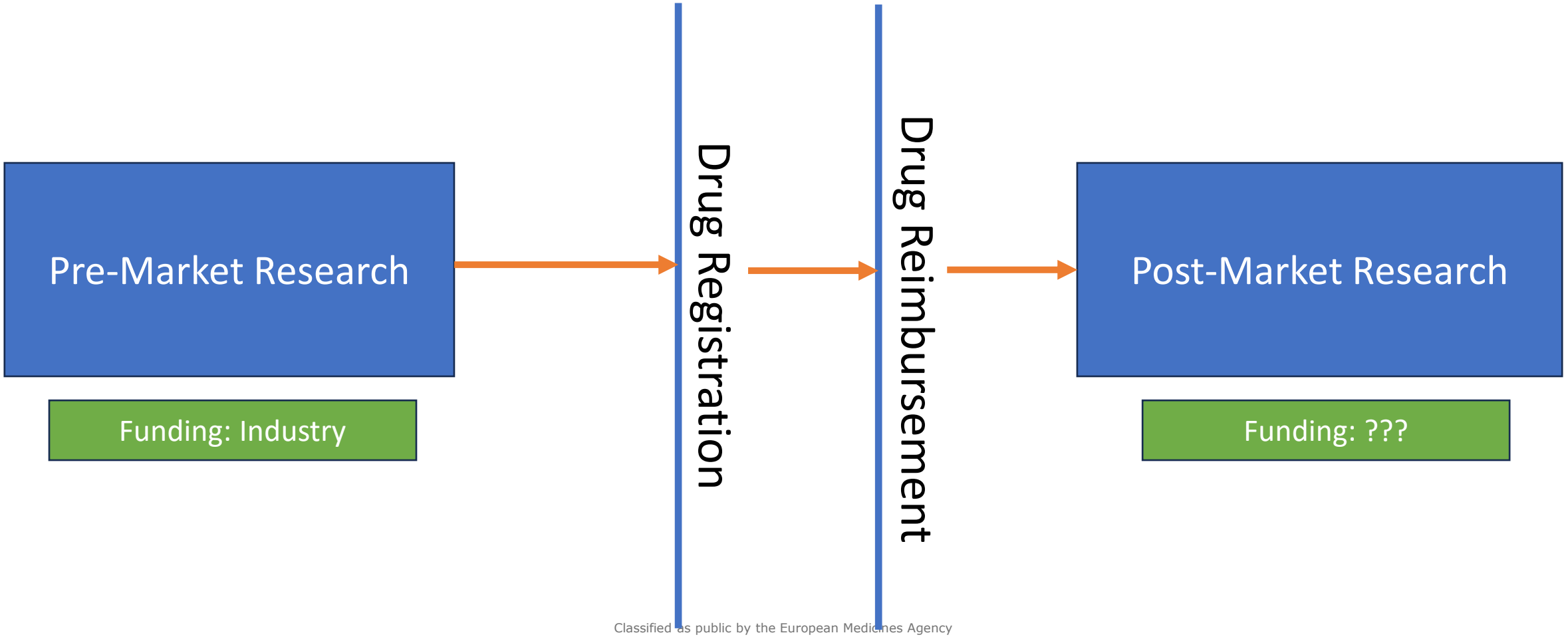
The Global Challenges of Post-Market Optimization Research

Daniel Goldstein MD

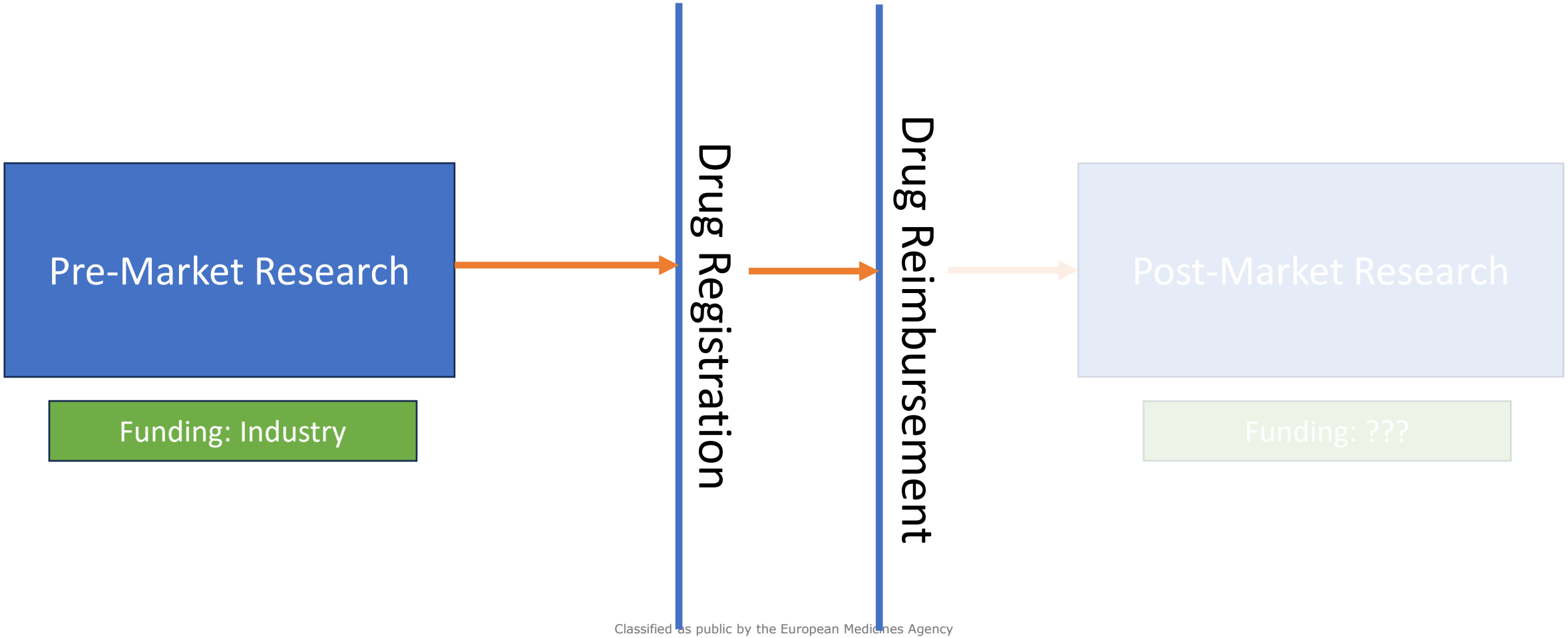
Professor of Medical Oncology and Internal Medicine, Davidoff Center, Rabin Medical Center, Tel Aviv University

