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Efficient use of Drugs in Oncology

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Patients want timely access to new cancer therapies, but they expect investigators to identify therapies that offer real benefits

Ian Tannock, Emeritus Professor of Medicine, University of Toronto

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Drug companies go for higher dose and longer duration to avoid a false negative result. The incentive will never be there to test dose optimization.

Joe Lennerz, Chief Scientific Officer, BostonGene

Examples

- **Duration of treatment**
  - Adjuvant trastuzumab in breast cancer
- **Dosing**
  - Maximum Tolerated Dose (MTD)
- **Combination treatments**
  - Lenvatinib + Pembrolizumab in endometrial cancer
- **Sequencing of treatments**
  - CDK4/6 inhibitors in advanced breast cancer

2023 ASCO ANNUAL MEETING

SONIA

Primary outcome of the phase 3 SONIA trial

Gabe Sonke, Annemiek van Ommen - Nijhof, Noor Wortelboer, Vincent van der Noort, Astrid Swinkels, Hedwig Blommestein, Aart Beeker, Karin Beelen, Lisanne Hamming, Joan Heijns, Aafke Honkoop, Paul de Jong, Quirine van Rossum - Schornagel, Christa van Schaik - van de Mheen, Jolien Tol, Cathrien Tromp - van Driel, Suzan Vrijaldenhoven, Elise van Leeuwen - Stok, Inge Konings, Agnes Jager

BOOG KNL borstkankervereniging nederland Zorgverzekeraars Nederland ZonMw

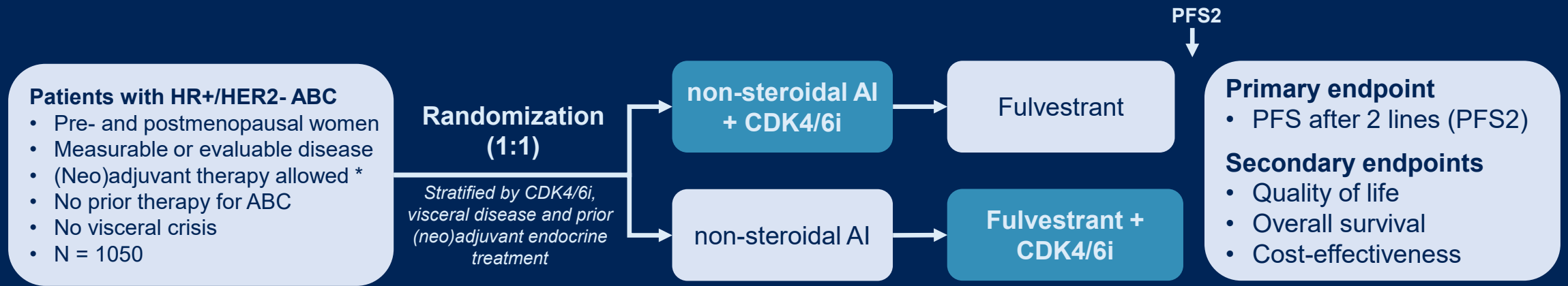
Background

SONIA

- CDK4/6 inhibitors improve outcome of patients with advanced breast cancer in first[1-3] and second line[4-6]
- First-line use is associated with prolonged side effects and higher drug costs
- Most guidelines advice first-line use despite a lack of comparative evidence
- ASCO and ESMO advocate equitable and sustainable cancer care

1. Finn R, et al. NEJM 2016; 2. Hortobagyi G, et al. NEJM 2016; 3. Goetz M, et al. J Clin Oncol 2017; 4. Cristofanilli M, et al. Lancet Oncol 2016; 5. Slamon D, et al. J Clin Oncol 2018; 6. Sledge G, et al. J Clin Oncol 2017

SONIA trial design



- Tumor assessments every 12 weeks
- PFS locally assessed per RECIST v1.1
- Primary analysis planned after 574 PFS2 events
  - 89% power to detect superiority according to ESMO MCBS (HR lower limit CI ≤0.65 and Δ ≥3 months) with two-sided α=5%[1]

HR+, hormone receptor positive; HER2- , HER2 negative; ABC, advanced breast cancer; AI, aromatase inhibitor; PFS, progression-free survival
* disease-free interval after non-steroidal aromatase inhibitor >12 months. ClinicalTrials.gov (NCT03425838)
1. Cherny NI, et al. Ann Oncol 2017

