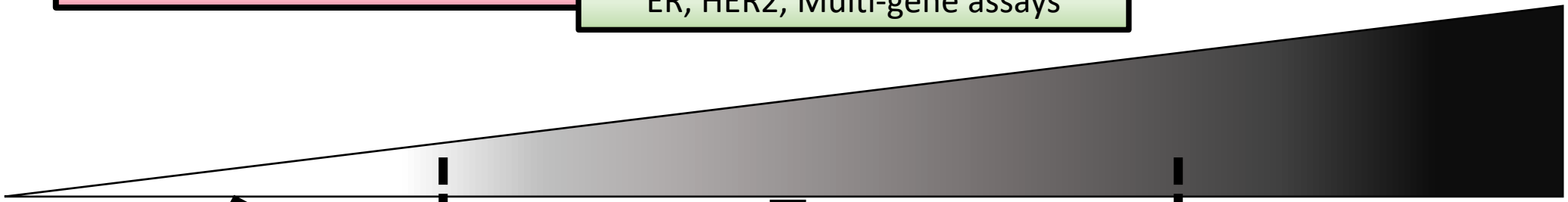

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ARGUMENT
Debate
Difference of Opinion
Controversy
Contention
DISAGREEMENT
DISSENT
Public Dispute

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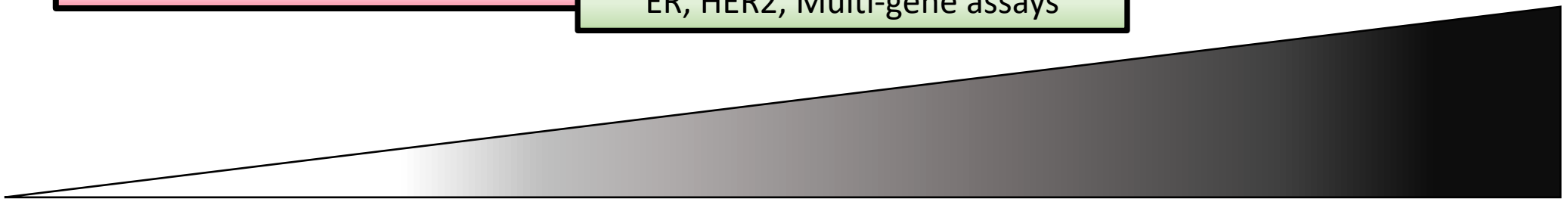