Medical Director of Drug and Technology Policies, Community Division, Clalit Health Services

Drug Development & Approval Process



Drug Development & Approval Process

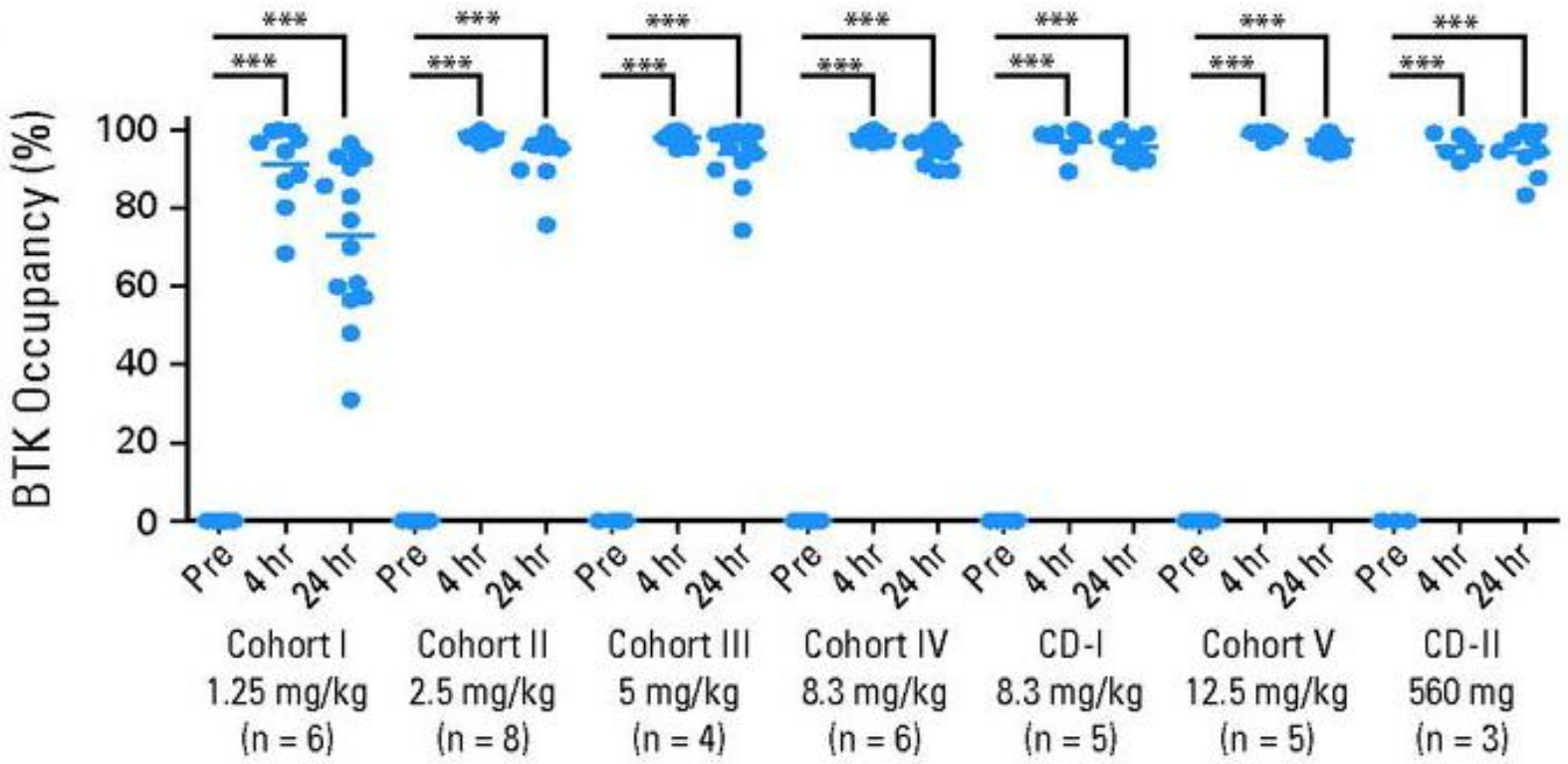


Why we need post-marketing research

- We often don’t know the optimal way to give these drugs
  - Dose
  - Duration
  - Sequence