Trial overview

SONIA

Inclusion period: November 23, 2017 - September 1, 2021

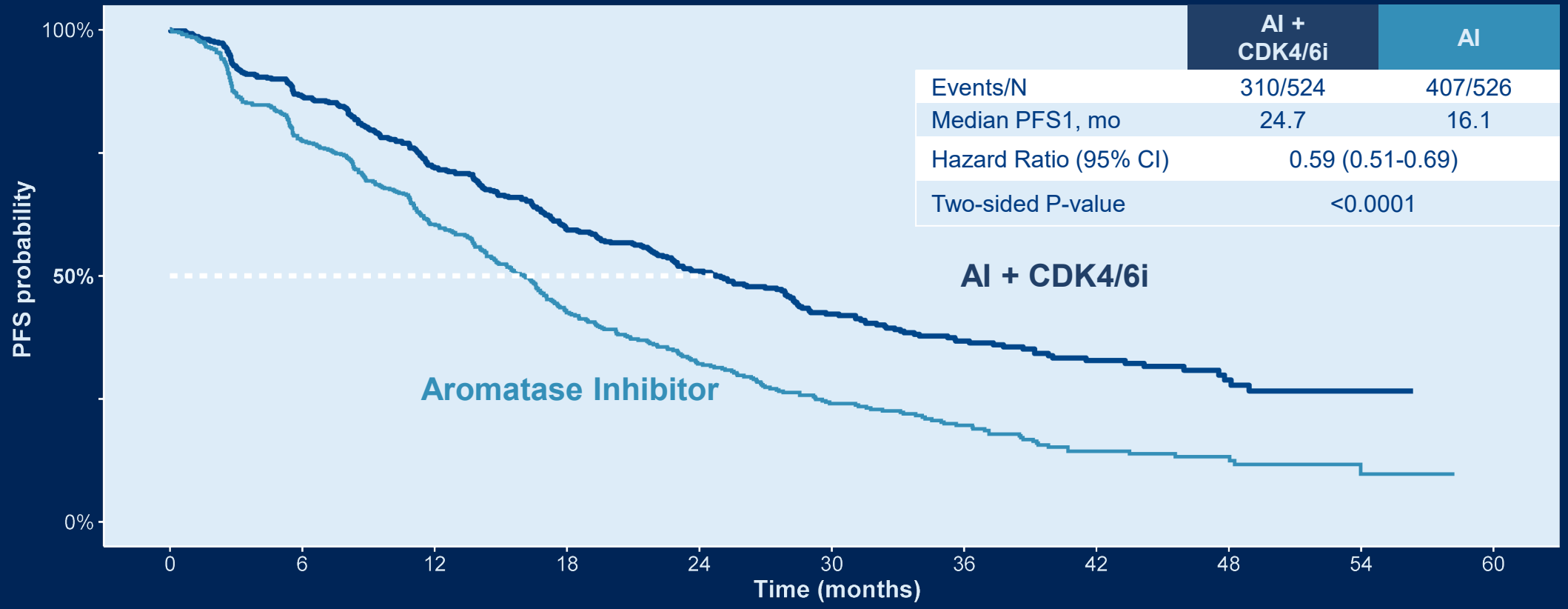
Data cut-off date: December 1, 2022

Median follow-up: 37.3 months

		First-line CDK4/6i N=524	Second-line CDK4/6i N=526
Patient status, n	First-line treatment ongoing	207	122
	Second-line treatment ongoing	16	82
	Follow-up	117	134
Number of events, n	PFS1	310	407
	PFS2	281	310
	OS	184	188
Median duration on CDK4/6i, months		24.6	8.1

