Pharmacological interventions to improve the efficacy – toxicity balance of anticancer drugs

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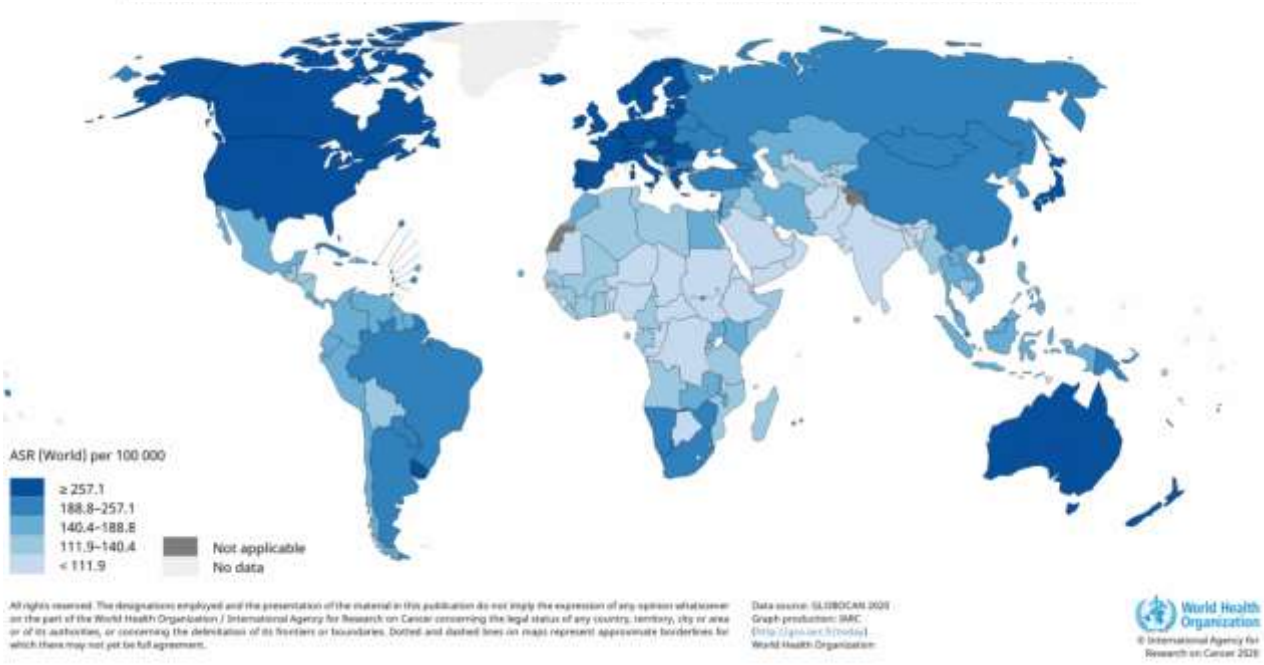
Conflict of Interest Disclosure

(Potential) conflict of interests	See below
Possible relevant relations with companies for symposiums	Company names: Astellas, Ipsen, Janssen-Cilag
Type of sponsoring: • Sponsoring of Investigator Driven Studies • Educational Grants • Honorarium • Stock owner • Other Relationship	Sponsoring of Investigator Driven Studies: Astellas, Ipsen, Janssen-Cilag

*** All grants are invoiced by the Radboudumc**

Prevalence of cancer worldwide - 2020



> 200 drugs for the treatment of cancer available

Classic Chemotherapy

Immuno-therapy

Targeted oral therapy

Targeted MoAbs

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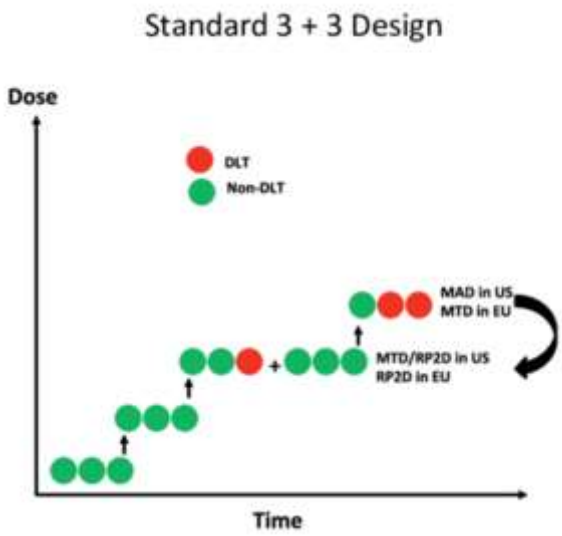
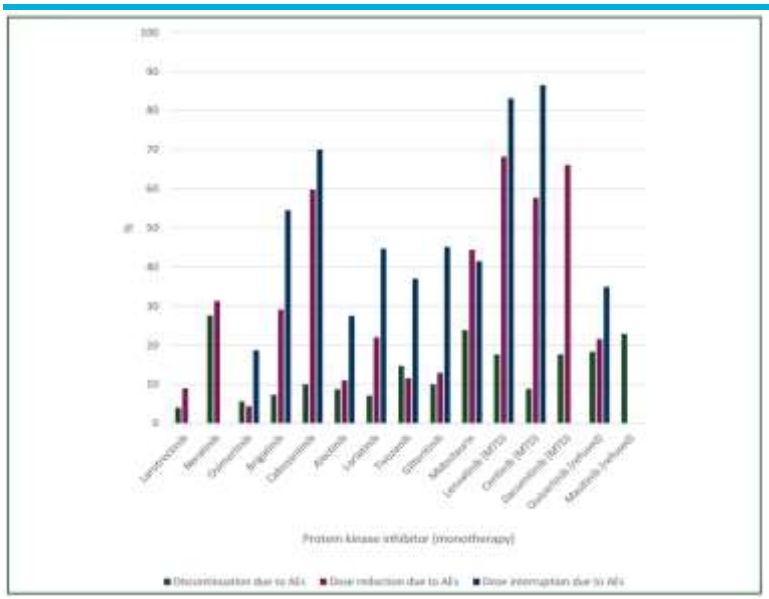
Dose selection is based on a very small group of patients



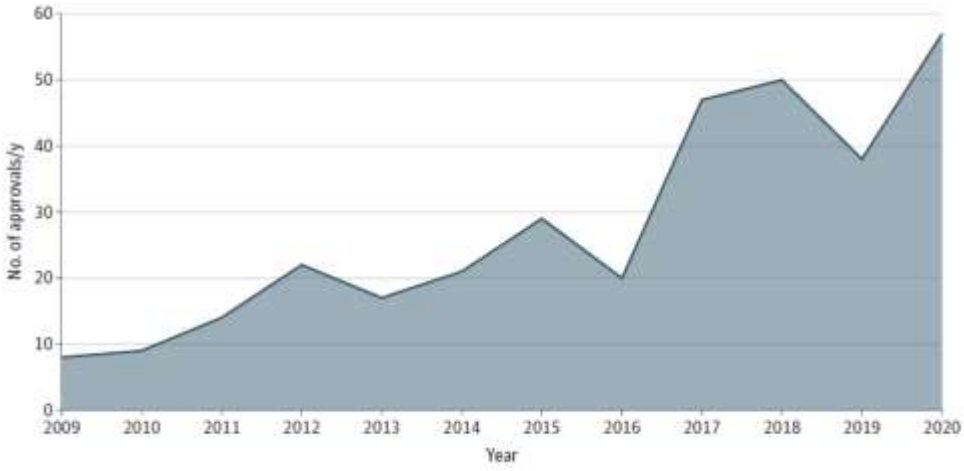
Cancer control Hansen et al. (2014) Vol 21, No. 3