Risk / Treatment Benefit

It is easier

Very HIGH RISK

Escalation

- Sequential CT (+/-dd)
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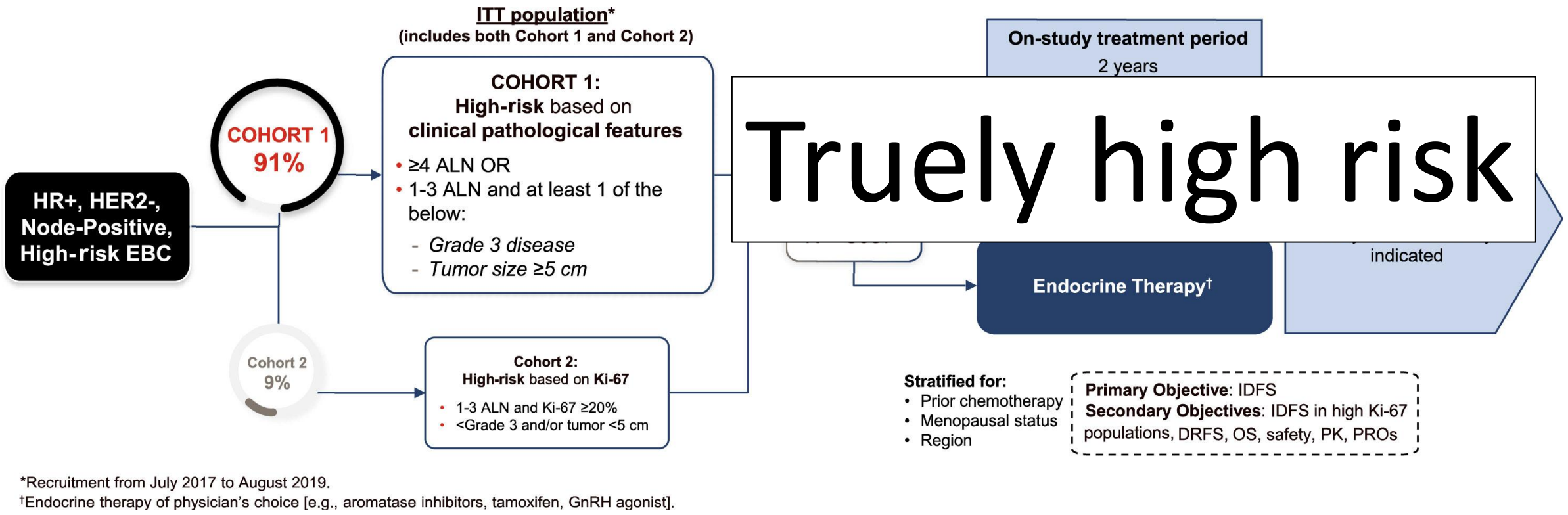
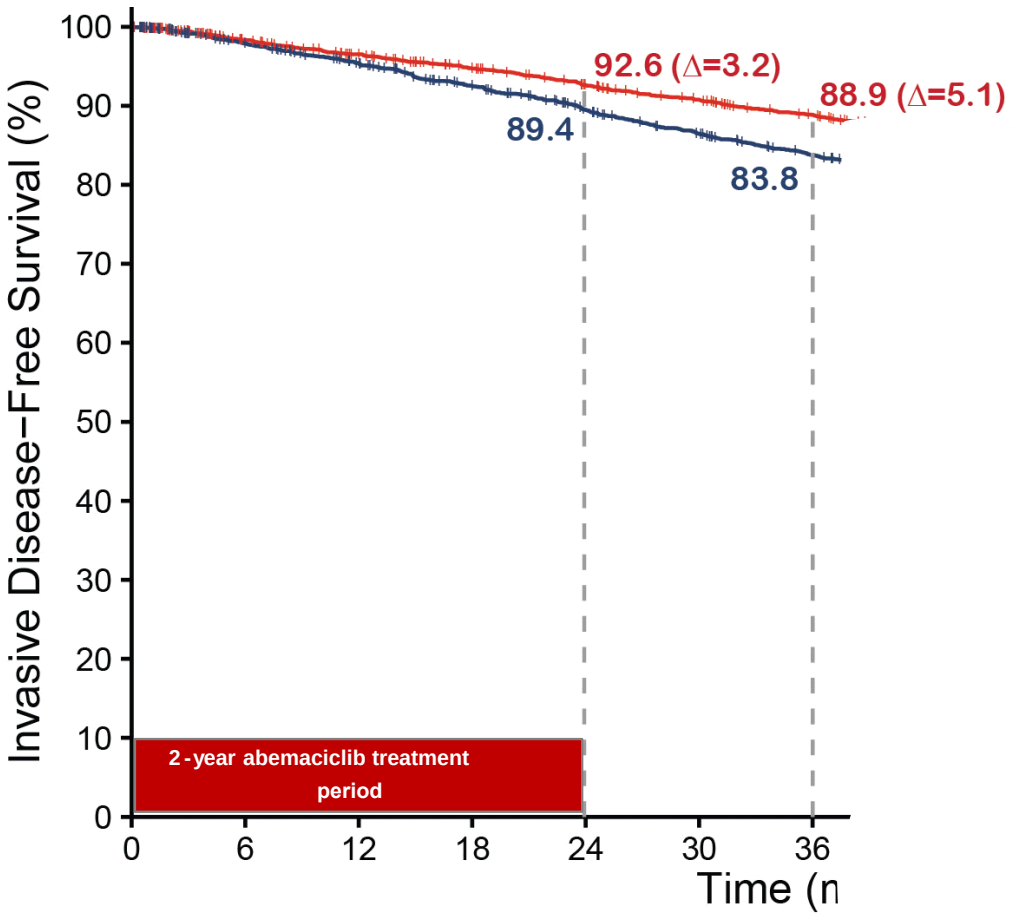
monarchE Study Design (NCT03155997)



*Recruitment from July 2017 to August 2019.
†Endocrine therapy of physician's choice [e.g., aromatase inhibitors, tamoxifen, GnRH agonist].