These knowledge gaps cause physical and financial toxicity

Ibrutinib - BTK occupancy

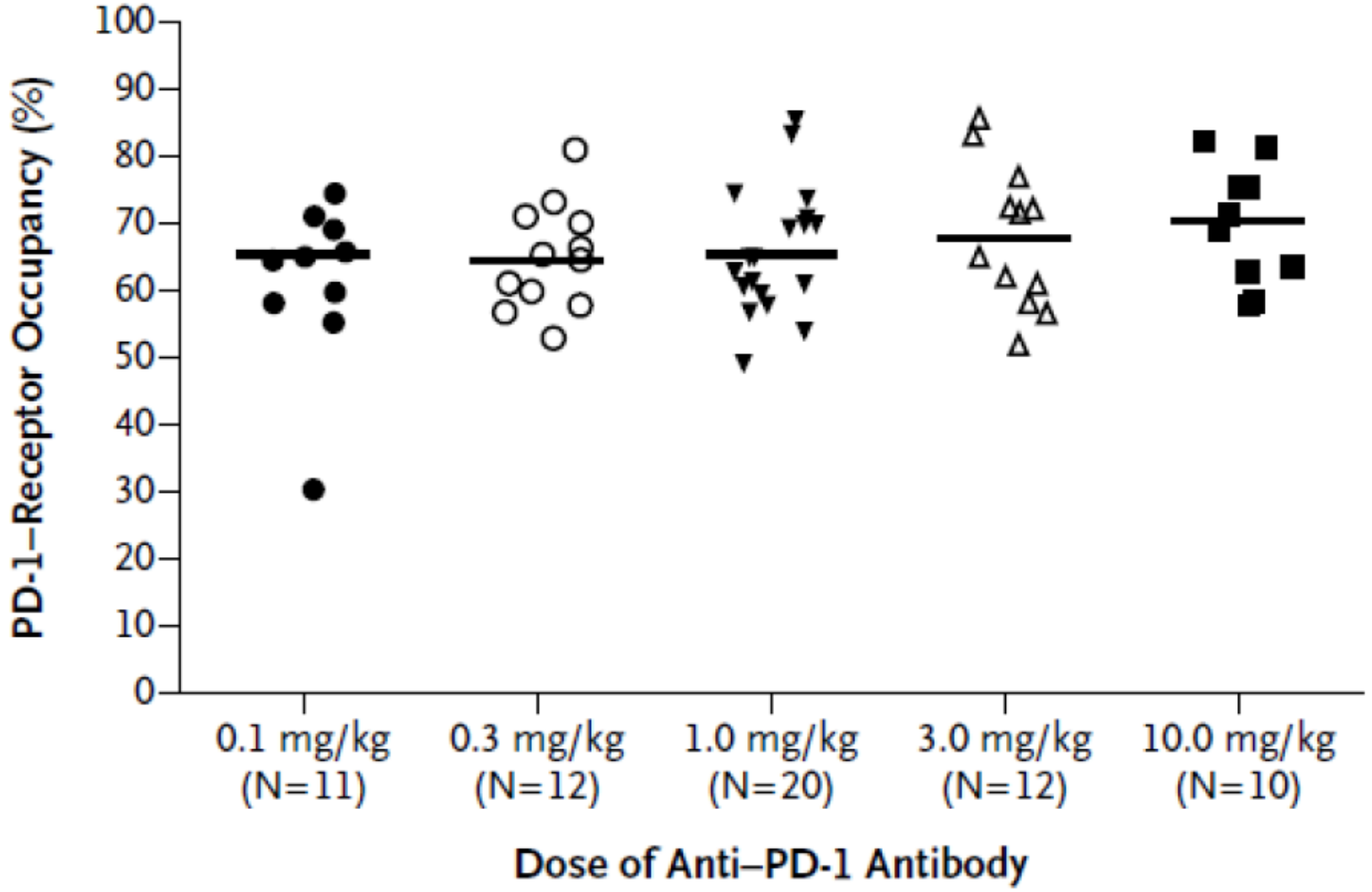


FDA approved dose = 420 mg/day

A Phase 3 optimization study of Ibrutinib?

