Cancer Education Day – Dec. 13, 2019

Updates in Hormone Receptor Positive Breast Cancer

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WINDSOR REGIONAL HOSPITAL
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COMPASSION is our PASSION

Disclosures

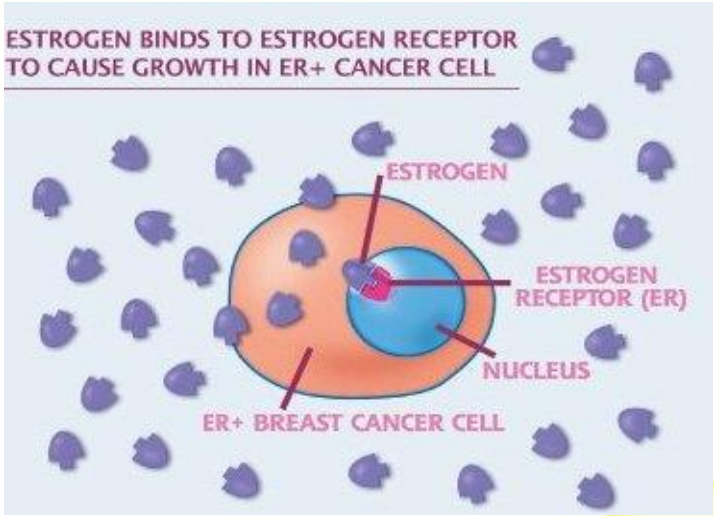
- Research - Novartis

Objectives

- To learn about new treatment options in hormone receptor positive metastatic breast cancer
- To learn about the efficacy of the treatments
- To know the side effects and the monitoring

What is Hormone Receptor Positive Breast Cancer?

- In 2019, 10,600 women will be diagnosed with breast cancer and 1900 will die in Ontario.
- Hormone receptor positive: 70-75%
- ER+ PR+
- ER+ PR-
- ER- PR+

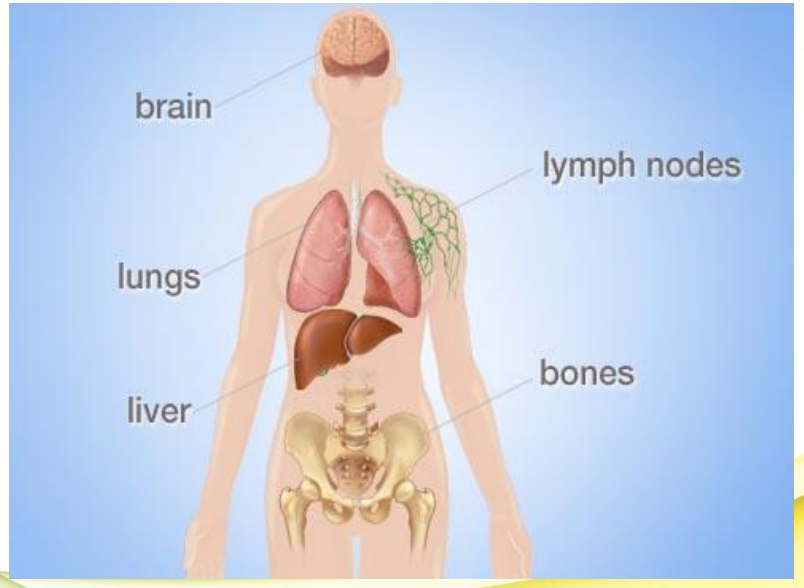


What Does This Mean?