Potential misleading interpretation IDFS benefit



Number of IDFS events	
Abemaciclib + ET	ET Alone
382	553
HR (95% CI): 0.670 (0.588, 0.764)	
Nominal p <0.001	

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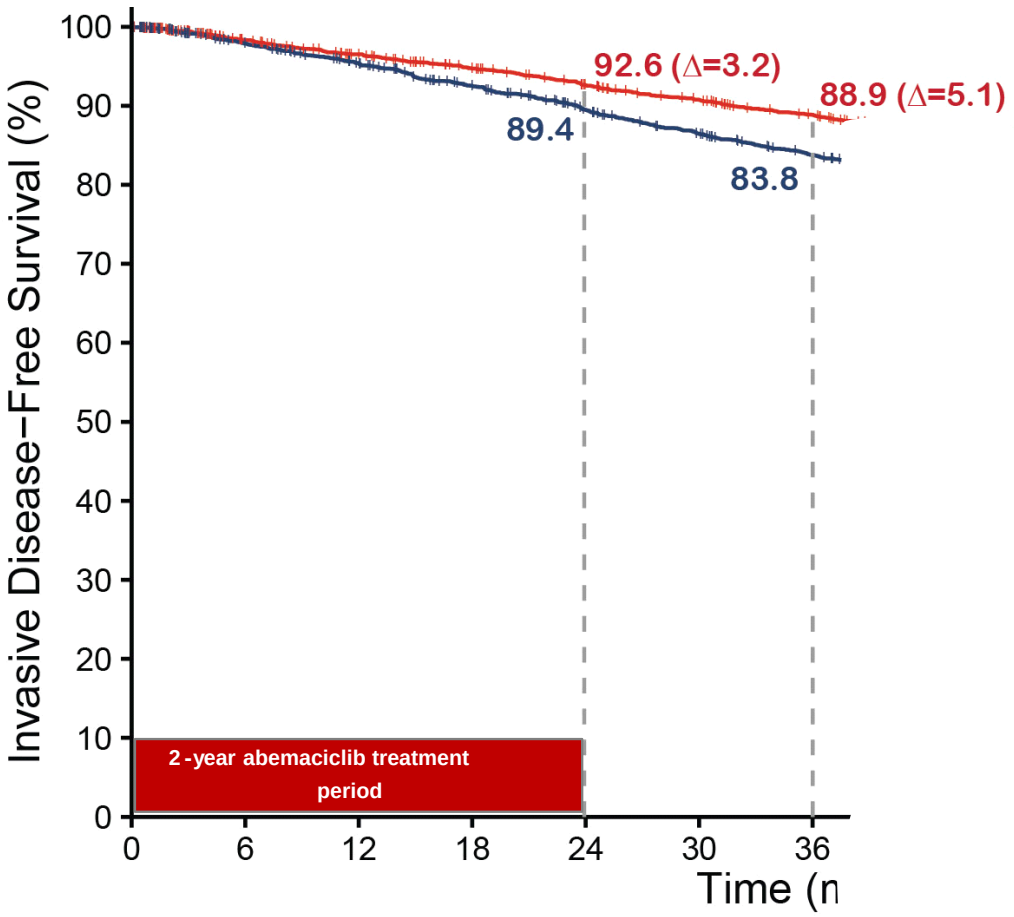

