Neoadjuvant Hormonal Therapy

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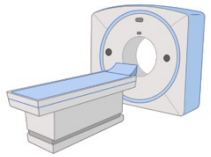
Conflict of Interest Disclosure

	Research Funding	Speakers Fee	Consultation Fee
Astellas	√	√	√
Astra Zeneca		√	
Bayer	√	√	√
Ferring	√	√	
GSK		√	
Ipsen		√	√
Janssen	√	√	√
MDX Health	√		
Pfizer		√	
Roche	√		√
Sanofi		√	

Treatment intensification in high-risk PCa patients is an unmet need

High-risk prostate cancer

New prostate cancer patients



Staging: CT and bone scan

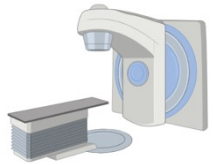
<10%

>90%

Metastatic prostate cancer

Localized prostate cancer

	PSA	Tumor stage	Gleason score
Low-risk	<10 ng/ml	cT2a	6
Intermediate-risk	10-20 ng/ml	cT2b	7
High-risk	>20 ng/ml	≥cT2c	8-10



Radiotherapy + 2 years hormonal treatment

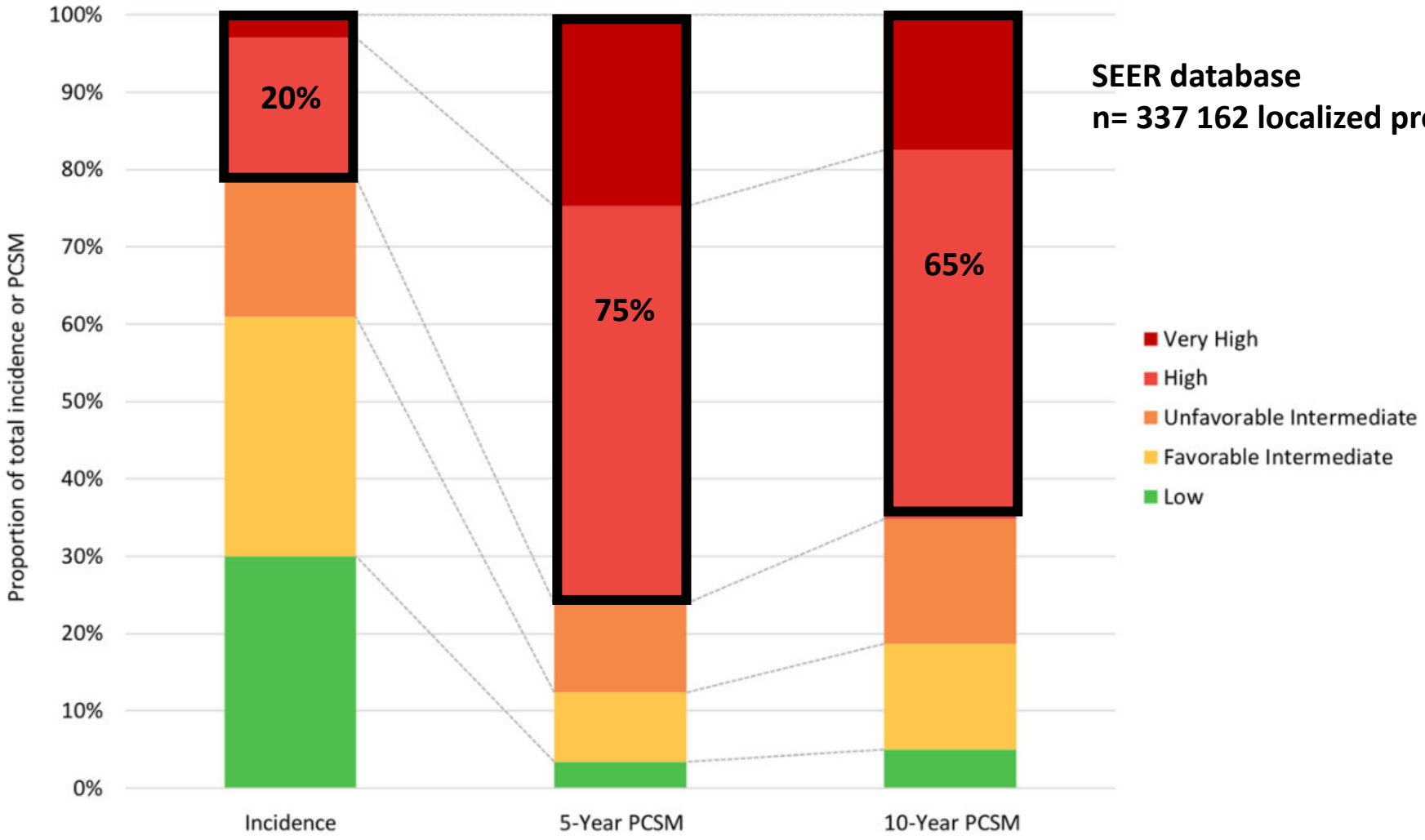
or

Radical prostatectomy + ePLND

> 50% PSA relapse (biochemical recurrence)