Progression-free survival in first line

SONIA

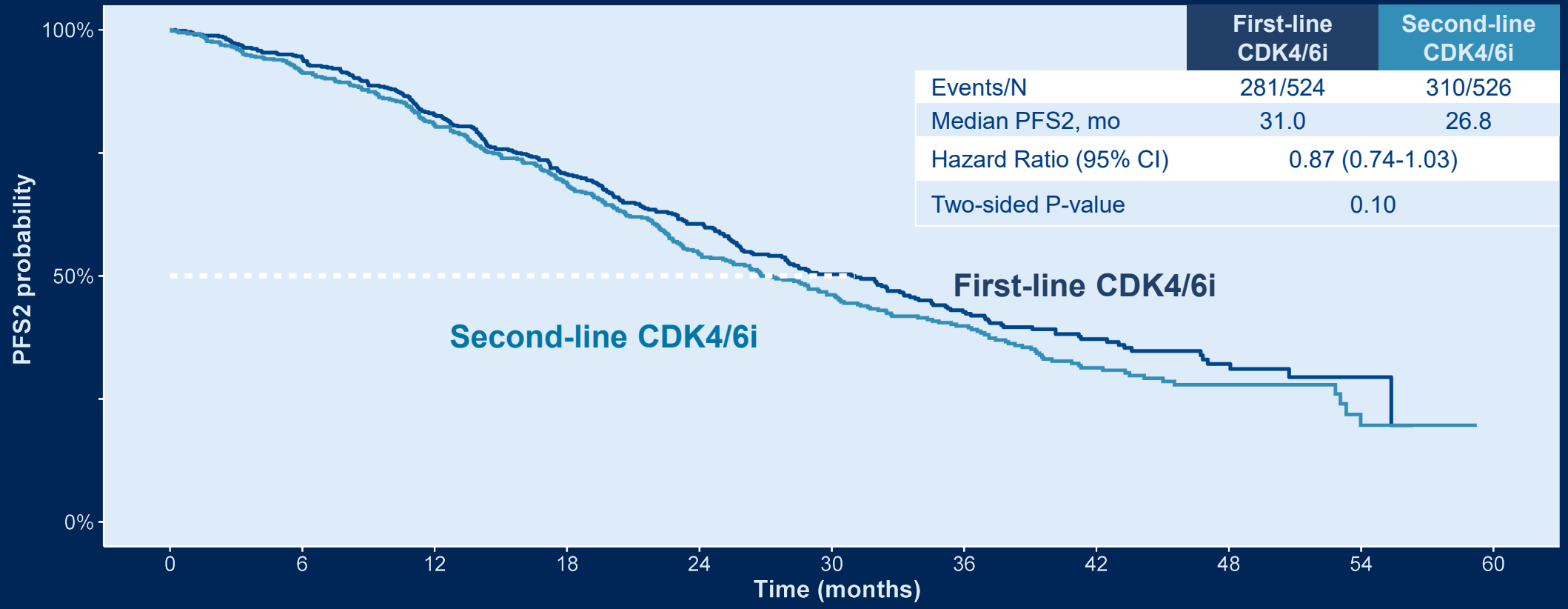


	AI + CDK4/6i	AI
Events/N	310/524	407/526
Median PFS1, mo	24.7	16.1
Hazard Ratio (95% CI)	0.59 (0.51-0.69)	
Two-sided P-value	<0.0001	

Numbers at risk (censored)											
AI + CDK4/6i	524 (0)	451 (3)	374 (4)	285 (30)	202 (76)	137 (110)	101 (129)	63 (158)	27 (189)	4 (210)	0 (214)
AI	526 (0)	406 (2)	315 (4)	203 (25)	128 (54)	84 (68)	57 (81)	31 (93)	17 (105)	5 (114)	0 (119)

Primary endpoint: PFS2

SONIA



	First-line CDK4/6i	Second-line CDK4/6i
Events/N	281/524	310/526
Median PFS2, mo	31.0	26.8
Hazard Ratio (95% CI)	0.87 (0.74-1.03)	
Two-sided P-value	0.10	