And even toxicity cannot be prevented by this approach



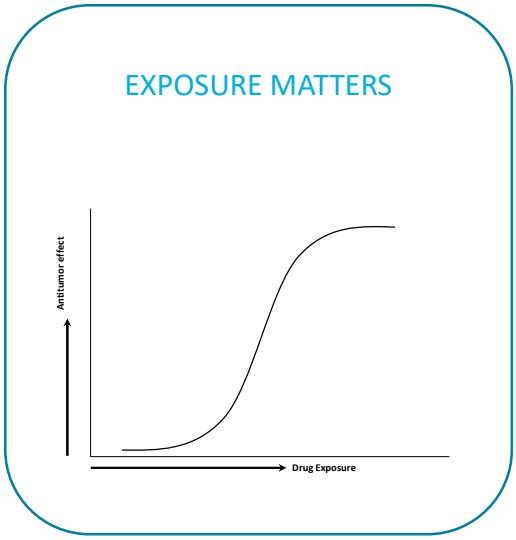
Maliepaard et al. ESMO Open 2021 Dec:6(6)

Registration anticancerdrugs FDA 2009-2020

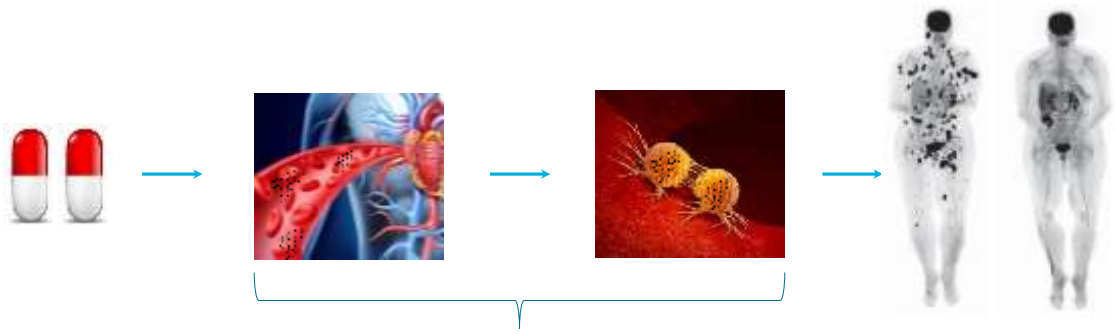


Oliver et al. JAMA Netw Open 2021; 4(12):e2138793

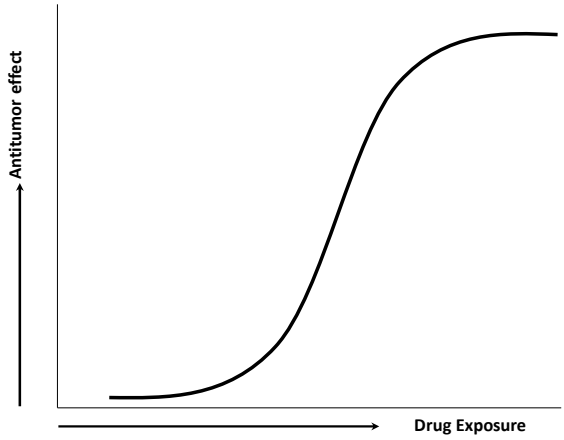
Much treatment benefit can be achieved by optimizing the dose



Basic principles of pharmacology

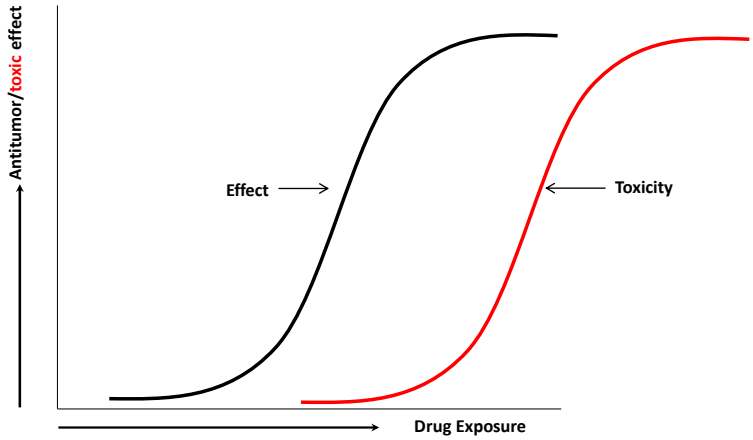


Pharmacological principles - graphically depicted

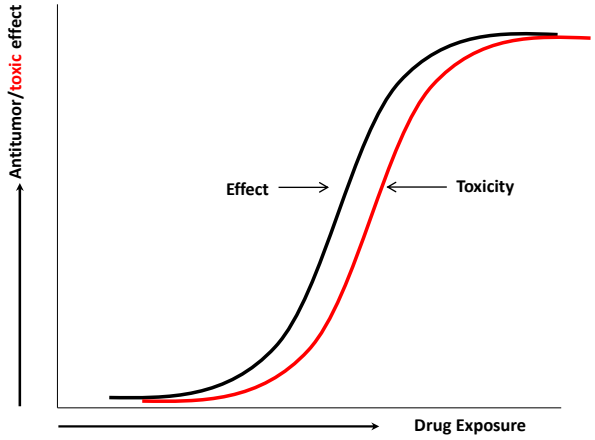


Dose – Effect relation
Or better:
Exposure – Effect relation

Why don't we simply increase the dose

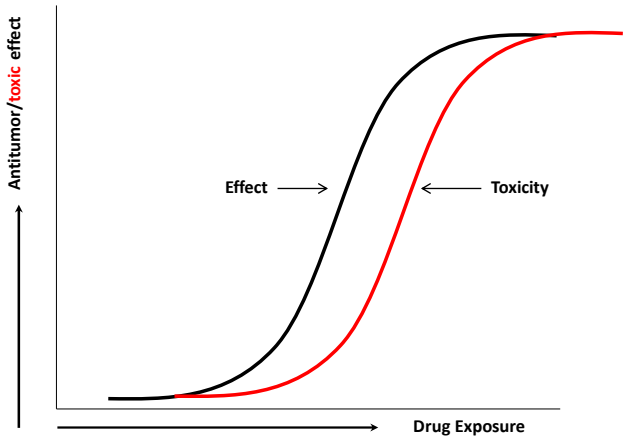


Due to a narrow "therapeutic window"