1. Positive surgical margins
2. Local extension
3. Micro-metastases

High-risk prostate cancer = ideal target

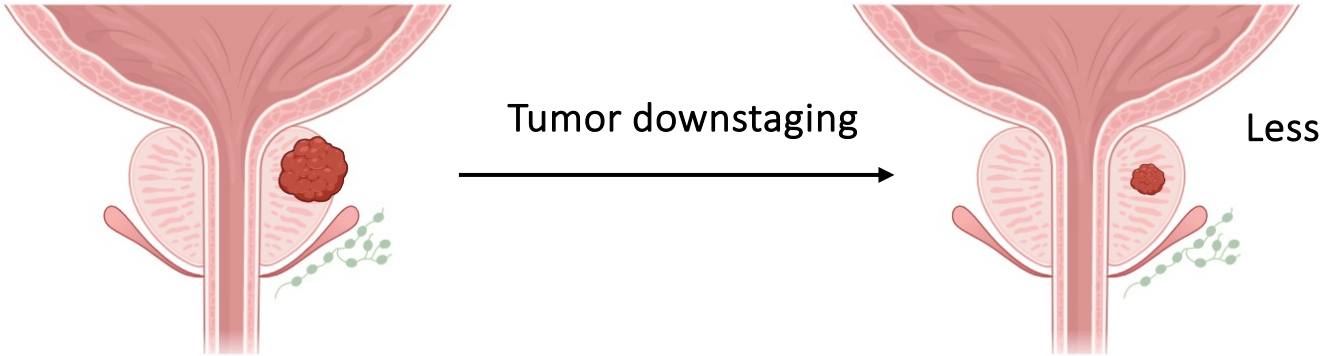


SEER database
n= 337 162 localized prostate cancer men

Dee EC et al. Prostate, 2020

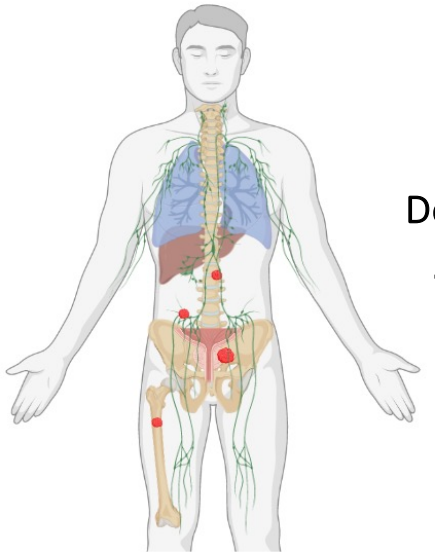
Rationale and results of neo-adjuvant therapy

Rationale for neoadjuvant therapy

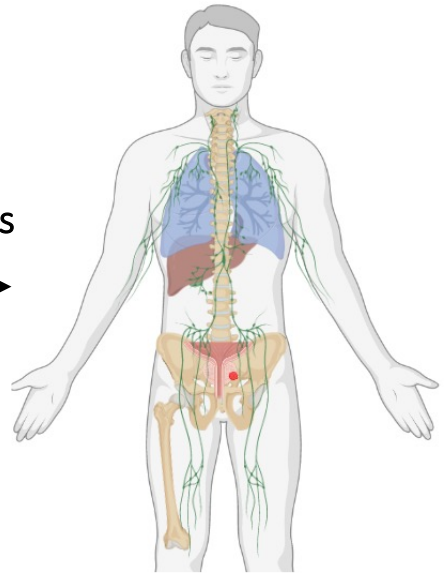


Tumor downstaging

Less positive surgical margins



Destroy micro-metastases



Radical prostatectomy

Improved oncological outcome?