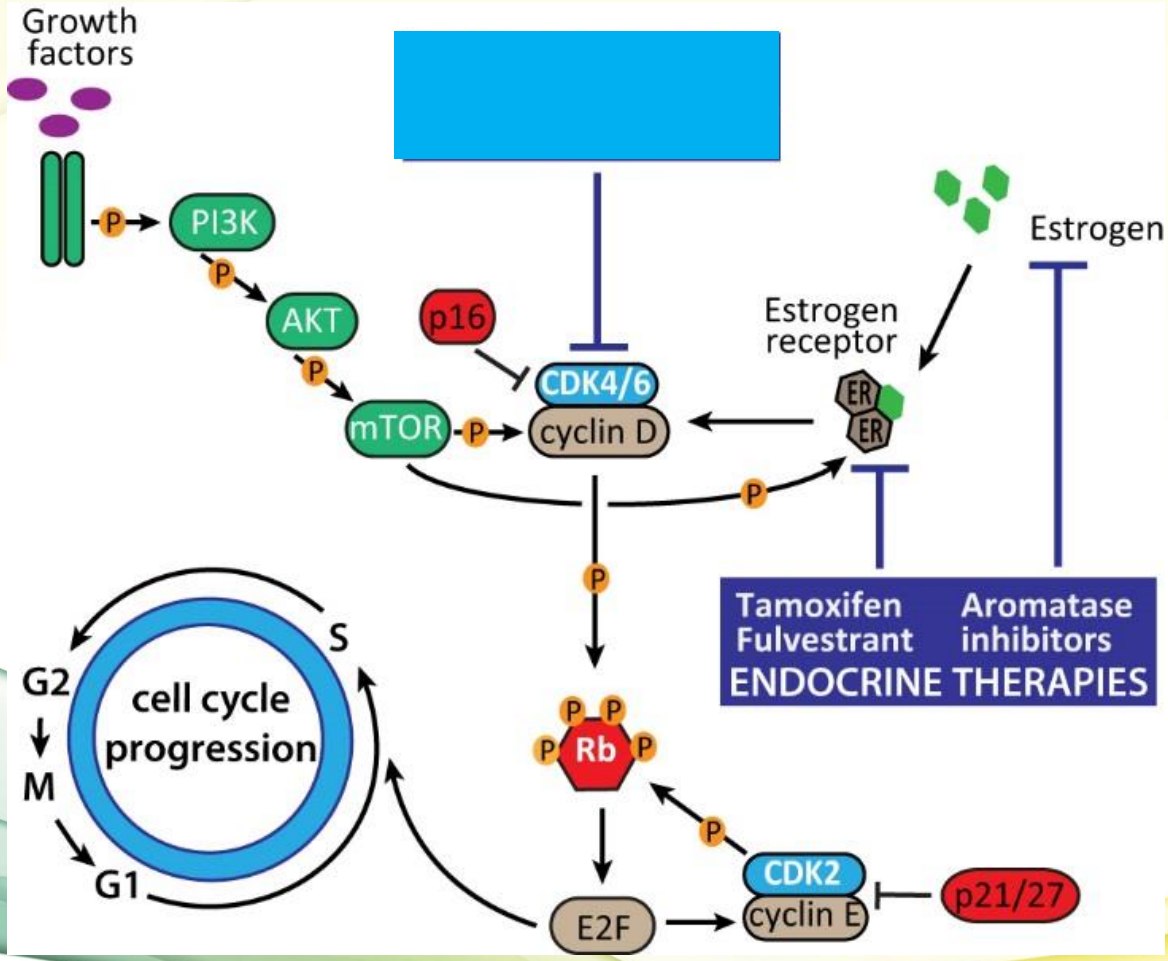
- Target the receptor – easy fix?
- Endocrine treatment = oral pill
- Premenopausal – Tamoxifen
- Postmenopausal:
  - Letrozole
  - Anastrozole
  - Exemestane
  - Fulvistrant injection

What Happens Next?

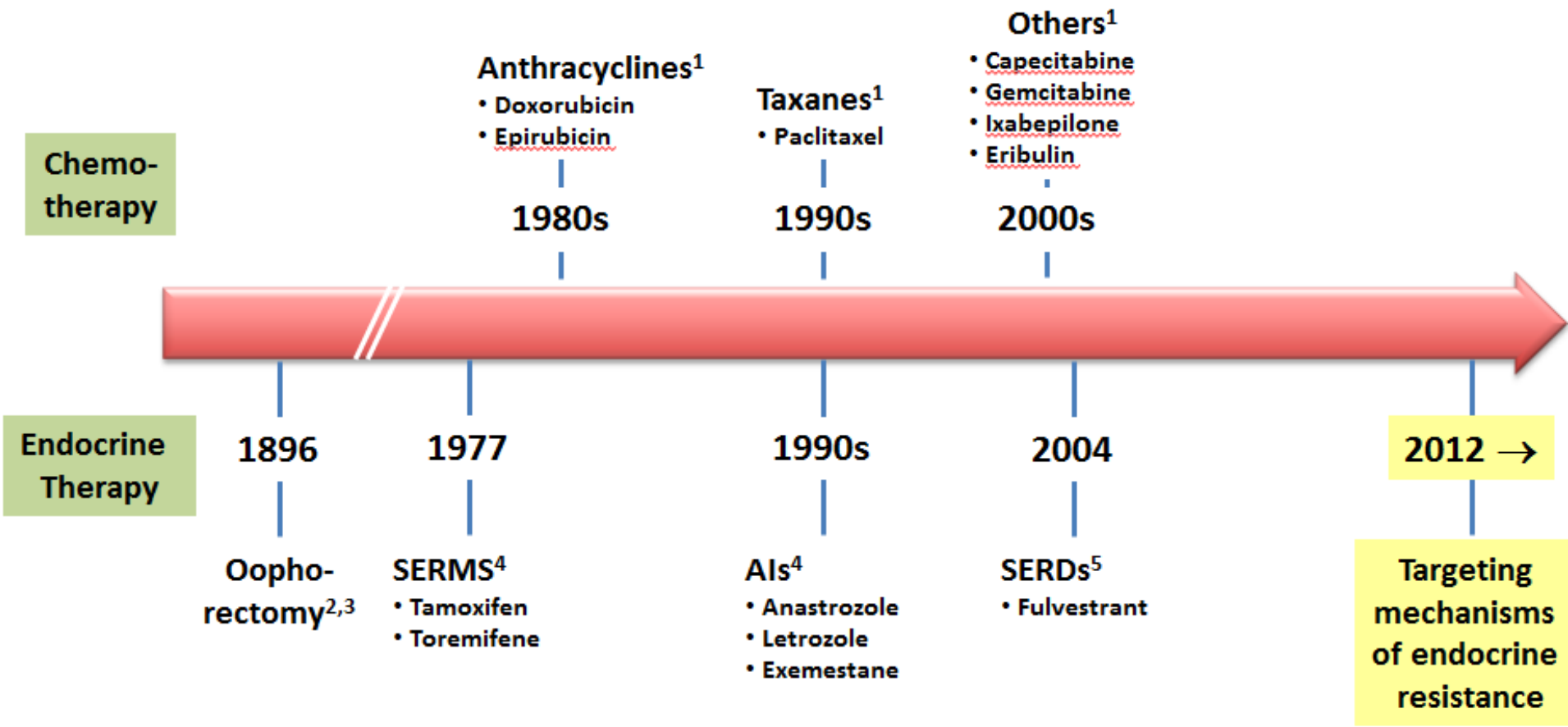
- 5 year survival 90% (SEER data)
- Based on TNM staging/other factors – patients can still develop metastases



Why?