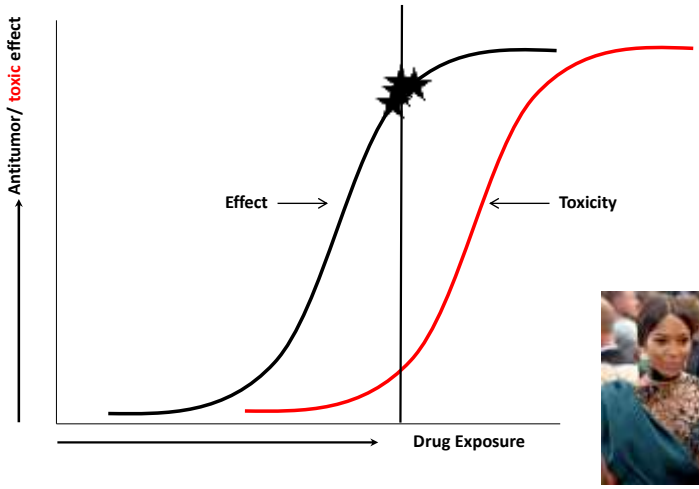


And every patient is on a different spot on the curve

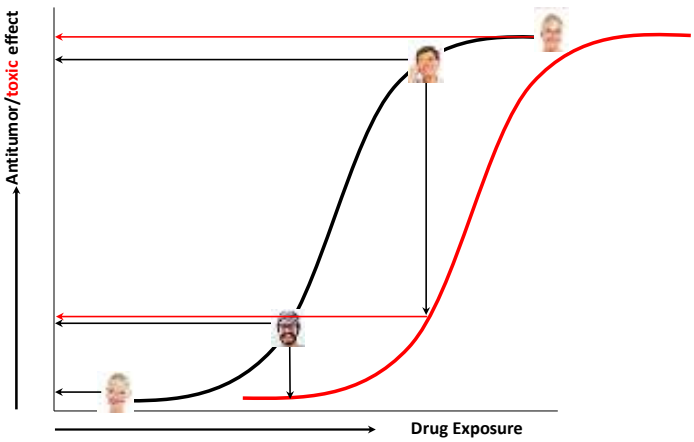
Large interpatient variability



In the ideal world "one dose fits all"…..



However in reality everybody is unique



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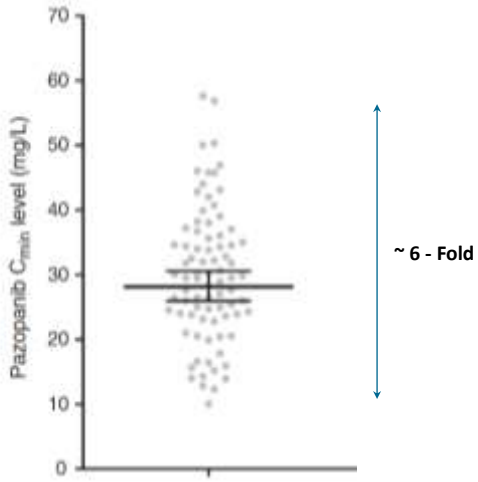
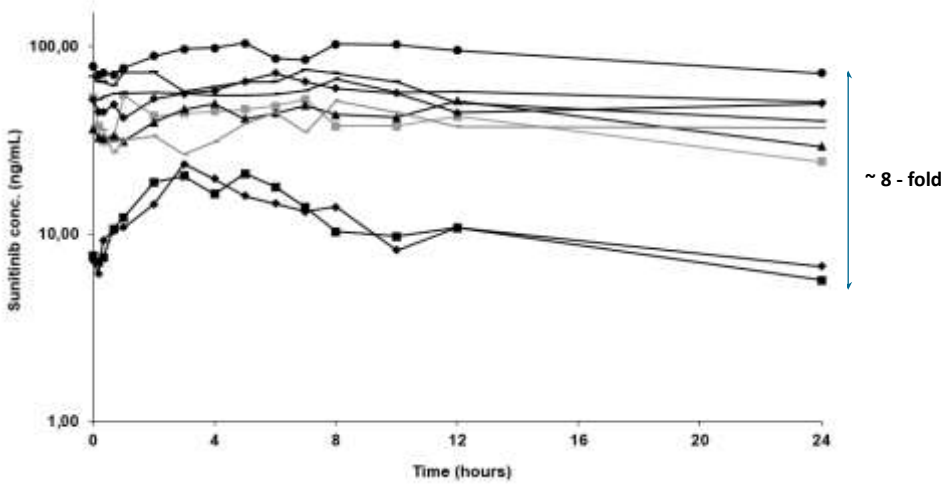
Examples from the clinic: *pazopanib*



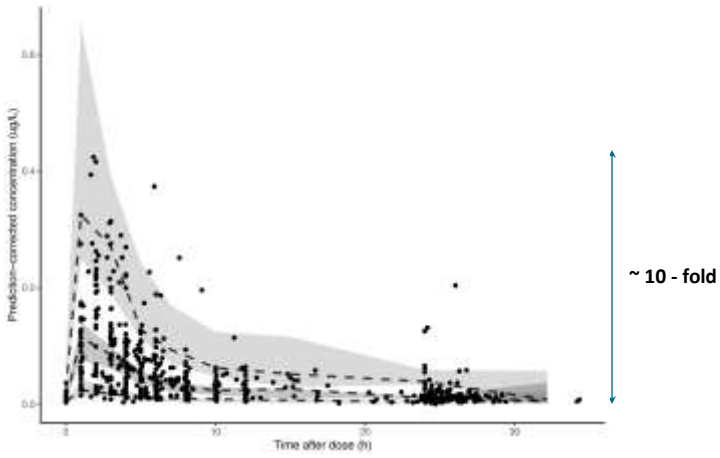
Krens et al. Int J Cancer 2021 Jun 1; 148(11): 2799-2806

Examples from the clinic: *sunitinib*



Adjusted - De Wit et al Cancer Chemother Pharmacol 2014 Jan;73(1):87-96

Examples from the clinic: *abiraterone*



Adjusted - Boerrigter et al. Br J Clin Pharmacol 2022 Mar;88(3): 1170-1178

Which affects treatment outcomes

Anticancer Effect

Toxicity profile

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Causes of this large variation in pharmacokinetics

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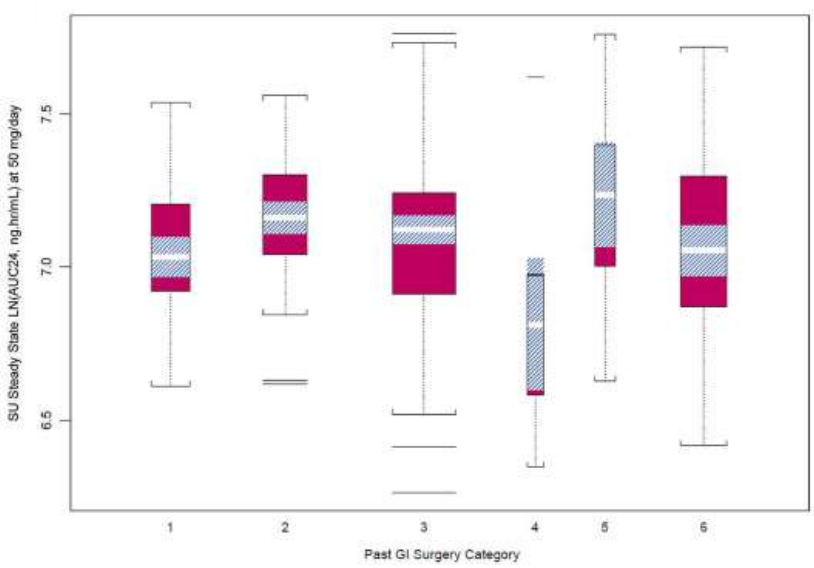
Causes for the large variation in pharmacokinetics