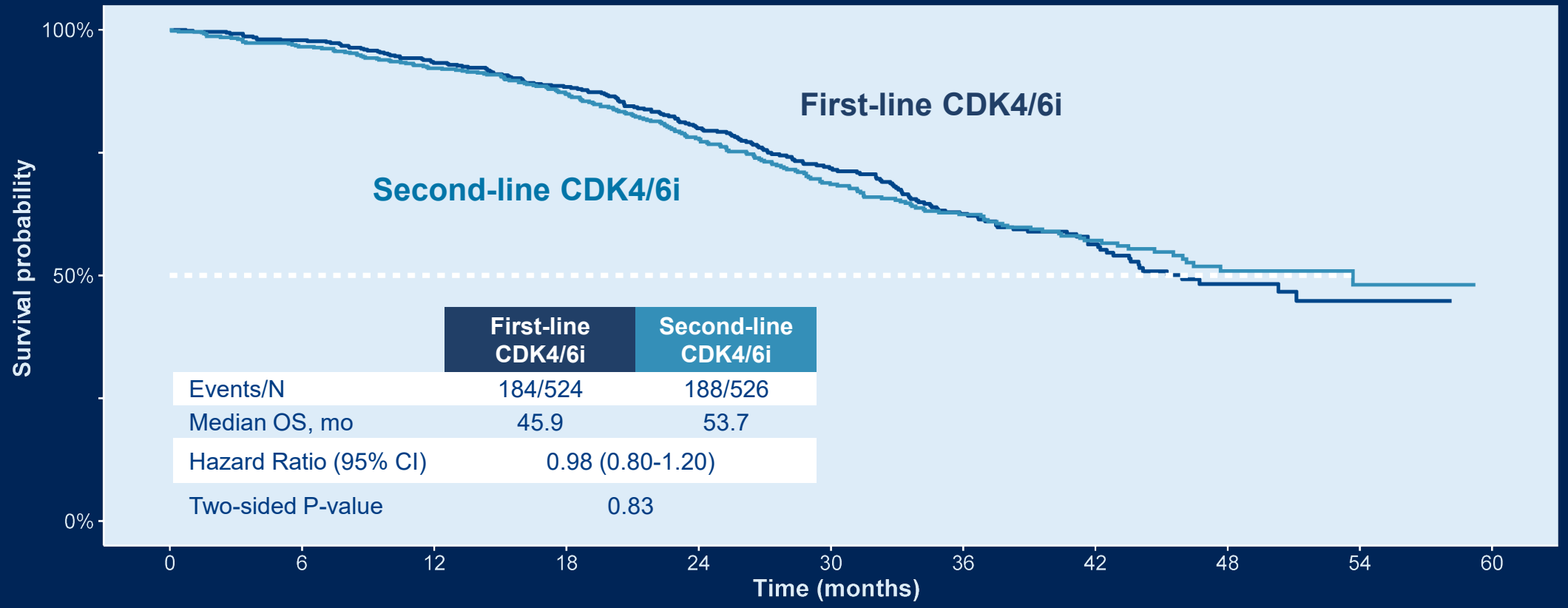
First-line	524 (0)	491 (3)	429 (5)	339 (34)	244 (84)	167 (123)	118 (148)	69 (184)	31 (215)	5 (239)	0 (243)
Second-line	526 (0)	478 (2)	418 (6)	330 (35)	225 (76)	164 (105)	115 (133)	65 (161)	30 (190)	9 (207)	0 (216)

Numbers at risk (censored)

PRESENTED BY: Prof. Gabe S. Sonke, MD, PhD

Overall survival

SONIA



	First-line CDK4/6i	Second-line CDK4/6i
Events/N	184/524	188/526
Median OS, mo	45.9	53.7
Hazard Ratio (95% CI)	0.98 (0.80-1.20)	
Two-sided P-value	0.83	

First-line	524 (0)	510 (3)	485 (4)	427 (37)	324 (103)	240 (157)	171 (197)	104 (250)	42 (300)	7 (333)	0 (340)
Second-line	526 (0)	506 (2)	483 (2)	426 (32)	328 (89)	242 (139)	175 (186)	112 (236)	52 (287)	16 (322)	0 (338)

Numbers at risk (censored)

PRESENTED BY: Prof. Gabe S. Sonke, MD, PhD

Quality of life

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- Quality of life was assessed using validated questionnaires
- Up to 11 timepoints
- FACT-B and EQ-5D-5L
- Completion rate 87% for FACT-B in both arms
- FACT-B subscores and cost-effectiveness analyses will follow

No difference in FACT-B total score between the study arms (p=0.4)