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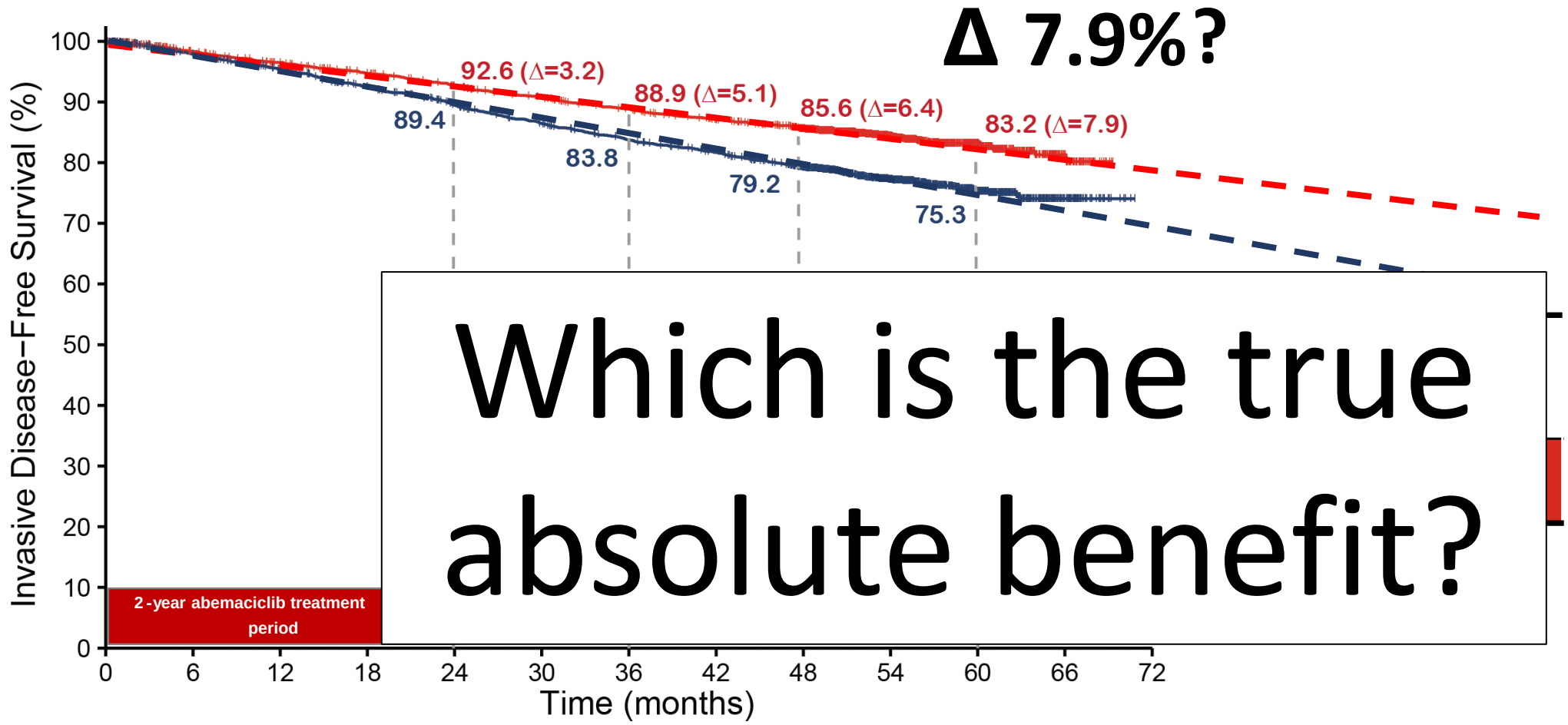
Increasing IDFS benefit



Which is the true absolute benefit?

CDK4/6i in node negative: misleading interpretation

ASCO Rapid Recommendations

Optimal Adjuvant Chemotherapy and Targeted Therapy for Early Breast Cancer—Cyclin-Dependent Kinase 4 and 6 Inhibitors: ASCO Guideline Rapid Recommendation Update