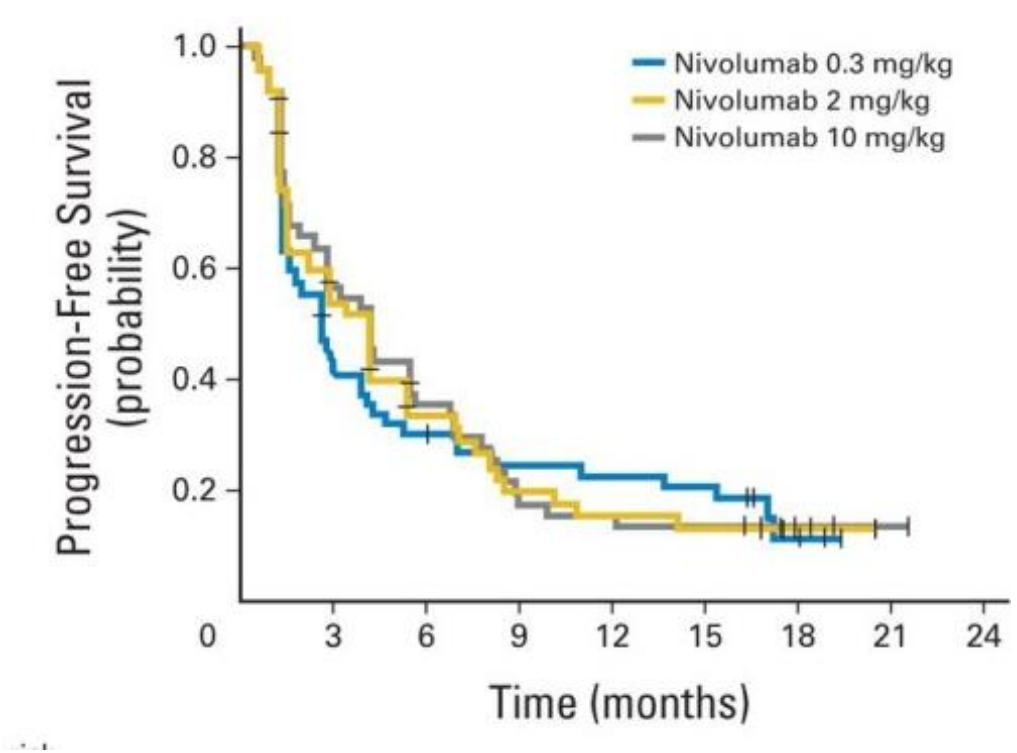
Advani et al., JCO 2013

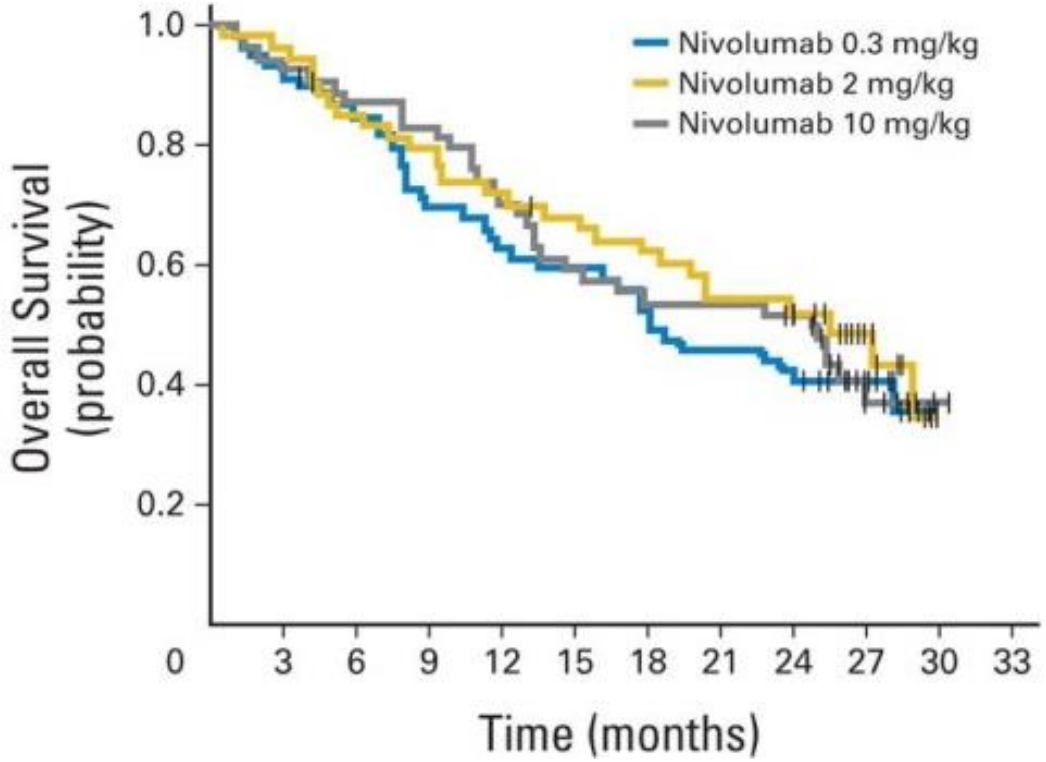
Nivolumab: PD-1 Receptor Occupancy



Topalian, NEJM, 2012

Nivolumab for metastatic renal cell carcinoma: randomized phase II trial

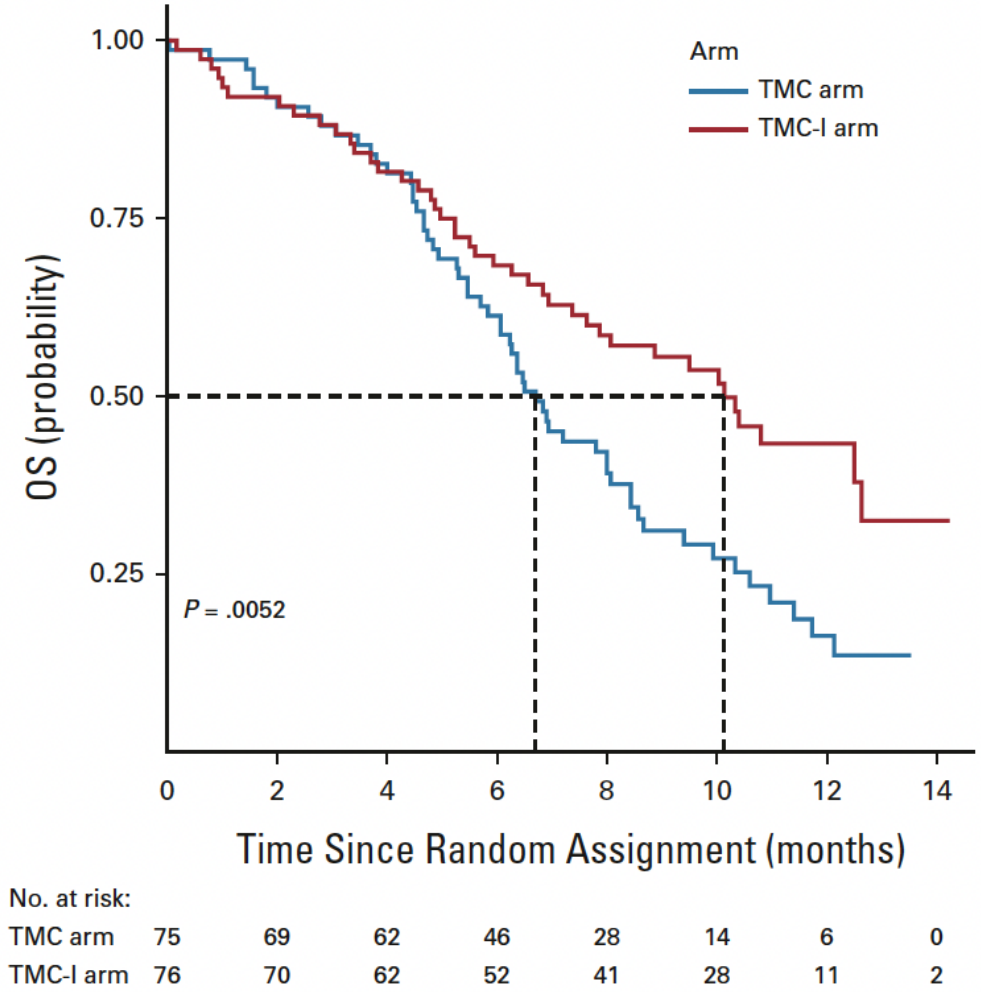




Flat dose-response over range of 0.3-10 mg/kg q3w