Safety summary

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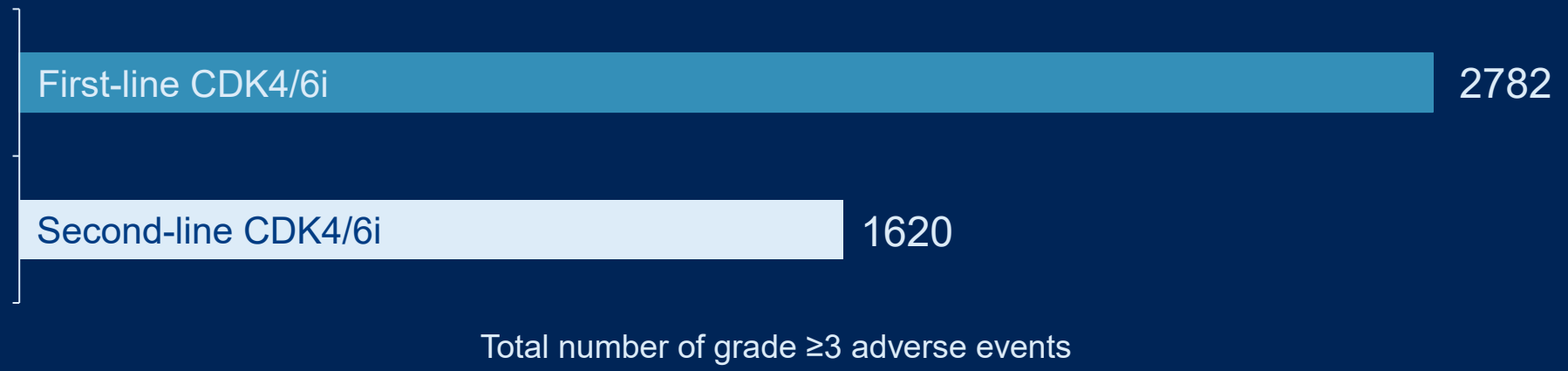
- The safety profile was characteristic for CDK4/6i
  - neutropenia, liver function abnormalities, anemia, thrombocytopenia
- 74% more grade ≥3 adverse events when CDK4/6i was used in first-line



Summary of the main findings

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CDK4/6 inhibition in first-line compared to second-line

- Does not improve Progression-Free Survival
- Does not improve Overall Survival
- Does not improve Quality of Life
- Extends time on CDK4/6i by 16.5 months
- Increases incidence of grade 3-4 toxicity by 74%
- Increases drug expenditure by €30.000 per patient ➔ €50 million per year (NL)

Self-funded study

- 1050 patients
- 50% randomized to 2nd line treatment
- 525 x 16.5 x €3200 = €26 million saved within the trial
- Trial costs €7.5 million

€18.5 million net saving

Conclusion

- Companies have no incentive to test dose optimization
- EMA does not evaluate if medicines are used efficiently
- Self-funded trials like SONIA will fill this gap in the post-approval setting
- Conditional reimbursement policies (e.g. de sluis) can facilitate these trials