Effect of GI resection on drug exposure

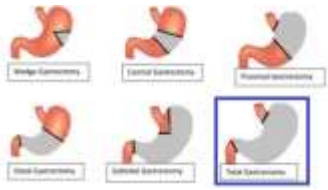
Causes for the large variation in pharmacokinetics

Djoeke de Wit, PharmD, PhD



De Wit et al. BMC Cancer 2014 Aug 8; 14:575

Causes for the large variation in pharmacokinetics



Effect of GI resection on drug exposure

Effect of co-medication on anticancer drug exposure

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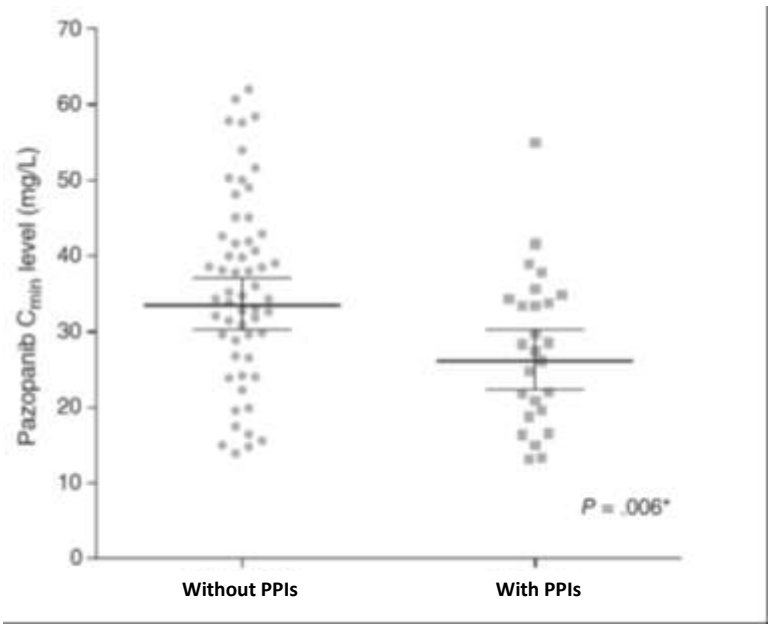
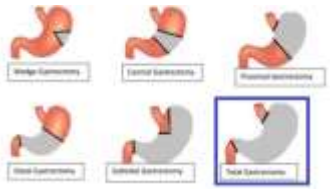
Causes for the large variation in pharmacokinetics

Stefanie Krens



Krens et al. Int J Cancer 2021 Jun 1; 148(11): 2799-2806

Summary:



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Pharmacological interventions to optimize drug exposure

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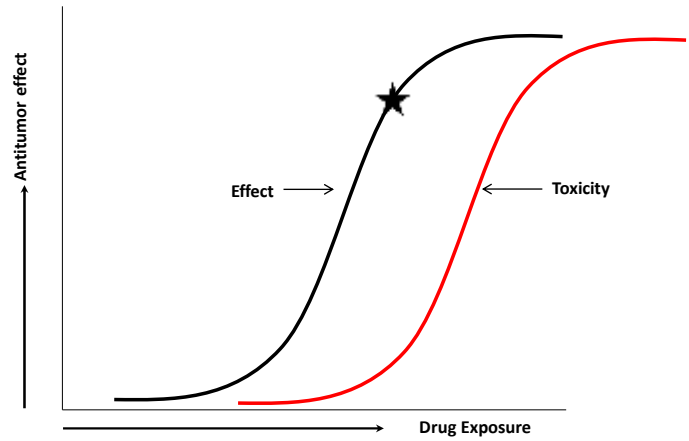
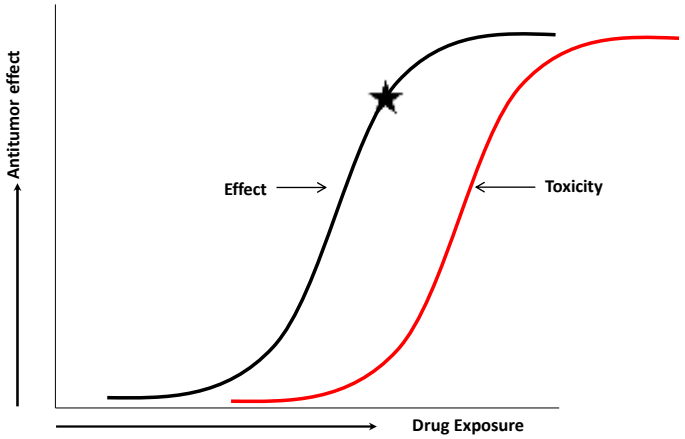
Pharmacological strategies to optimize anticancer drug exposure

Intake with food to increase drug uptake and reduce GI toxicity

A food intervention was used in the DIET & SNACK study



Anticancer drug intake with a continental breakfast



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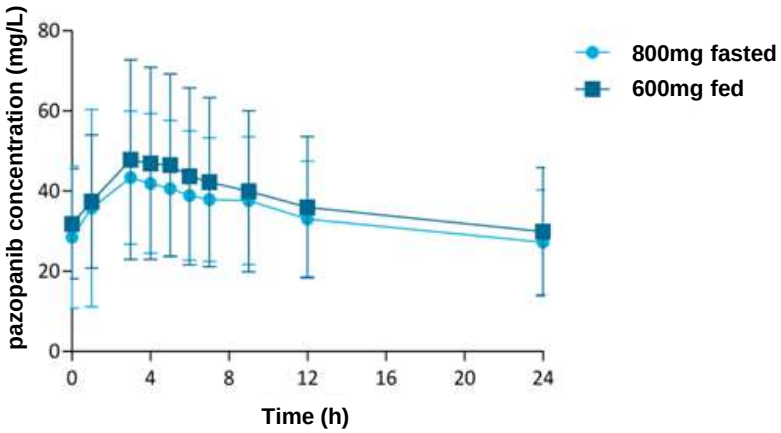
Results DIET study