Motzer, JCO, 2015

Ultra-Low dose nivolumab in Head & Neck Cancer



More studies of ultra low dose immunotherapy?

Patil et al, JCO, 2022

Other dose reduction opportunities


THE CANCER LETTER

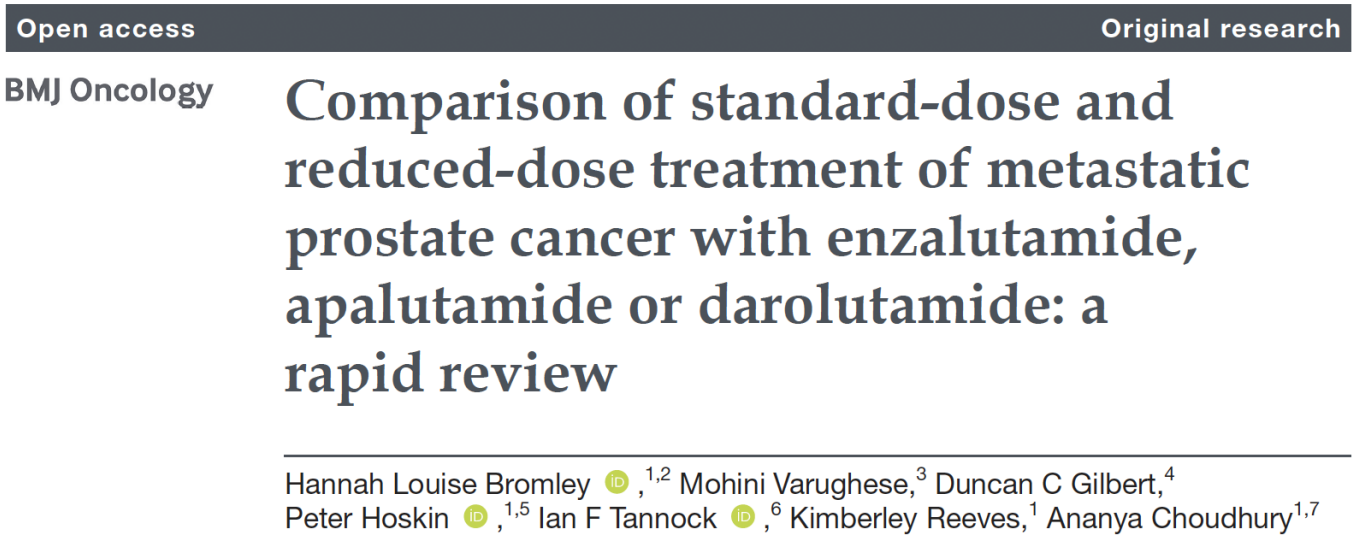
ABOUT CURRENT ISSUE EVENTS STORE

GUEST EDITORIAL

What's the right dose of sotorasib? Is it 240 mg qd or 4x that?