Other examples

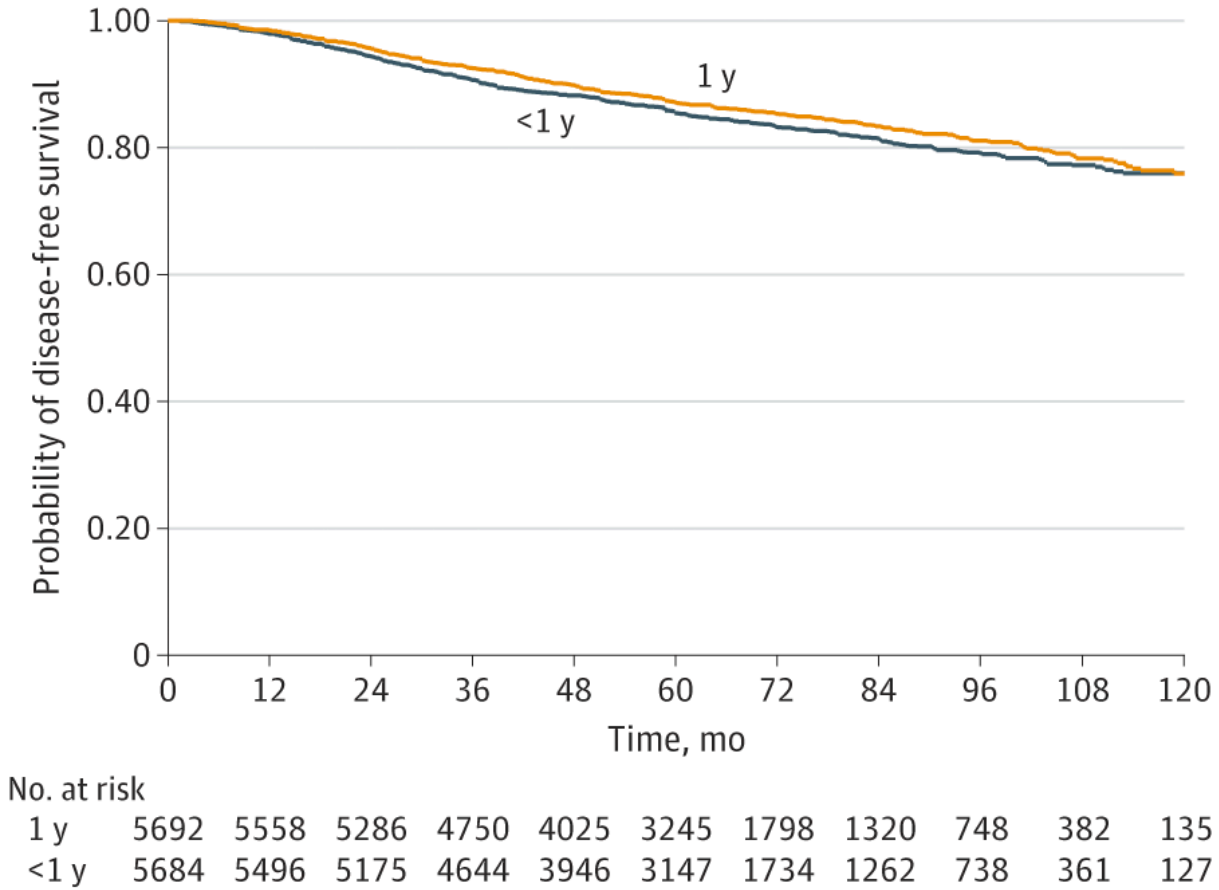
- Niraparib ovarian cancer
- Pembrolizumab breast cancer
- Abemaciclib / ribociclib breast cancer
- Osimertinib non-small cell lung cancer
- Lenvatinib / pembrolizumab endometrial cancer
- etc

Acknowledgements

- Patients and their families, data monitoring committee members, steering committee members, study coordinators, data managers, and all study staff
- Members of the Dutch Breast Cancer Patient Organization
- This study was funded by Dutch Health Insurers and the Netherlands Organization for Health Research and Development

To download a plain language summary

Adjuvant trastuzumab 12 vs 6 months



No. at risk

1 y	5692	5558	5286	4750	4025	3245	1798	1320	748	382	135
<1 y	5684	5496	5175	4644	3946	3147	1734	1262	738	361	127

Gulia et al. JAMA Network Open 2020

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Hybrid dosing of immune therapy

Alternative dosing strategies for immune checkpoint inhibitors to improve cost-effectiveness: a special focus on nivolumab and pembrolizumab

Ruben Malmberg, Michiel Zietse, Daphne W Dumoulin, Jeroen J M A Hendrikx, Joachim G J V Aerts, Astrid A M van der Veldt, Birgit C P Koch, Stefan Sleijfer, Roelof W F van Leeuwen