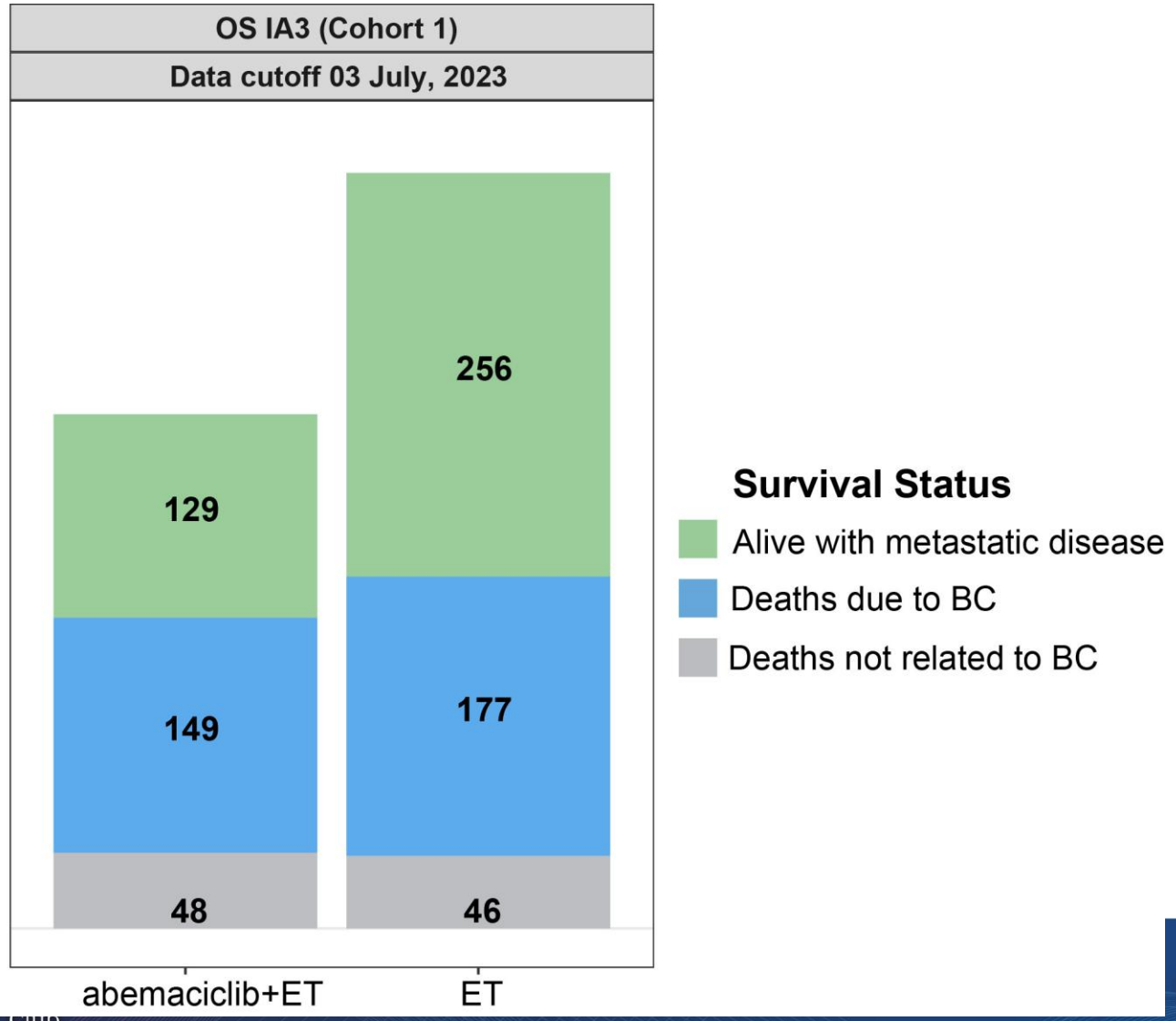
Rachel A. Freedman, MD, MPH[1]; Jennifer L. Caswell-Jin, MD[2]; Michael Hassett, MD, MPH[1]; Mark R. Somerfield, PhD[3]; and Sharon H. Giordano, MD, MPH[4]; for the Optimal Adjuvant Chemotherapy and Targeted Therapy for Early Breast Cancer Guideline Expert Panel

DOI https://doi.org/10.1200/JCO.24.00886

The Panel believes that adjuvant CDK4/6 inhibitor therapy may not provide meaningful clinical benefit to all patients who would have been eligible for the available trials, especially the lower-risk patients who were included in the NATALEE trial. For example, for most patients with node-negative disease, the risks of ribociclib may outweigh the benefits, with the exception of some patients with the highest risk, node-negative disease. However, the Panel acknowledges that there are insufficient data to specify which subgroups of patients do or do not warrant therapy. The Panel thus recommends considering the benefits, risks, costs, and preferences for each individual patient when deciding whether to recommend therapy.