Growth factors
PI3K
AKT
mTOR
p16
CDK4/6
cyclin D
Estrogen
Estrogen receptor
ER
ER
Tamoxifen
Fulvestrant
Aromatase inhibitors
ENDOCRINE THERAPIES
cell cycle progression
G2
M
G1
S
Rb
CDK2
cyclin E
p21/27
E2F

Timelines for Treatments in Advanced Breast Cancer

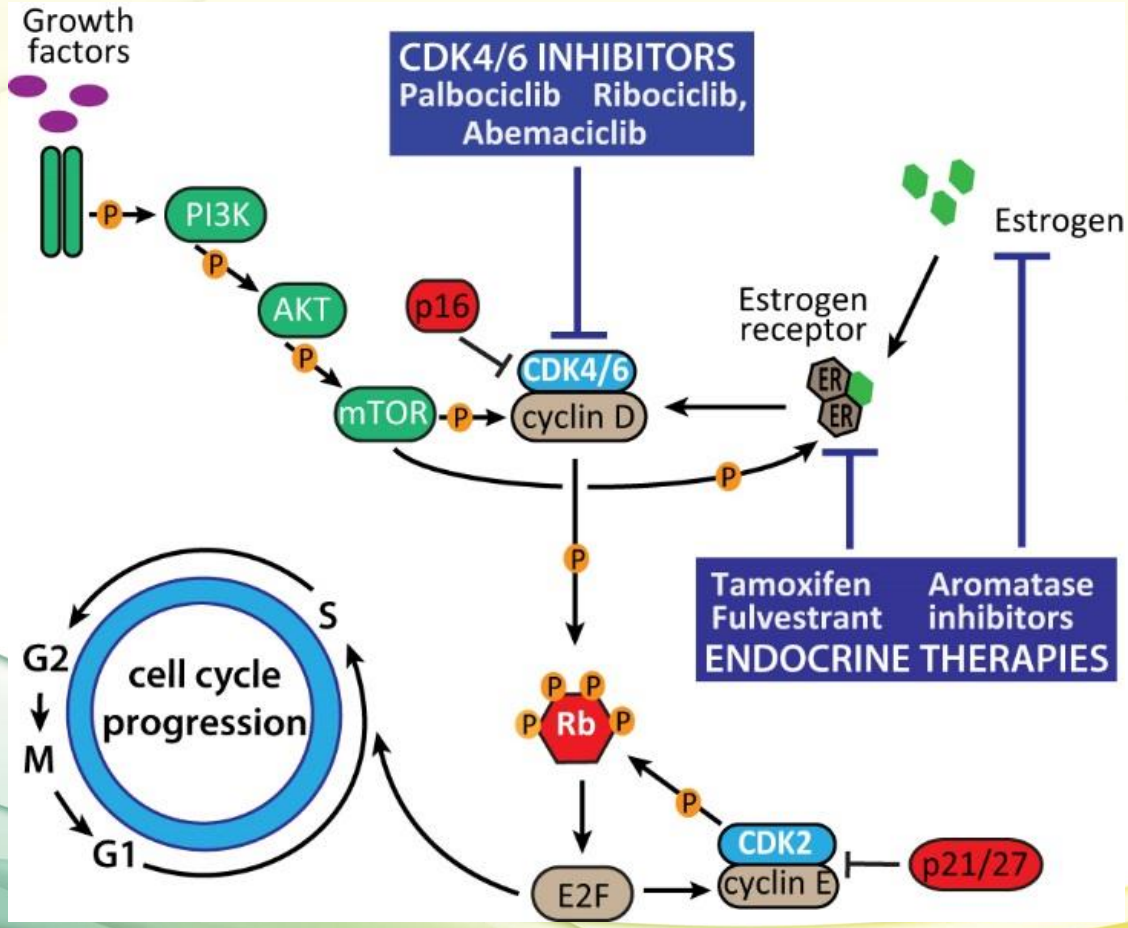


Abbreviations: AI, aromatase inhibitor; ERDs, estrogen receptor downregulator; HR+; hormone receptor positive; SERMS, selective estrogen receptor modulators.

What is New in Metastatic Breast Cancer?

- **CD4/6 K inhibitors:** Palbociclib, Ribociclib, Abemaciclib
- **PI3kinase inhibitor:** Alpelicib
- **MTOR inhibitors:** Everolimus

How?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Metastatic Evidence

ORIGINAL ARTICLE

Overall Survival with Ribociclib plus Endocrine Therapy in Breast Cancer

Seock-Ah Im, M.D., Ph.D., Yen-Shen Lu, M.D., Ph.D., Aditya Bardia, M.D., Nadia Harbeck, M.D., Ph.D., Marco Colleoni, M.D., Fabio Franke, M.D., Louis Chow, M.D., Joohyuk Sohn, M.D., Kaun-Seok Lee, M.D., Ph.D., Saul Campos-Gomez, M.D., Rafael Villanueva-Vazquez, M.D., Kyung-Hae Jung, M.D., et al.