- In NL: 60,000,000 euro
- Global: 5,000,000,000 euro

nvmo

ADVIES | JULI 2021

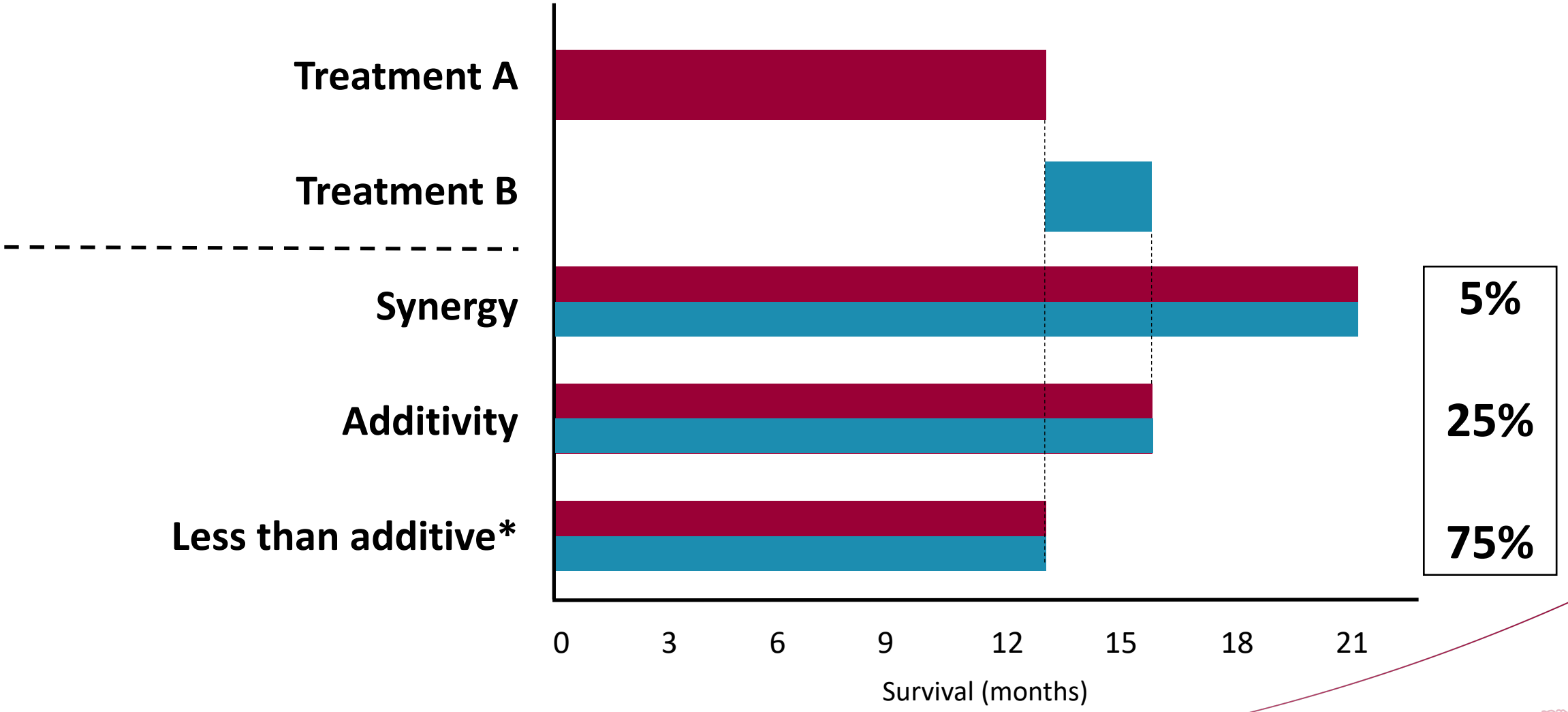
Doseringsadviezen voor nivolumab en pembrolizumab

Het NVMO-bestuur heeft recent enkele malen gesproken met vertegenwoordigers van ZN en VNZ en later met vertegenwoordigers van ziekenhuisapothekers (SIG Oncologie en NVZA) over het doseren van pembrolizumab en nivolumab. Als alle internist-oncologen deze middelen op een andere manier zouden doseren dan het gebruikelijke doseren per kg lichaamsgewicht, dan zou in Nederland jaarlijks tot € 40 miljoen kunnen worden bespaard. Het NVMO-bestuur vindt dat "maatschappelijk verantwoord handelen" tot de competenties van alle internist-oncologen behoort.

Inmiddels is een aantal ziekenhuizen reeds gestart met andere doseringsschema's; hierover is vakliteratuur beschikbaar. Ook is hierover bericht in *Medische Oncologie* en in landelijke dagbladen. In het besloten deel van de NVMO-website kunt u vakliteratuur hierover raadplegen.

Na genoemde besprekingen zijn betrokkenen gekomen tot de volgende adviezen voor het doseren van nivolumab en pembrolizumab.

Malmberg et al. Lancet Oncol 2022



Hwangbo et al. Nat Cancer October 2023