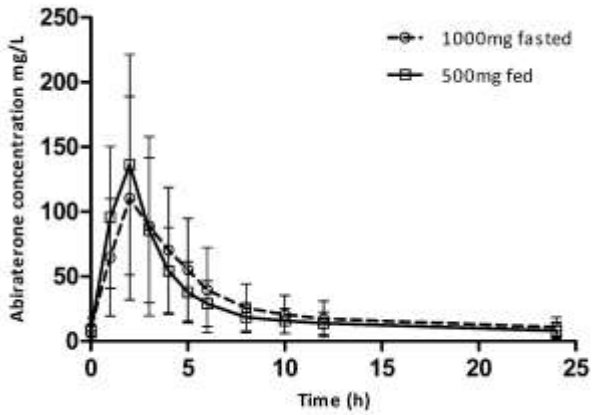
Floor Lubberman, PharmD, PhD



Lubberman et al. Clin Pharmacol Ther (2019) Nov; 106(5):1076-1082

Results SNACK study


Mette Benoist PharmD, PhD *Floor Lubberman PharmD, PhD*



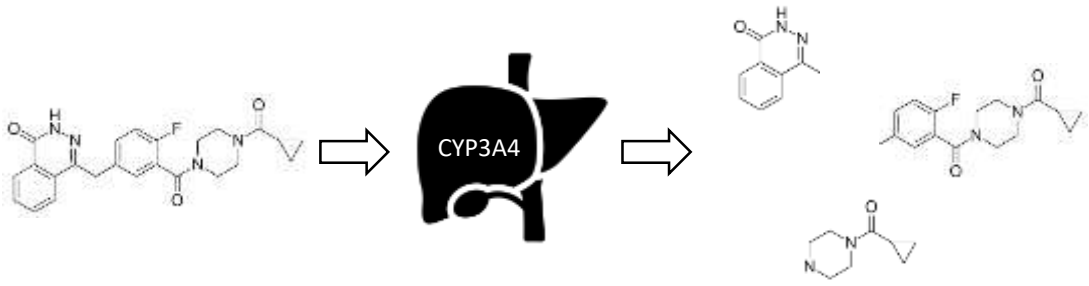
Lubberman et al. CCP 2019 Dec; 84(6):1179-1185

Pharmacological strategies to optimize anticancer drug exposure

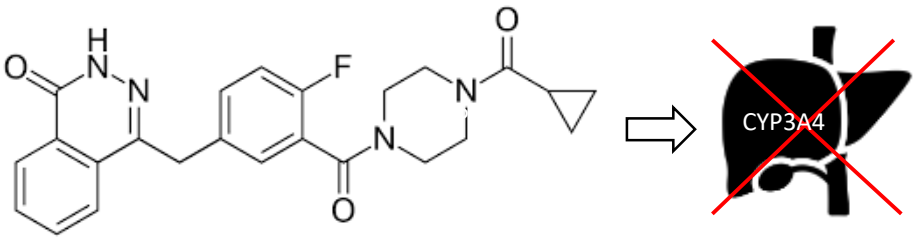
Intake with food to increase drug uptake and reduce GI (and financial) toxicity

Interations on purpose to reduce interpatient PK variability and reduce (financial) toxicity

Principle of boosting – "intentional" drug interaction

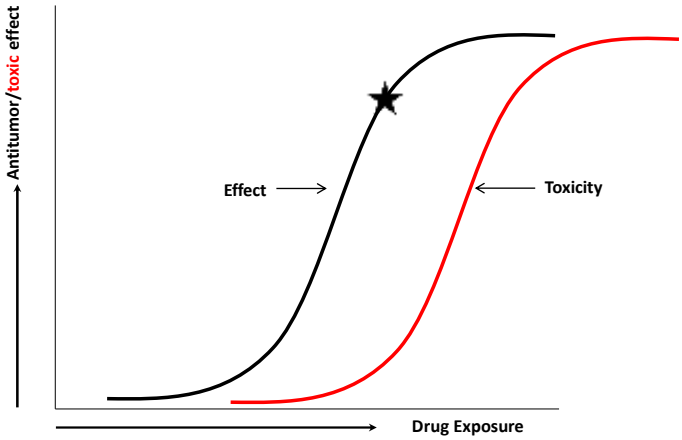


Principle of boosting – "intentional" drug interaction



PROACTIVE study - uses the effect of boosting (recruiting)


Joanneke Overbeek



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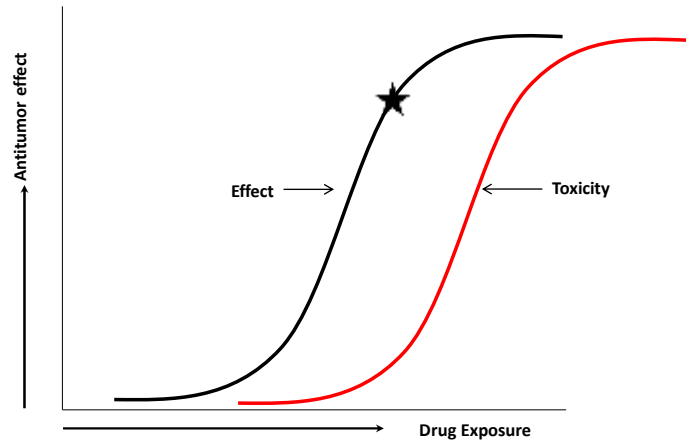
PROACTIVE study - uses the effect of boosting (recruiting)


Joanneke Overbeek

olaparib

booster - cobicistat



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Aim & hypothesis

Aim: Determine equivalence of the boosted olaparib (100mg BID) vs. monotherapy (300mg BID)

Effect of Itraconazole and Rifampin on the Pharmacokinetics of Olaparib in Patients With Advanced Solid Tumors: Results of Two Phase I Open-Label Studies

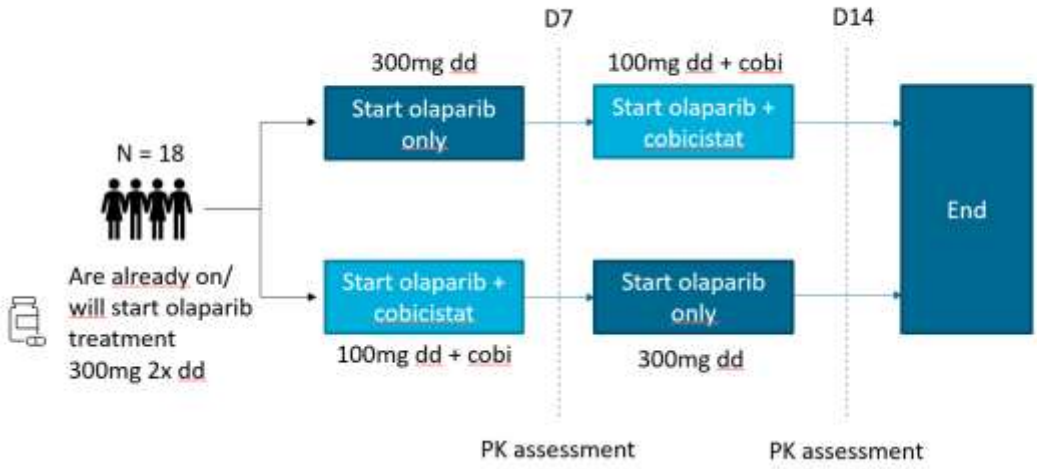
Luc Dirix, MD, PhD[1]; Helen Swaisland[2,*]; Henk M.W. Verheul, MD, PhD[3];