ORIGINAL ARTICLE

Palbociclib and Letrozole in Advanced Breast Cancer

Richard S. Finn, M.D., Miguel Martin, M.D., Hope S. Rugo, M.D., Stephen Jones, M.D., Seock-Ah Im, M.D., Ph.D., Karen Gelmon, M.D., Nadia Harbeck, M.D., Ph.D., Oleg N. Lipatov, M.D., Janice M. Walshe, M.D., Stacy Moulder, M.D., Eric Gauthier, Pharm.D., Ph.D., Dongrui R. Lu, M.Sc., et al.

npj Breast Cancer

NPJ Breast Cancer. 2019; 5: 5.
Published online 2019 Jan 17. doi: 10.1038/s41523-018-0097-c

PMCID: PMC6336850
PMID: 30675515

MONARCH 3 final PFS: a randomized study of abemaciclib as initial therapy for advanced breast cancer

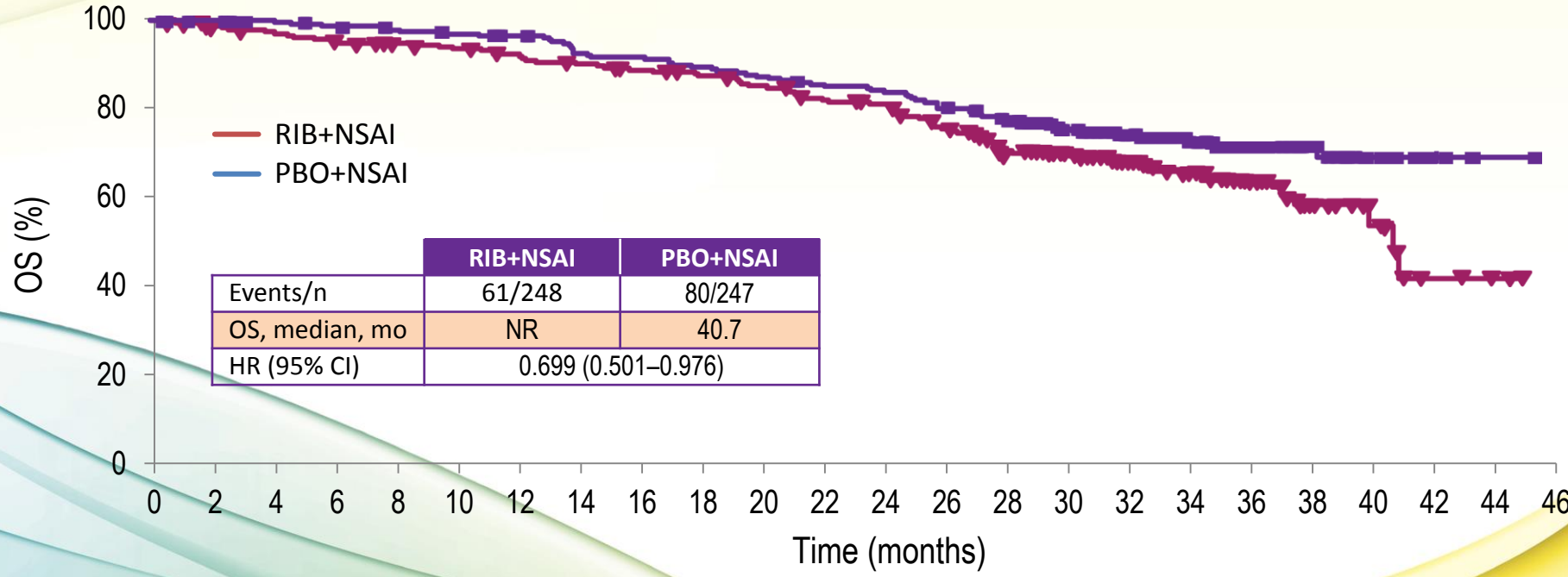
Stephen Johnston,[X1] Miguel Martin,[2] Angelo Di Leo,[3] Seock-Ah Im,[4] Ahmad Awada,[5] Tammy Forrester,[6] Martin Frenzel,[6] Molly C. Hardebeck,[7] Joanne Cox,[8] Susana Barriga,[9] Masakazu Toi,[10] Hiroji Iwata,[11] and Matthew P. Goetz[12]

How Much is the Benefit?