Devos et al, nature reviews urology, 2021

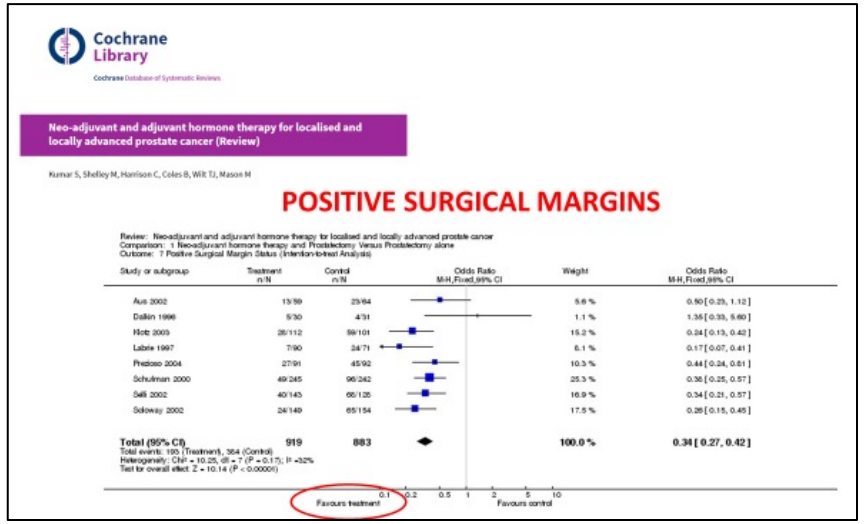
Rationale for neo-adjuvant hormonal therapy

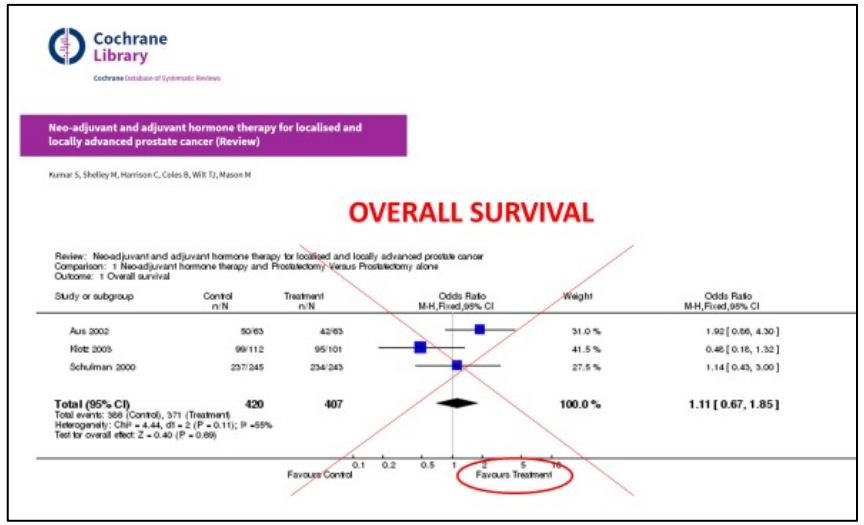
Multiple (old) trials investigated the role of neoadjuvant hormonal therapy prior to radical prostatectomy.[1]

- Benefit in terms of pathological response
- No benefit in terms of survival

However…

- First generation anti-androgens / LHRH agonists.
- Not powered for hard end-points
- Low- and intermediate-risk prostate cancer patients.



