SONIA

Selecting the **O**ptimal positio**n**
of CDK4/6 **I**nhibitors in HR+
Advanced breast cancer

the SONIA study
BOOG 2017-03

BOOG · KNL integraal kankercentrum Nederland · borstkankervereniging nederland · ZonMw

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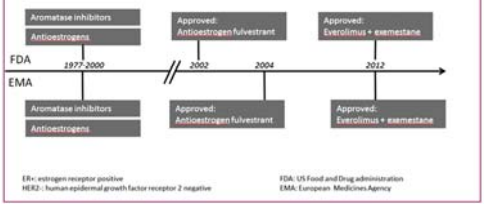
Behandeling mBC

Limited treatment advances for patients with HR+/HER2- mBC over the last 20 years



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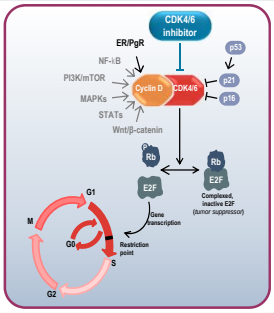
CDK4/6 bij HR+ BC

- Binding aan Rb inactiveert E2F, wat genen reguleert die belangrijk zijn bij G1/S transitie in de celcyclus
- Cycline D verhoogd tot expressie in HR+ BC
- Toegenomen CDK4/6 activiteit is geassocieerd met resistentie tegen hormonale therapie



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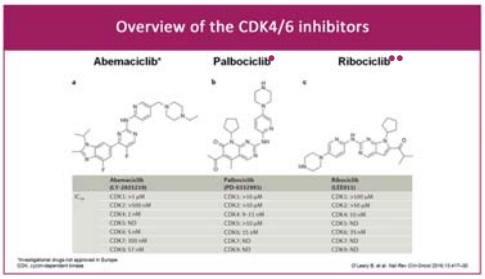
CDK4/6-remmers

Overview of the CDK4/6 inhibitors



- Sinds 1-8-2017 in basispakket (1e & 2e lijn)
- Sinds 1-5-2018 in basispakket (alleen 1e lijn)

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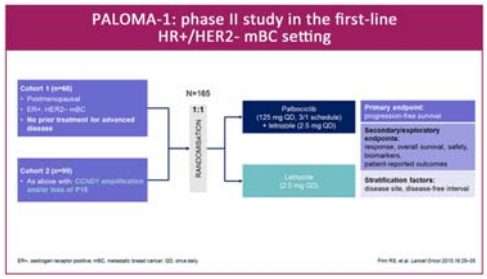
Klinische studies

PALOMA-1: phase II study in the first-line HR+/HER2- mBC setting



Finn RS *et al.* Lancet Oncology. Jan 2015

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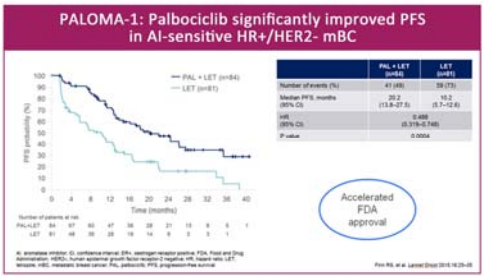
Klinische studies

PALOMA-1: Palbociclib significantly improved PFS in AI-sensitive HR+/HER2- mBC



Finn *Lancet Oncology* 2015

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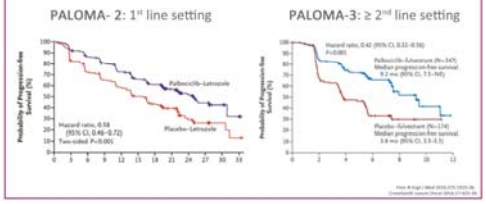
Klinische studies

PALOMA-2 and PALOMA-3: Palbociclib significantly improved PFS in both 1st line and ≥2nd line HR+/HER2- mBC



Finn *N Engl J Med* 2016
Cristofanilli *Lancet Oncol* 2016

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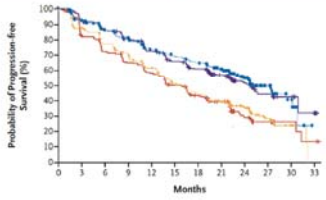
Klinische studies

PALOMA-2 and MONALEESA-2:In first-line similar results in PFS for palbociclib and ribociclib



MONARCH-3 (abemaciclib): median PFS not reached vs 14.3 mo

Finn *N Engl J Med* 2016
Hortobagyi *JCEM* 2016

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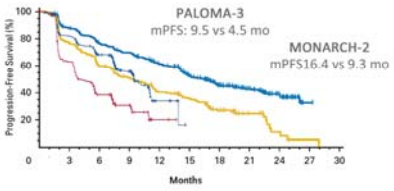
Klinische studies

PALOMA-3 and MONARCH-2: In second-line similar results in PFS for palbociclib and abemaciclib