Caveat:
before ESMO 2024

Half patients with Metastatic Disease with abemaciclib



OS?

Efficacy Outcomes by Ki-67 Index in Cohort 1

	Cohort 1 Ki-67 High		Cohort 1 Ki-67 Low	
	Abemaciclib + ET	ET	Abemaciclib + ET	ET
	n=1017	n= 986	n=946	n=968
IDFS				
Number of events, n				171
HR (95% CI)				**22, 0.839)**
Nominal p-value				001
5-year IDFS rate, % (95				80.2 (77.2, 82.9)
DRFS				
Number of events, n				143
HR (95% CI)				**12, 0.861)**
Nominal p-value		p<0.001		p=0.002
5-year DRFS rate, % (95% CI)	83.4 (80.7, 85.8)	75.2 (72.1, 78.0)	88.6 (86.1, 90.7)	83.5 (80.7, 86.0)
OS (immature)				
Number of events, n	92	121	56	62
HR (95% CI)	**0.717 (0.546, 0.941)**		**0.911 (0.633, 1.309)**	
Nominal p-value	p=0.016		p=0.613	

These compounds (will) improve OS

OXFORD

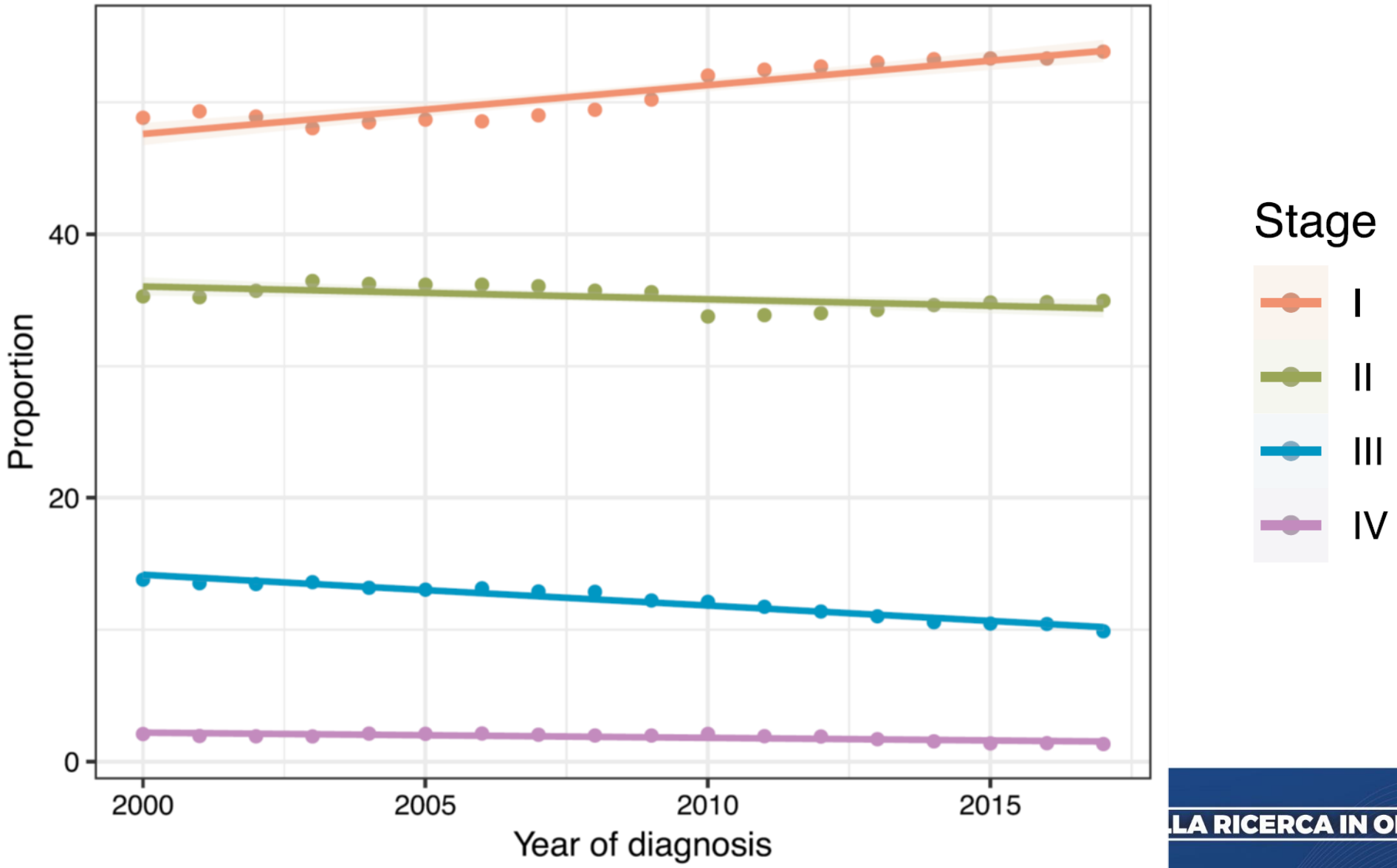
JNCI: Journal of the National Cancer Institute, 2024, **00(0)**, 1–9