- Increase in progression free survival is between 11-14 months
- ***Pre****menopausal women:* median overall with AI + Ribociclib + Goserlin survival 40 months Vs not reached at 3 years (Monaleesa-7 ESMO)
- ***Post****menopausal women:* similar benefit with combination of Fulvestrant and Ribociclib (Monaleesa-3 ESMO)

OS in NSAI Cohort

– Median duration of follow-up was 34.6 months



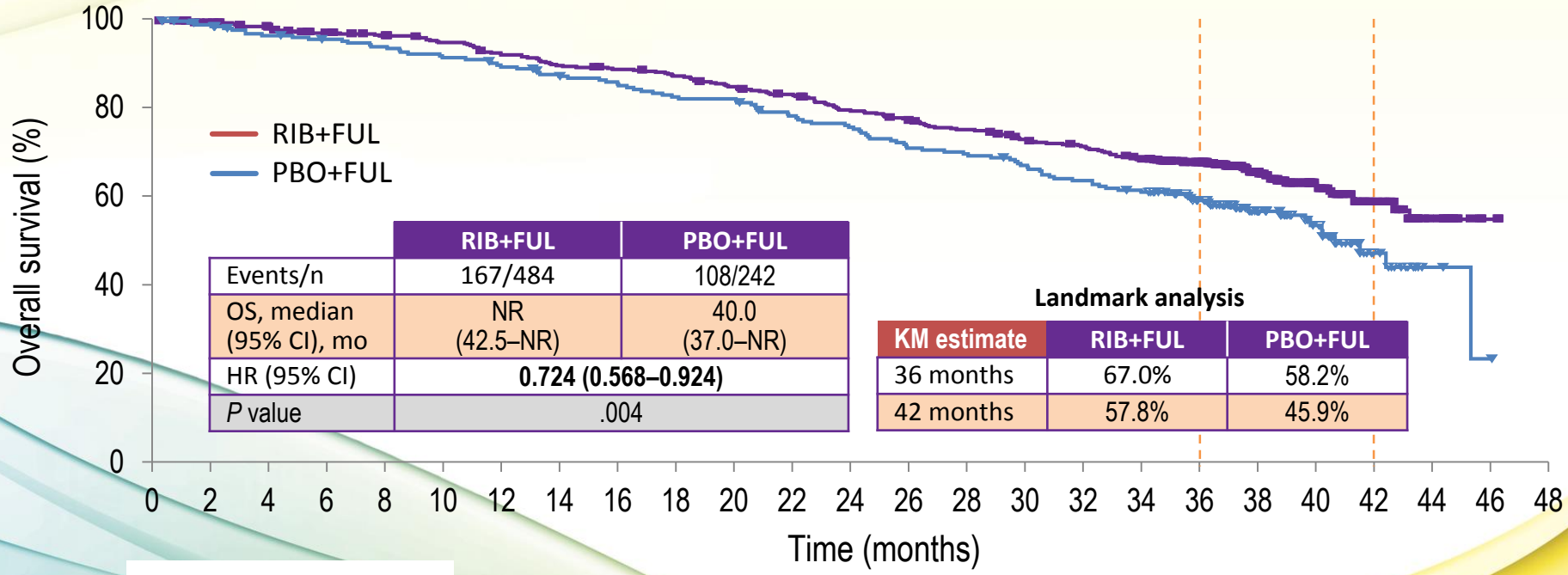
	RIB+NSAI	PBO+NSAI
Events/n	61/248	80/247
OS, median, mo	NR	40.7
HR (95% CI)	0.699 (0.501–0.976)	

No. of patients at risk

RIB+NSAI	248	245	241	236	233	230	226	216	213	206	201	196	192	184	174	142	113	80	49	29	16	5	2	0
PBO+NSAI	247	240	236	232	225	221	215	209	204	199	193	183	179	165	145	116	87	67	46	24	12	4	2	0

Overall Survival

- Reduction in relative risk of death with RIB was 28%



	RIB+FUL	PBO+FUL
Events/n	167/484	108/242
OS, median (95% CI), mo	NR (42.5–NR)	40.0 (37.0–NR)
HR (95% CI)	**0.724 (0.568–0.924)**	
P value	.004	