MONALEESA-3 (ribociclib): median PFS 20.5 vs 12.5

Cristofanilli *Lancet Oncol* 2016
Sledge *JCO* 2017, Slamon *JCO* 2018

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Overzicht klinische studies

	PALOMA-1	PALOMA-2	MONARCH-3	MONALEESA-2	PALOMA-3	MONARCH-2	MONALEESA-3
Design	phase 2, open label	phase-3, placebo	phase-3, placebo	phase-3, placebo	phase-3, placebo	phase-3, placebo	phase-3, placebo
Hormonal therapy	letrozol	letrozol	letrozol / anastrozol	letrozol	fulvestrant	fulvestrant	fulvestrant
CDK4/6 inhibitor	palbociclib	palbociclib	abemaciclib	ribociclib	palbociclib	abemaciclib	ribociclib
N (patients)	165	666	493	668	521	669	726
Primary endpoint: PFS							
HR	0.49	0.58	0.54	0.56	0.46	0.55	0.59
Median (months)	20.2 vs 10.2	24.8 vs 14.5	NR vs 14.7	25.3 vs 16.0	9.5 vs 4.6	16.4 vs 9.3	20.5 vs 12.8
		First line			Second/subsequent lines		

Finn *Lancet Oncol* 2015; Finn *NEJM* 2016; Hortobagyi *NEJM* 2016;
Cristofanilli *Lancet Oncol* 2016; Sledge et al. *JCO* 2017; Di Leo *ESMO* 2017; Slamon *JCO* 2018

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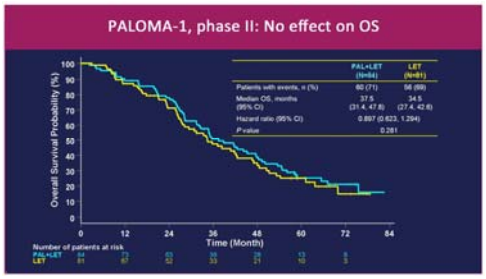
Overall survival

PALOMA-1, phase II: No effect on OS



Finn *JCO* 2017

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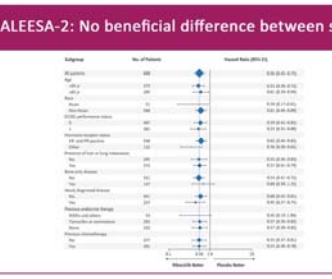
Subgroep analyses

MONALEESA-2: No beneficial difference between subgroups



Hortobagyi *ASCO* 2017

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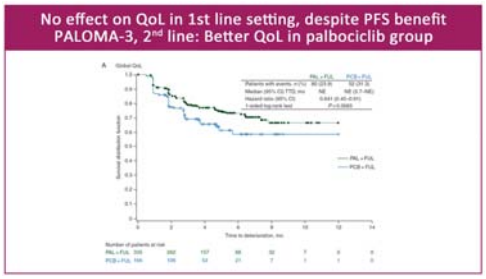
Kwaliteit van leven

No effect on QoL in 1st line setting, despite PFS benefit PALOMA-3, 2nd line: Better QoL in palbociclib group



Harbeck *Ann Oncol* 2016

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SONIA-studie: rationale

- CDK4/6 remmers verbeteren PFS bij ER+/HER2- mammacarcinoom
- Behandelduur in 1e vs 2e lijn (25 vs 9-16 mnd)
  - langer bijwerkingen
  - meer kosten
- Veel patiënten prima met alleen hormonaal
- Geen aangetoonde verbetering OS

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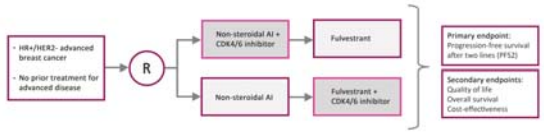
Study design



Aromataseremmers: anastrozol of letrozol

CDK4/6 inhibitor: palbociclib (1e en 2e lijn) of ribociclib (1e lijn)

Fulvestrant: datum 1e en laatste toediening vastleggen in EPD

Inclusieduur: 3,5 jaar

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Primaire eindpunt

- Primaire eindpunt: PFS2
- Stratificatie
  - Adjuvante endocriene therapie (ja/nee)
  - Viscerale metastasering (ja/nee)
  - Ziekenhuis
  - Type CDK4/6-remmer

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Secundaire eindpunten

- Adverse events
- Quality of Life
- Overall Survival
- Kosteneffectiviteit
- (Bio)markers
  - PET Imaging
  - DNA/RNA profiling
  - Circulating tumorcells / cell free DNA
  - Pharmacokinetics –dynamics, and –genomics
  - etc…

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Inclusiecriteria

1. Volwassen **vrouwen** (≥ 18 jaar) met bewezen diagnose van adenocarcinoom van de borst met locoregionale recurrent of gemetastaseerde ziekte; niet in aanmerking voor curatieve behandeling; geen indicatie voor chemotherapie
2. Bewezen **histologische/cytologische bevestiging** van ER en/of PR >10%, HER2-negatieve borstkanker
3. Nog **niet eerder behandeld** met systemische anti-kankertherapie voor locoregionaal recurrent of gemetastaseerde ziekte
4. Defintief **postmenopausaal**; premenopausale vrouwen: ovariectomie/ LHRH-agonist
5. Volgens RECIST v.1.1 **evalueerbare ziekte (ook bone only!)**
6. ECOG performancestatus (**PS) 0-2**
7. Adequate **orgaan- en beenmergfuncties**:
   a. ANC ≥1,000/mm3 (1.0 x 10e9 /L);
   b. Platelets ≥50,000/mm3 (50 x 10e9 /L);
   c. Geschatte kreatinineklaring ≥ 30 mL/min
   d. Total serum bilirubin ≤1.5 x ULN (≤3.0 x ULN if Gilbert's disease);
   e. AST and/or ALT ≤3 x ULN (≤5.0 x ULN if liver metastases present);

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