The Oct. 5 ODAC will be a nailbiter

September 08, 2023 | Vol.49 No.33


Open access Original research

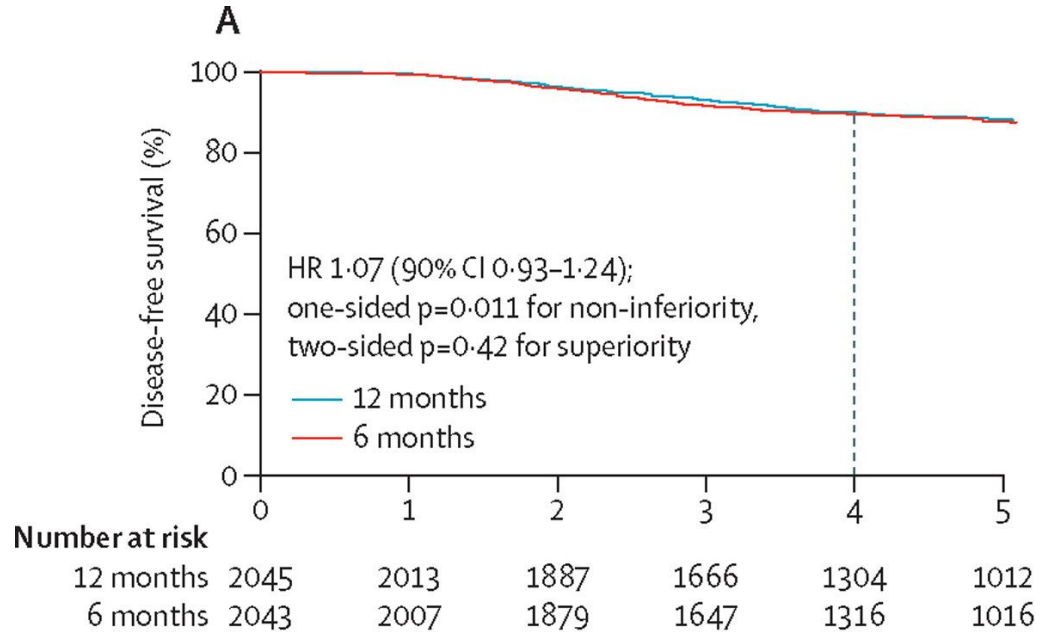
BMJ Oncology

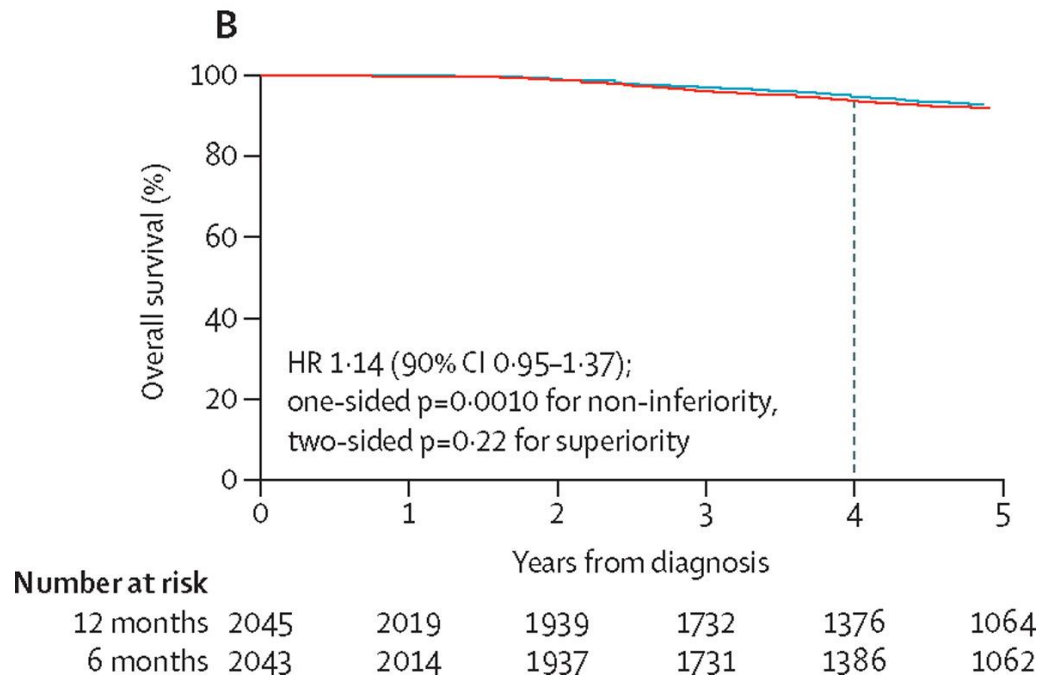
Comparison of standard-dose and reduced-dose treatment of metastatic prostate cancer with enzalutamide, apalutamide or darolutamide: a rapid review

Hannah Louise Bromley ,[1,2] Mohini Varughese,[3] Duncan C Gilbert,[4] Peter Hoskin ,[1,5] Ian F Tannock ,[6] Kimberley Reeves,[1] Ananya Choudhury[1,7]