GMR – for stating equivalence

Parameter	Monotherapy	Boosted	Geometric Mean Ratio
AUC	*Geometric mean 1*	*Geometric mean 2*	*Ratio GM2:GM1*

between 0.57 - 1.25 = equivalent
90% CI

Study design



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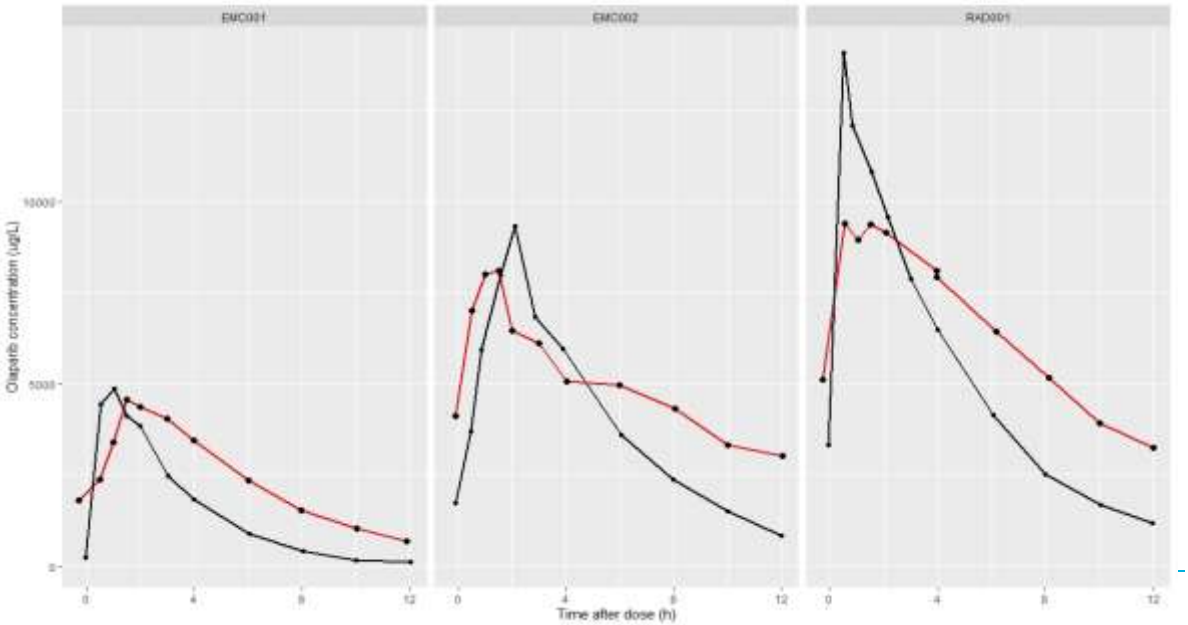
Red = monotherapy (300mg olaparib)
Black = boosted (100mg olaparib + cobicistat)



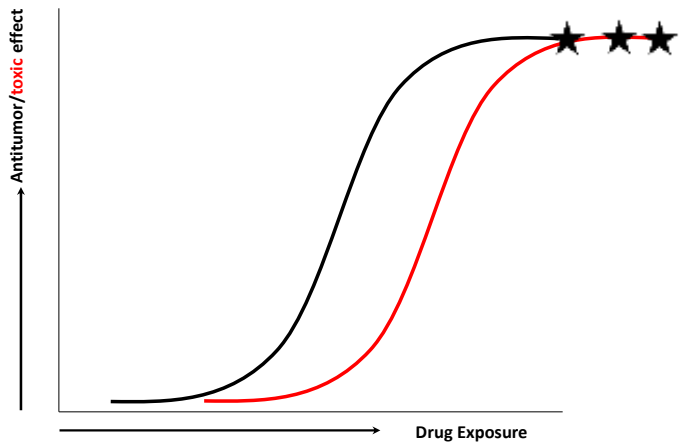
Pharmacological strategies to optimize anticancer drug exposure

Intake with food to increase drug uptake and reduce GI (and financial) toxicity

Interations on purpose to reduce interpatient PK variability and reduce (financial) toxicity

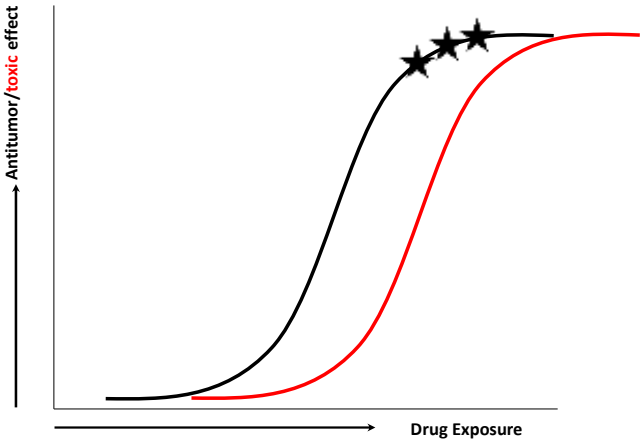
Reduced dose to prevent toxicity while preserving efficacy

If NO exposure-effect relation is observed



REDOSE study: less enzalutamide in frail patients (recruiting)

Emmy Boerrigter



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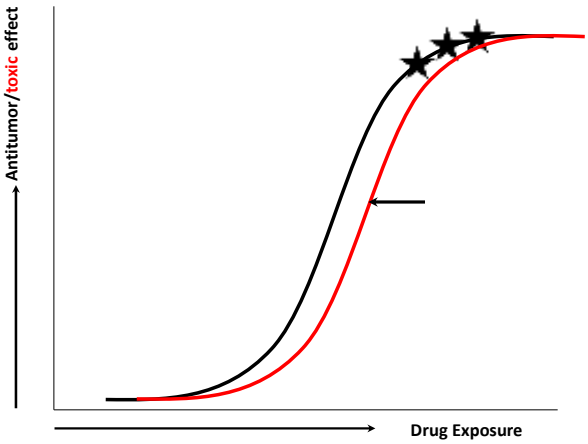

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Preliminary results

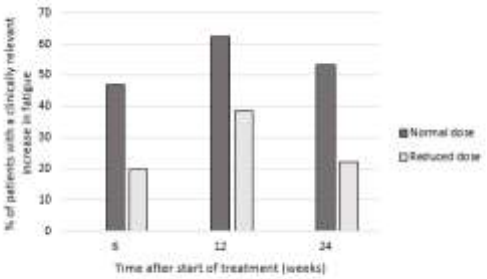

Figure 3: Percentage of patients with a clinically relevant increase in fatigue compared with baseline FACIT-F score.

Functional Assessment of Chronic Illness Therapy- Fatigue

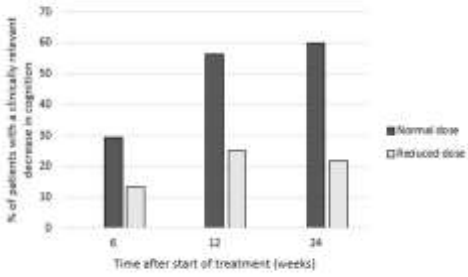

Figure 5: Percentage of patients with a clinically relevant decrease in cognition compared with baseline FACT-Cog score.