https://doi.org/10.1093/jnci/djae241
Advance Access Publication Date: September 30, 2024
Article

Trends in breast cancer–specific death by clinical stage at diagnoses between 2000 and 2017

Michal Marczyk, PhD[1,2], Adriana Kahn, MD[2], Andrea Silber, MD[2], Mariya Rosenblit, MD[2], Michael P. Digiovanna, MD, PhD[2], Maryam Lustberg, MD[2], Lajos Pusztai, MD, DPhil[2,*]

Temporal trends in stage at diagnosis



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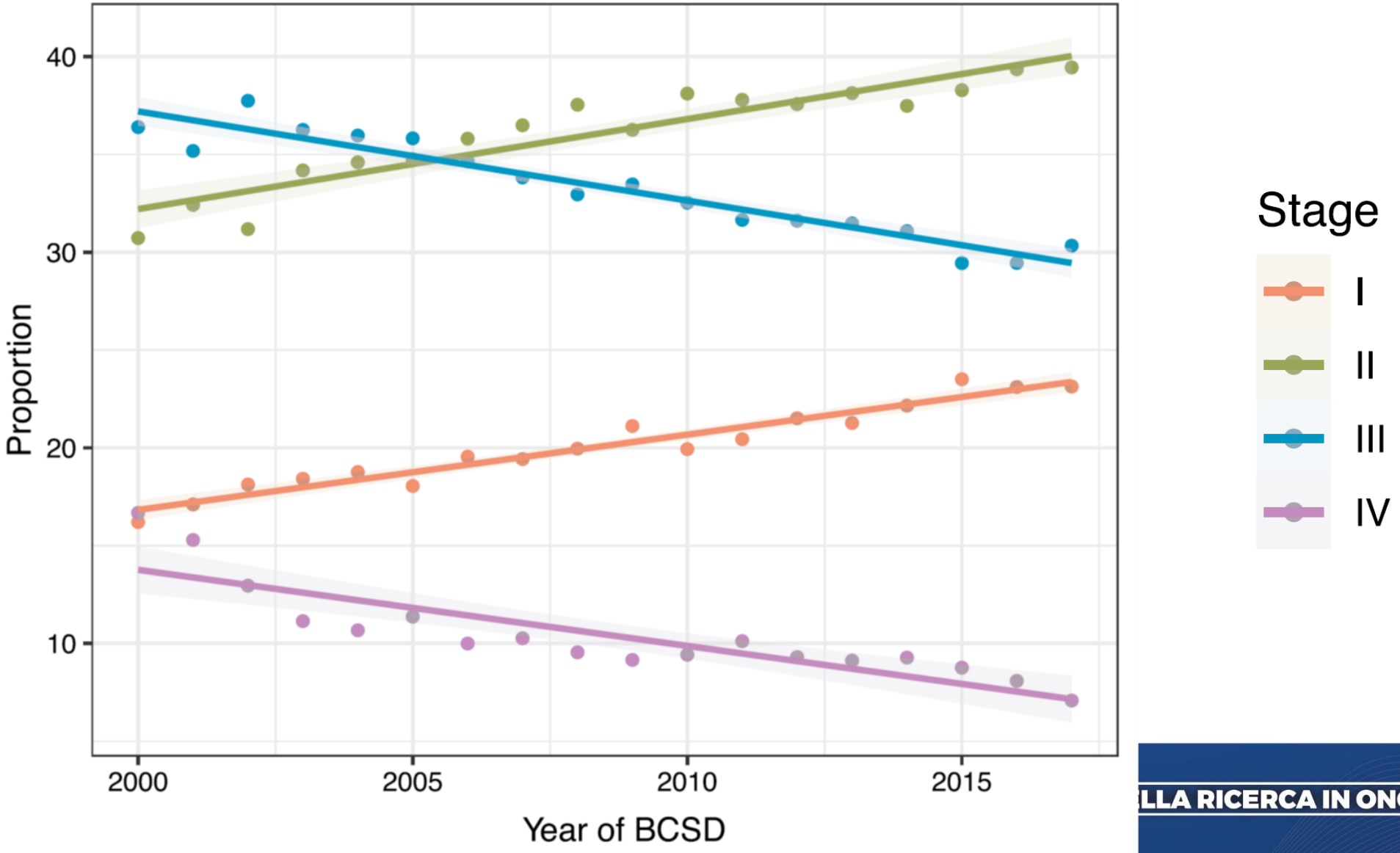
Temporal trends in stage contribution to annual breast cancer–specific death