Duration of adjuvant trastuzumab

- Persephone trial
- 12 months vs 6 months of trastuzumab





Earl et al., Lancet, 2019

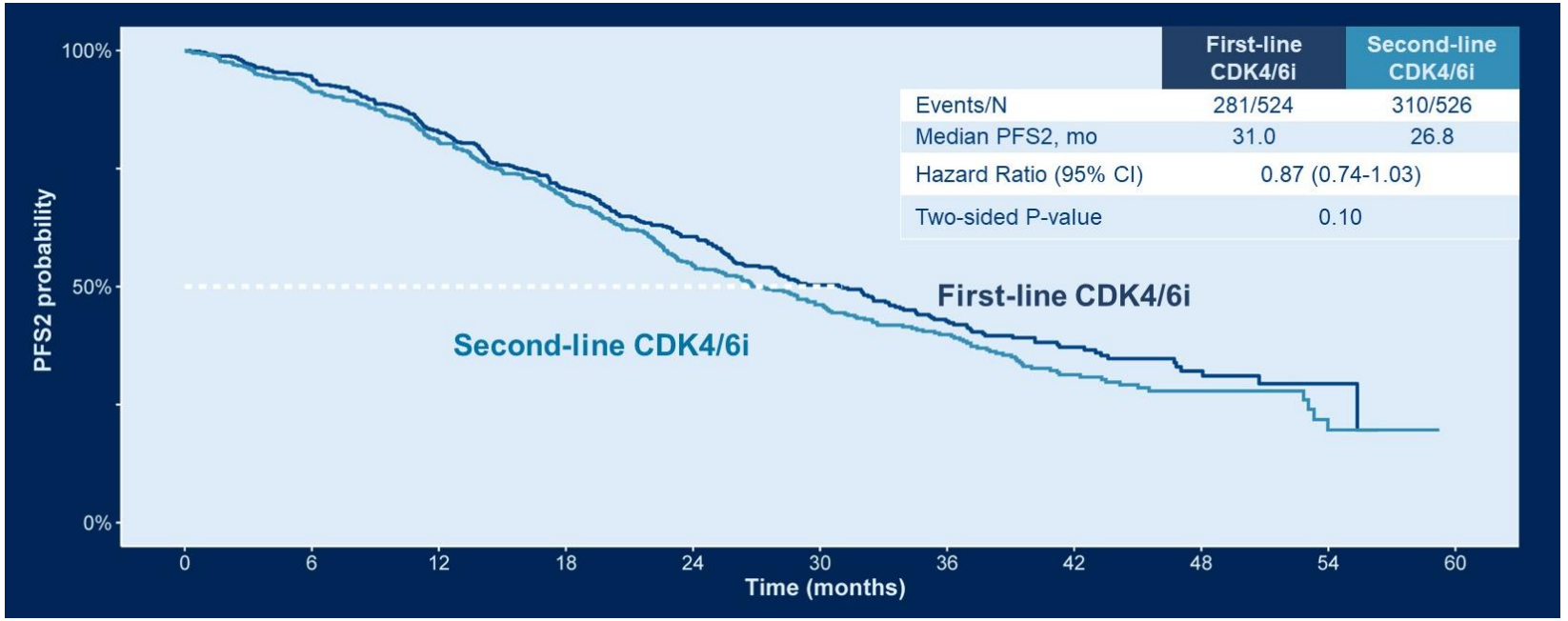
Reduced Duration Pembrolizumab trials

Trial	Indication	Design	Planned *n*	Country	Registration number
DANTE	Melanoma	Randomized between stop at 1 year vs continue to 2 years in responding patients	1,208	UK	ISRCTN15837212
STOP-GAP	Melanoma	Randomized between stop at response (restart at progression) vs continuous treatment to 2 years	614	Canada	NCT02821013
SAFE STOP	Melanoma	Stop on complete response, single-arm cohort, PFS at 2 years	200	The Netherlands	NL7293 (NTR7502)
PET-STOP	Melanoma	Stop on PET-CR, single-arm cohort, PFS	150	USA	NCT04462406
SAVE	NSCLC	ICI after chemotherapy randomized to stop at 1 year vs continuation	216	Japan	JCOG1701
STOP	Renal cell carcinoma	ICI responding at 1 year randomized to stop at 1 year vs continuation	216	Japan	JCOG1905
DIAL	NSCLC	Randomized between 6 months and 2 years of pembrolizumab after chemotherapy	114	France	NCT05255302
OPTIMICE-pCR	TNBC	Observation vs adjuvant ICI after chemo-immunotherapy combination	1,295	USA	TBC

Is recruitment optimal?

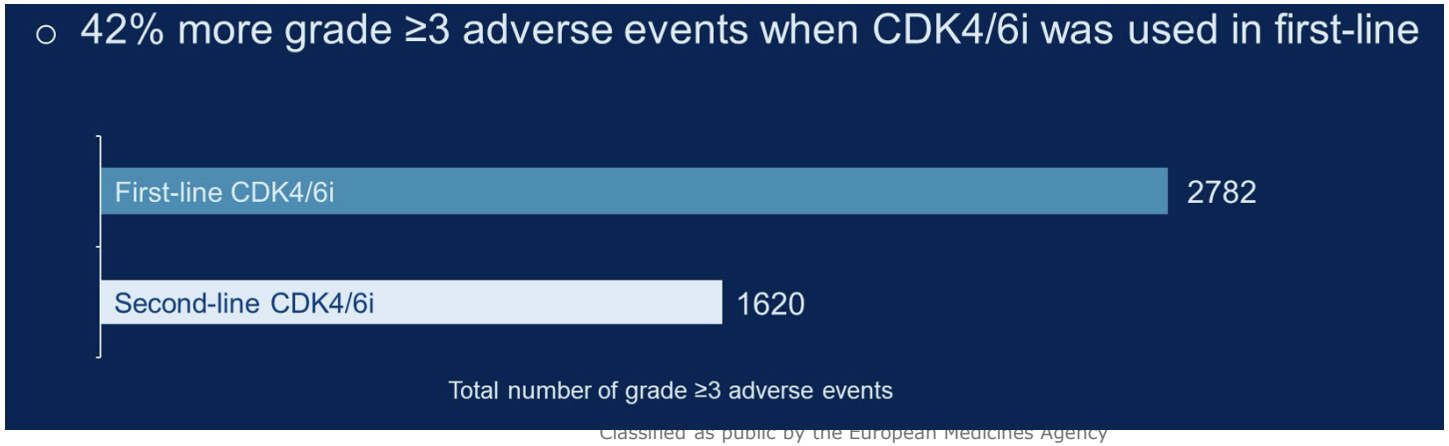
Hirsch et al., Nature Medicine, 2022

CDK4/6 inhibitors in 1st or 2nd line met breast cancer



	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	

- 42% more grade ≥3 adverse events when CDK4/6i was used in first-line



Sonke et al, ASCO 2023

More Sequence studies?