Functional Assessment of Cancer Therapy – Cognitive Function

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Preliminary results

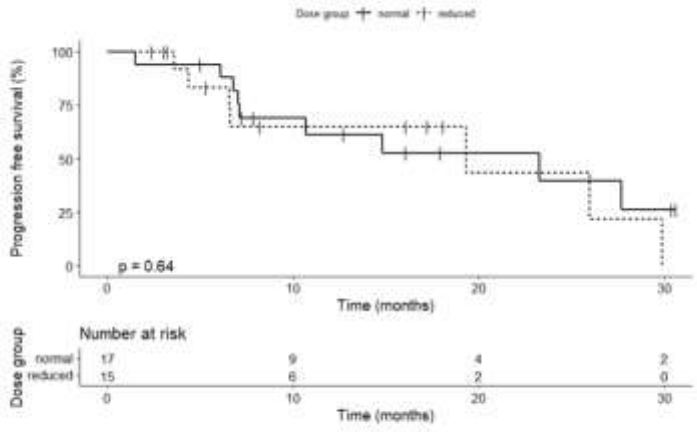

Figure 51: Progression free survival according to dose group of enzalutamide: normal dose vs. reduced dose in patients with metastatic castration resistant prostate cancer.

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Summary

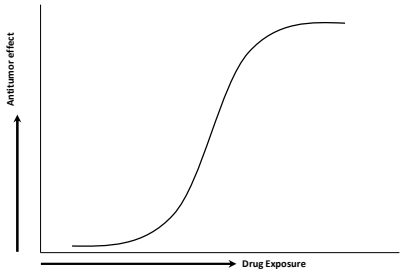
Food

Booster

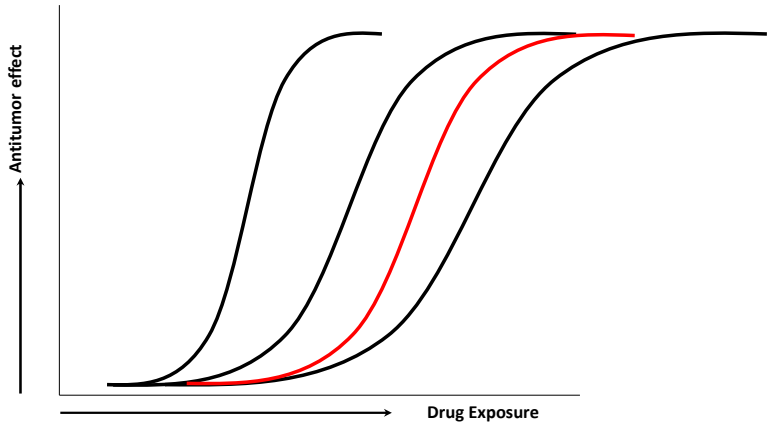
Reduced dose

Is the optimal dose the same for every patient

EXPOSURE MATTERS



Tumor(subtypes) might show differences in drug sensitivity



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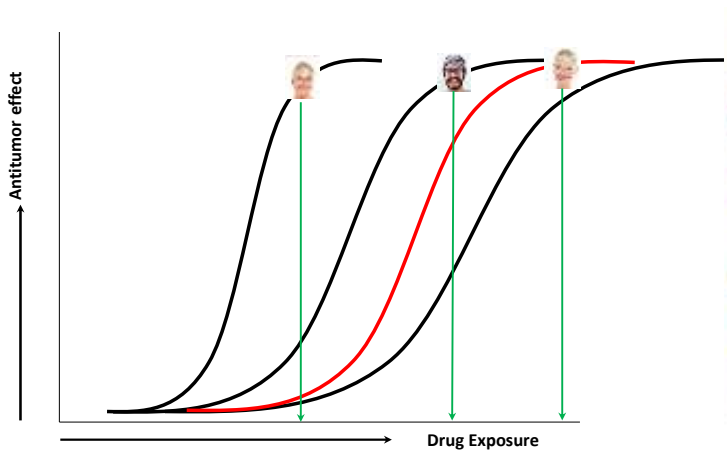
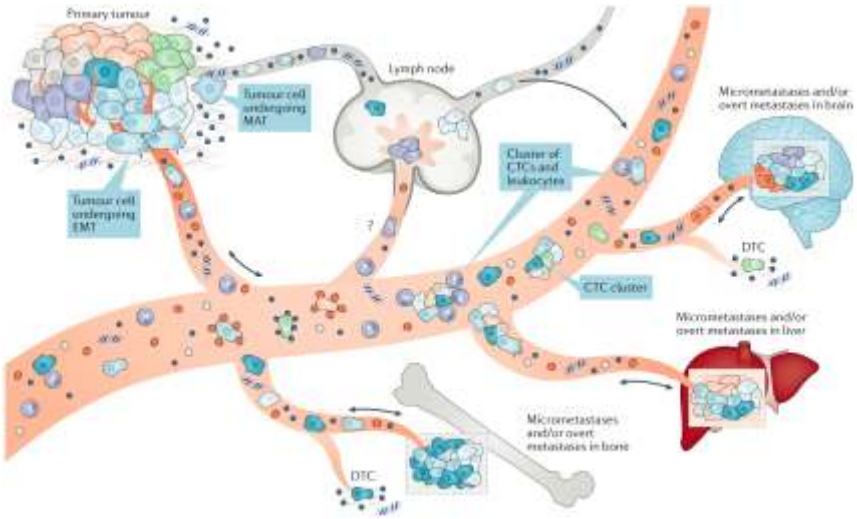


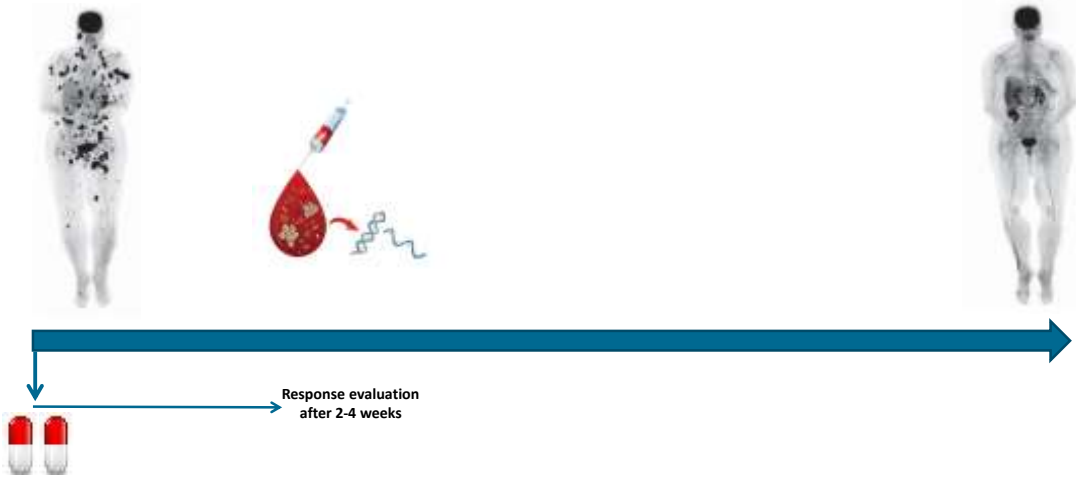
But how can we timely observe treatment benefit…….

By following tumor specific biomarkers…..