Landmark analysis

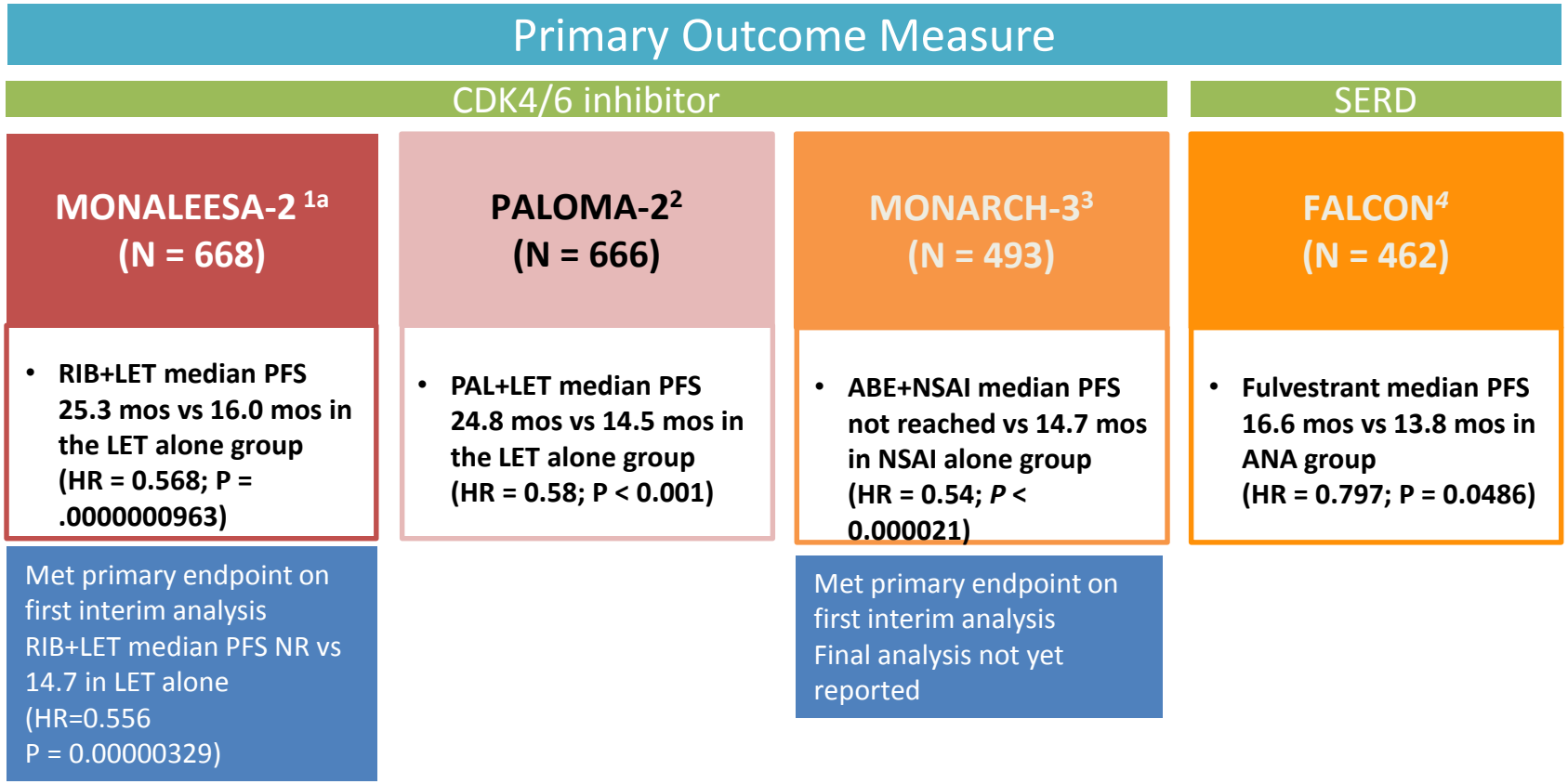
KM estimate	RIB+FUL	PBO+FUL
36 months	67.0%	58.2%
42 months	57.8%	45.9%

No. of patients at risk

Ribociclib	484	470	454	444	436	428	414	402	397	389	374	365	348	334	326	309	300	287	237	159	92	41	14	2	0
Placebo	242	233	227	223	218	213	207	199	194	187	184	174	169	159	155	147	141	134	107	64	37	14	3	0	0

– The *P* value of .004 crossed the prespecified boundary ($P < .01129$) to claim superior efficacy

Metastatic Efficacy - PFS in 1st-Line Setting: MONALEESA-2, PALOMA-2, MONARCH-3, FALCON