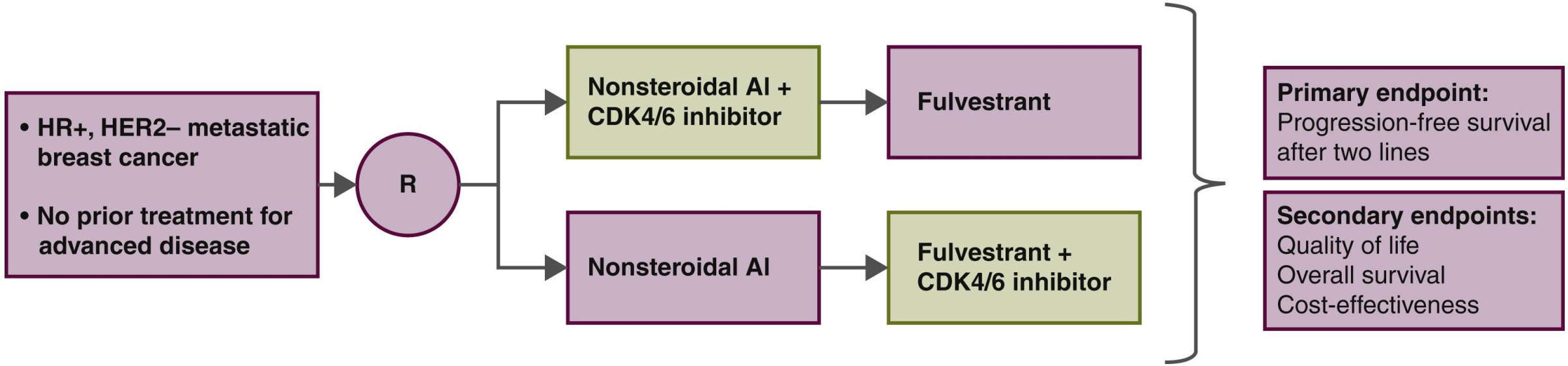
- Daratumumab: 1st line vs 2nd line in myeloma
- Kidney cancer: TKI/IO combo vs sequential

Why is Running Optimization Studies So Hard?

- Minimal / No Funding
- Not Sexy
- Drug already funded

The Solution: Payer funded research linked to regulatory and reimbursement decisions

A revolving research fund to study efficient use of expensive drugs: big wheels keep on turning

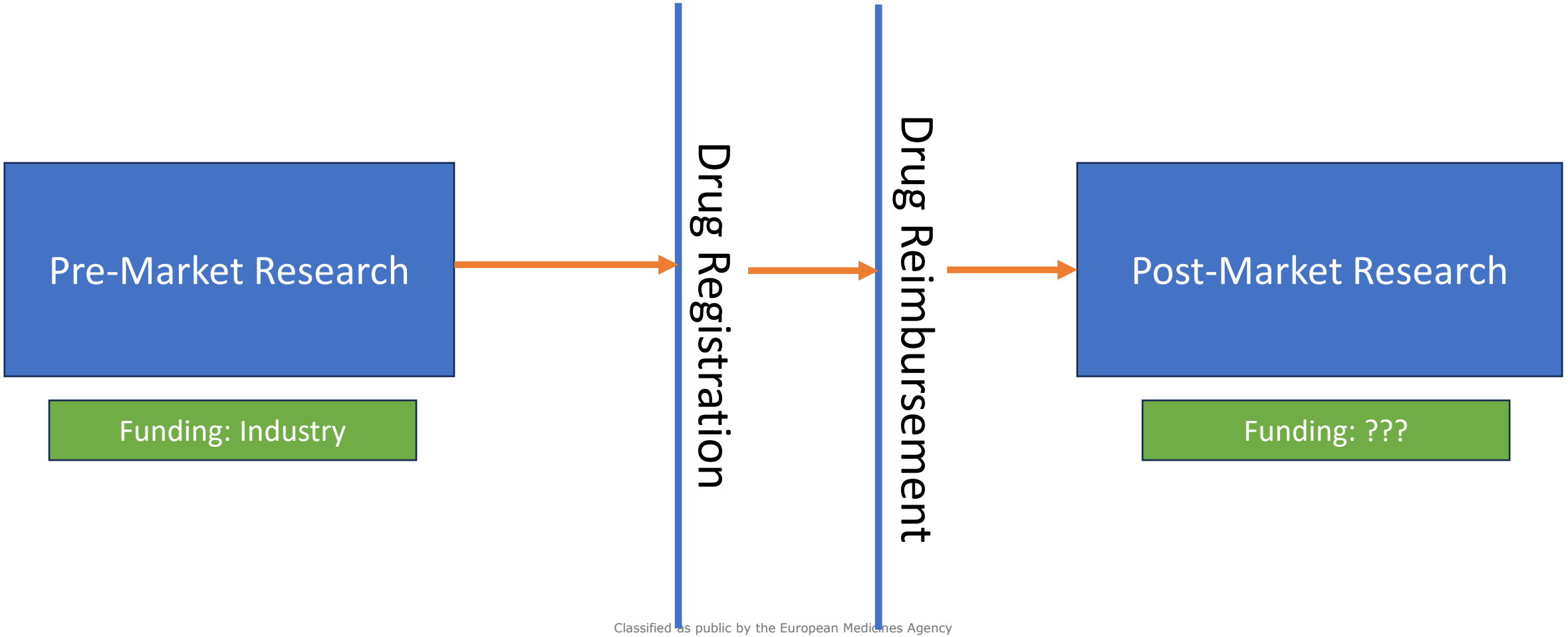


Van Ommen Nijjjhof et al, Annals of Oncology 2021

OPTIMAL CANCER CARE ALLIANCE

Optimal Dosage. Best Outcome.

Drug Development & Approval Process



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