Keller et al Nat Rev Cancer 2019 Oct; 19(10):553-567

Might indicate treatment response shortly after treatment initiation



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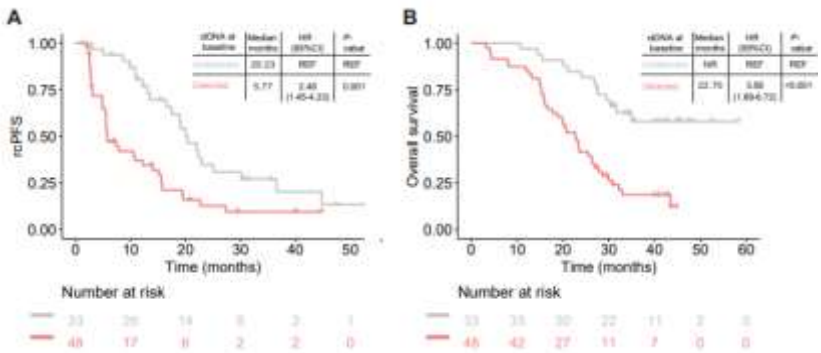
Results of the REFINE project

Emmy Boerrigter



Submitted

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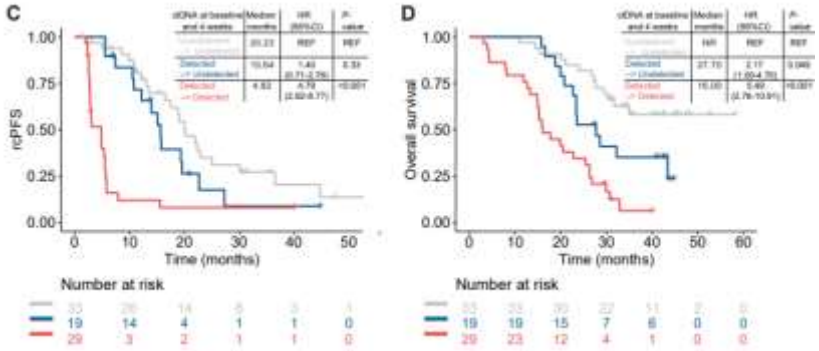

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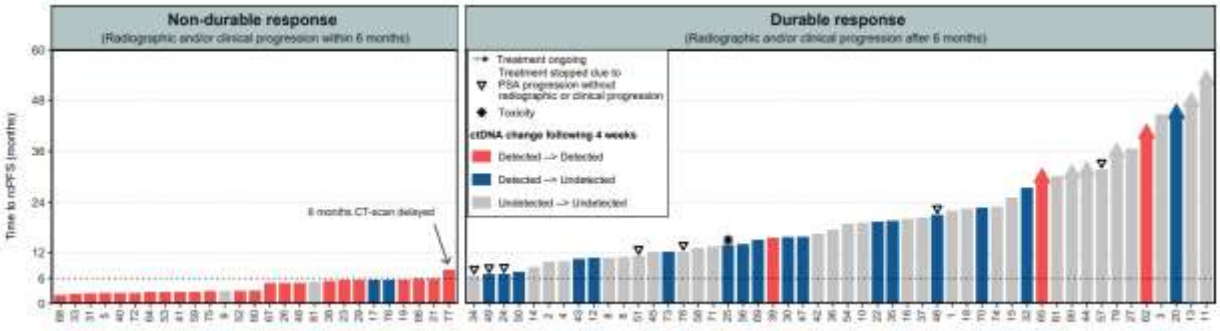

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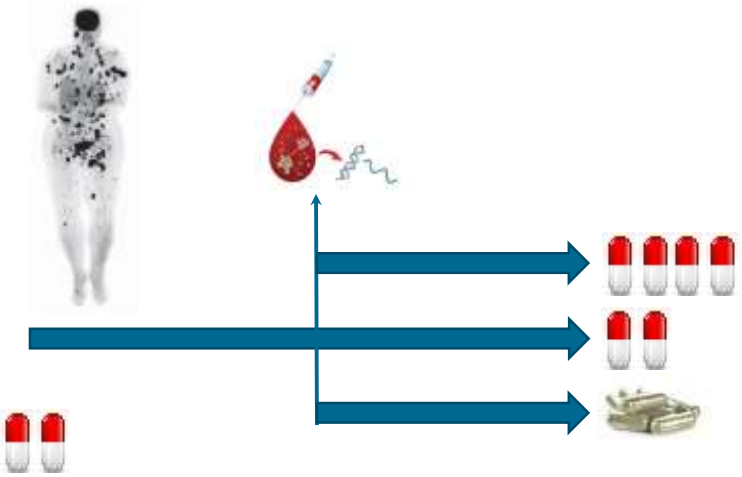
Results of the REFINE project

			Radiographic/clinical progression free survival					Overall survival				
				Univariate analysis		Multivariate analysis			Univariate analysis		Multivariate analysis	
Clinical marker	Subgroup	No. patients	Median (months)	HR (95% CI)	P-value	HR (95% CI)	P-value	Median (months)	HR (95% CI)	P-value	HR (95% CI)	P-value
	ND > ND	33	20.23	ref	ref	ref	ref	Not reached	ref	ref	ref	ref
ctDNA% change following 4 weeks	D > ND	19	15.64	1.4 (0.71-2.76)	0.325	1.16 (0.57-2.33)	0.681	27.7	2.17 (1-4.7)	0.049	1.82 (0.8-4.12)	0.15
	D > D	29	4.82	4.79 (2.62-8.77)	<0.001	4.98 (2.08-11.93)	<0.001	16	5.49 (2.76-10.91)	<0.001	3.69 (1.5-9.08)	0.005
ctDNA% at baseline		61	NA	1.04 (1.02-1.05)	<0.001	1.01 (0.99-1.03)	0.229	NA	1.03 (1.02-1.04)	<0.001	1.02 (1-1.04)	0.019
PSA (ng/mL)	<=median	39	18.85	ref	ref	ref	ref	32.2	ref	ref	ref	ref
	>median	42	5.8	2.48 (1.48-4.15)	0.001	2.41 (1.38-4.22)	0.002	21.85	2.2 (1.26-3.82)	0.005	1.67 (0.92-3.03)	0.091
LDH (ULN)	<= ULN	53	16.49	ref	ref	ref	ref	27.7	ref	ref	ref	ref
	> ULN	26	5.66	2.47 (1.45-4.21)	0.001	1.61 (0.9-2.89)	0.108	27.2	1.34 (0.76-2.36)	0.319	0.67 (0.36-1.27)	0.225

Submitted

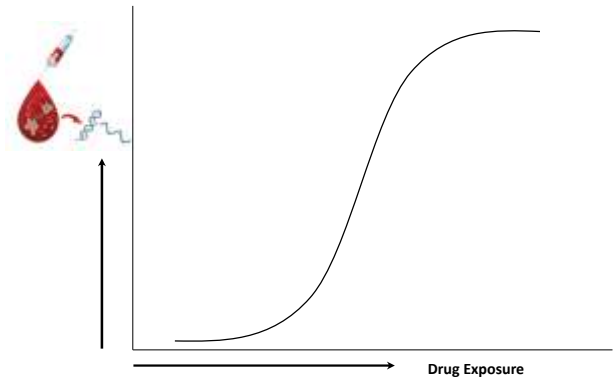
Results of the REFINE project

Emmy Boerrigter



Radboudumc

Potentially ctDNA will be our response indicator - to optimize treatment



Thanks for your attention