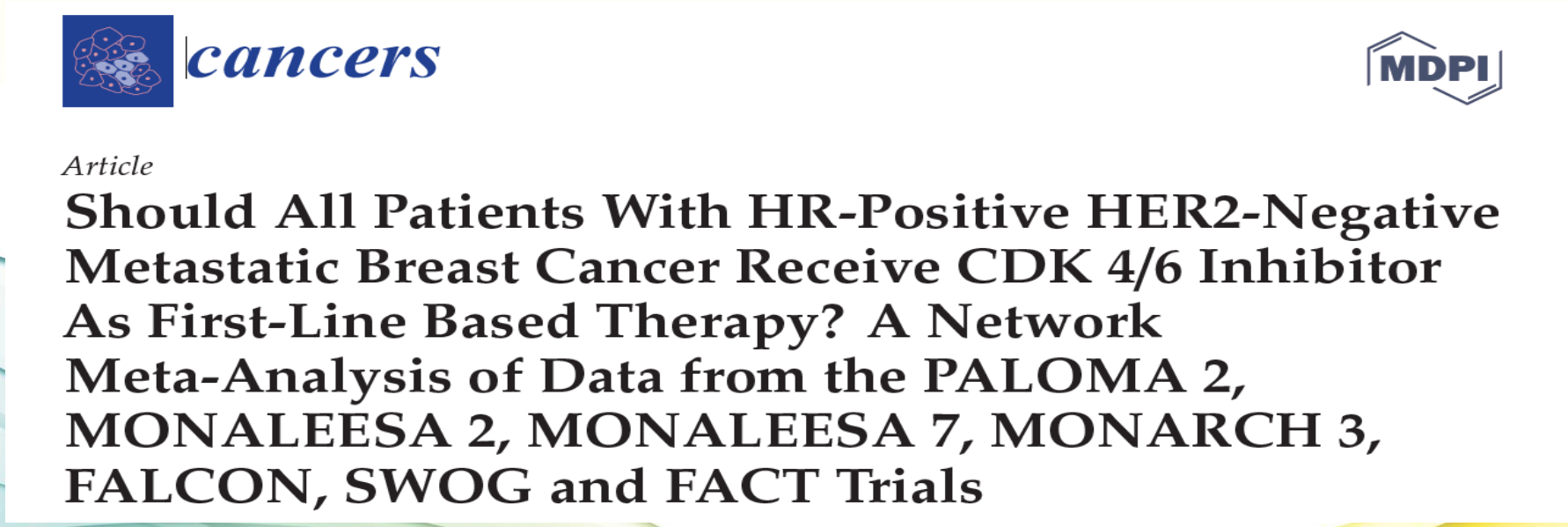


ABE, abemaciclib; ANA, anastrozole; CBR, clinical benefit rate; CDK, cyclin-dependent kinase; HR, hazard ratio; HER2–, human epidermal growth factor receptor-2–negative; HR+, hormone receptor-positive; LET, letrozole; PFS, progression-free survival; ORR, objective response rate; NSAI, non-steroidal aromatase inhibitor (LET or ANA); PAL, palbociclib; RIB, ribociclib; SERD, selective estrogen receptor down-regulator/degrader.

. 75.6155 ; 4. Robertson JFR, et al. Lancet. 2016. 388(10063):2997-3005.

Can all the Metastatic Breast Cancer Patients get the Treatment?

- Yes unless patient declines.



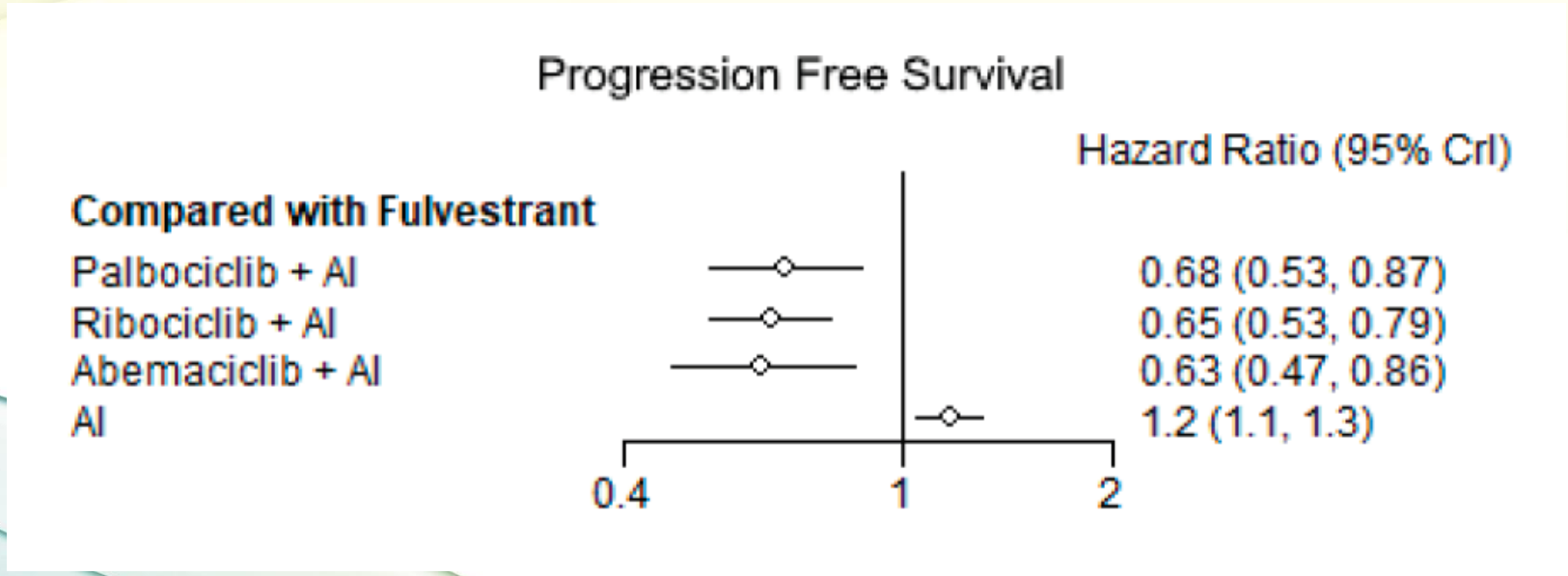
cancers

MDPI

Article

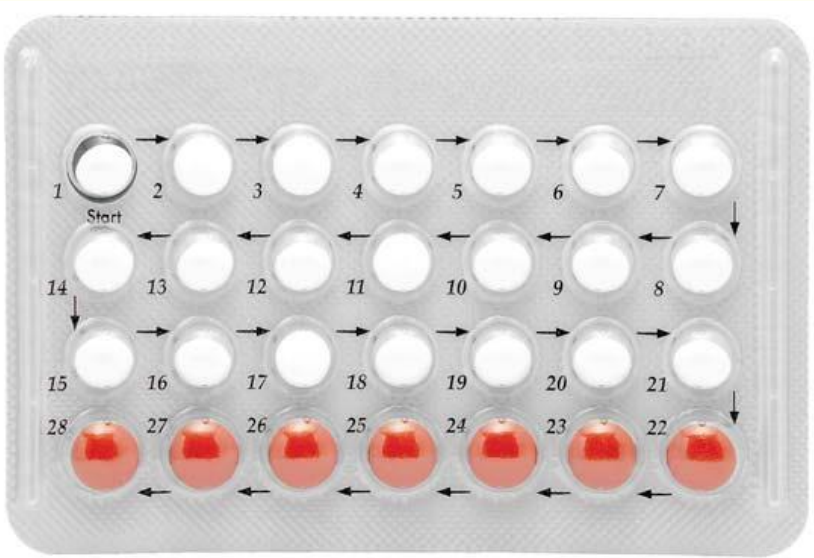
Should All Patients With HR-Positive HER2-Negative Metastatic Breast Cancer Receive CDK 4/6 Inhibitor As First-Line Based Therapy? A Network Meta-Analysis of Data from the PALOMA 2, MONALEESA 2, MONALEESA 7, MONARCH 3, FALCON, SWOG and FACT Trials

Combination Compared with Single Agent Fulvestrant



How do you Take it?