Conclusions: Patients with stage I and II breast… account for more than 60% of current breast cancer–specific death. **To further reduce breast cancer death, strategies are needed to identify and treat patients with stage I and II disease who remain at risk for recurrence.**

The decision-making process for ER+/HER2- EBC

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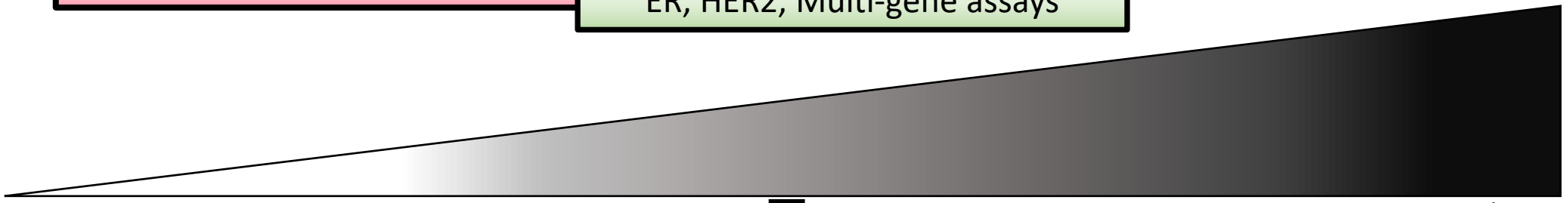
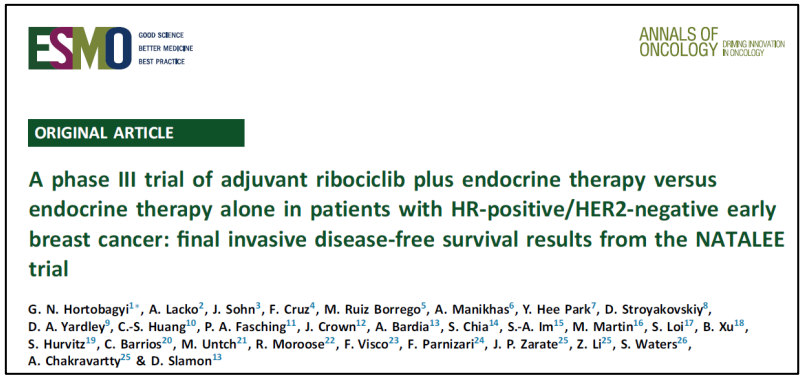


Risk / Treatment Benefit



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The tremendous progress in breast cancer is due to “incrementalism”

Incrementalism

A believing that huge advancement
can be also achieved
with subsequent change by degrees