- Just like oral contraceptive pills with endocrine treatment
  - Palbociclib & Ribociclib
  - Abemaciclib is daily

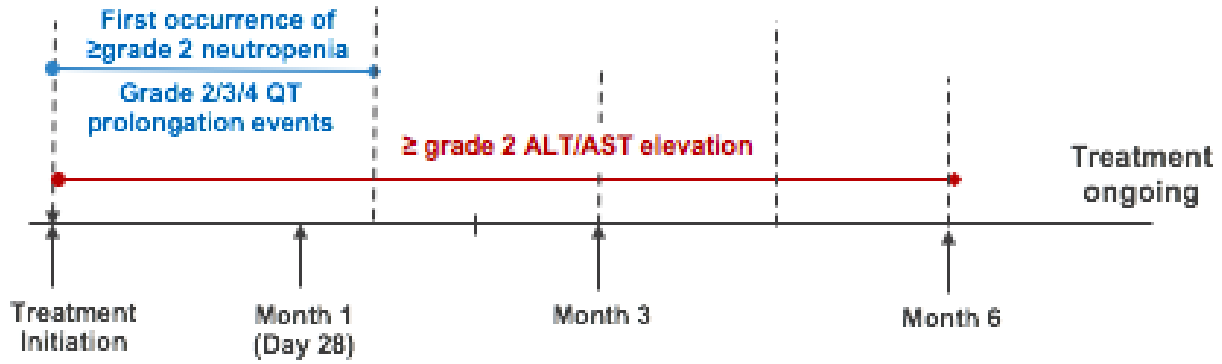


Side Effects

- **Neutropenia:** 45-60% (most common)
- **Leucopenia:** 15-20%
- **Anemia:** 5-6%
- **Fatigue:** 2-5%
- **Diarrhea:** 2-3%
- **Rash:** 2-3%
- **Nausea:** 3-5%

MONALEESA-2: Timing of AE for Patients Receiving Ribociclib + Letrozole

Adverse Event	Time to Onset and Resolution
Neutropenia	Median time to onset (grades 2-4): 16 days Median time to resolution: 15 days
QT Interval	Median time to onset (>480 msec): 15 days
Liver Enzyme Elevation	Median time to onset (≥ grade 3): 57 days Median time to normalization or ≤ grade 2: 24 days



AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase.
LEE011 (Ribociclib) Investigator's Brochure. 10th ed. East Hanover, NJ: Novartis; 2016:1-124.

Monitoring

- CBC every 2 weeks initially then every 4 weeks
- LFT: can increase
- Electrolytes first few cycles
- EKG: can result in Q-T prolongation, especially Ribo, no arrhythmia
- DVT with Abema
- Side effects settle in few cycles

Avoid

Medications causing Q-T prolongation:

- *Antiepileptic:* Phenytoin, Carbamazepine
- *Antinausea:* Zofran, Haldol, Emend
- *Antibiotics:* Azithromycin, Clarithromycin
- *Antifungal:* Ketoconazole, Voriconazole
- *OTC:* Cannabinoids, St. John's wort, grape fruit juice
- Other CYP3A4 inducers/inhibitors

Second Line Treatment

- PI3kinase inhibitors + Fulvestrant (injected)
- Ribo/palbo + Fulvestrant (injected)
- Exemestane + Everolimus
- Single endocrine agents

PI3kinase Inhibitors

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Alpelisib for *PIK3CA*-Mutated, Hormone Receptor–Positive Advanced Breast Cancer

F. André, E. Ciruelos, G. Rubovszky, M. Campone, S. Loibl, H.S. Rugo, H. Iwata, P. Conte, I.A. Mayer, B. Kaufman, T. Yamashita, Y.-S. Lu, K. Inoue, M. Takahashi, Z. Pápai, A.-S. Longin, D. Mills, C. Wilke, S. Hirawat, and D. Juric, for the SOLAR-1 Study Group*

About 40% of hormone receptor positive tumors are PI3K mutated

Benefit

- Median progression free survival: 11 months vs. 5.6 months
- Overall response: 35% vs. 16%
- Side effects:
  - Hyperglycemia
  - Diarrhea
  - Nausea
  - Rash
  - Fatigue

Summary

- Newer treatments improve overall and progression free survival in hormone receptor positive metastatic breast cancer patients
- Improved quality of life
- Manageable side effects

Next Steps

- Adjuvant trials in early stage hormone receptor positive breast cancer
- PALLAS- with Palbociclib
- NATALEE- with Ribociclib

❖ NATALEE is open at Windsor Regional Cancer Centre

Thank you!