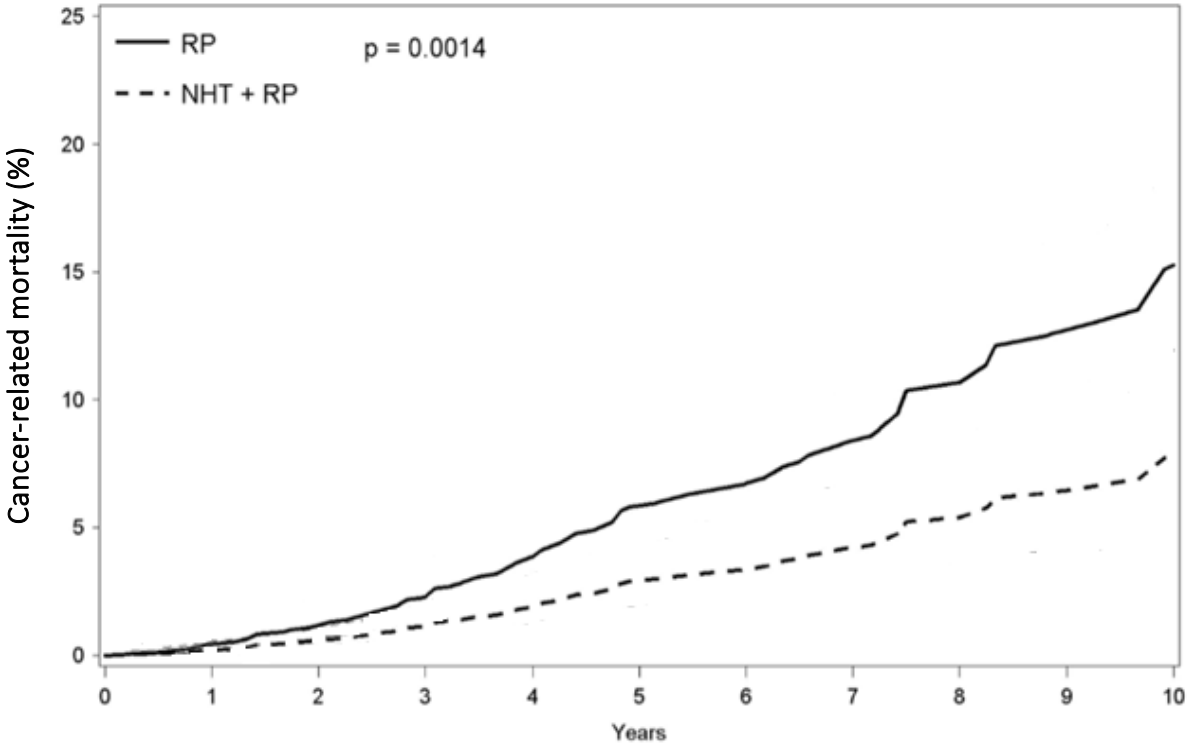


Shelley et al. Cancer treat rev., 2009

Neoadjuvant therapy in high-risk PCa

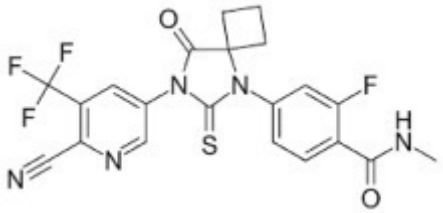
- Multi-institutional retrospective database
- High-risk prostate cancer:
  (≥ cT3 or preop PSA > 20 ng/ml or biopsy GS ≥ 8)
- RP + PLND
- 1573 patients

Retrospective data demonstrates survival benefit in high-risk prostate cancer patients!

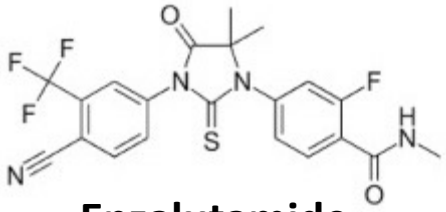


Tosco et al. Prostate cancer and prostatic diseases, 2017

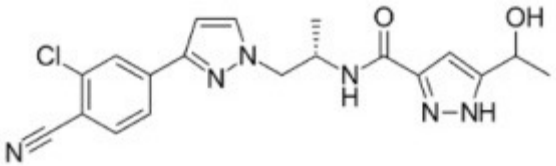
Rationale for intense neoadjuvant hormonal therapy



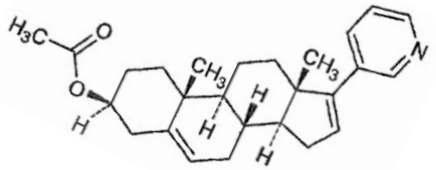
Apalutamide



Enzalutamide



Darolutamide



Abiraterone

mCRPC	Non-mCRPC	mHSPCa	High-risk localized PCa
• Abiraterone (COU-AA-322, COU-AA-301) • Enzalutamide (PREVAIL, AFFIRM)	• Apalutamide (SPARTAN) • Enzalutamide (PROSPER) • Darolutamide (ARAMIS)	• Abiraterone (STAMPEDE, LATITUDE) • Enzalutamide (ARCHES, ENZAMET) • Apalutamide (TITAN) • Darolutamide (ARASENS)	• Radiotherapy + Abiraterone (STAMPEDE) • Radical prostatectomy ?

Key neoadjuvant RCTs with intense neoadjuvant hormonal therapy

	ADT + Abi (24 weeks)[1]	ADT + Enz (24 weeks)[2]	ADT + Abi (12 weeks)[3]	ADT + Enz (24 weeks)[4]	ADT + Abi + Enz (24 weeks)[4]	ADT + Apa (24 weeks)[5]	ADT + Abi + Apa (24 weeks)[5]	ADT + Abi (24 weeks)[6]	ADT + Abi + Apa (24 weeks)[6]	ARNEO (ADT + Apa) (12 weeks)[7]
pCR	10%	4%	NR	8%	10%	0%	6%	10%	13%	0%
MRD	52%	74%	NR	16%	30%	16%	3%	10%	9%	38%
R1	10%	22%	5%	12%	18%	9%	19%	12%	7%	18%
pN1	24%	26%	34%	12%	10%	31%	32%	17%	7%	20%

- Pathological Complete Response (pCR): <10%
- Minimal Residual Disease (MRD): 3%-74%
- Positive surgical margins: 5%-22%
- Positive lymph nodes: 7%-34%

[1]Taplin et al, JCO 2014
[2]Montgomery et al, Clin Can Res, 2017
[3]Efstathiou et al, European Urology, 2019
[4]McKay et al, JCO, 2019
[5]Efstathiou et al, JCO, 2020
[6]McKay et al, Journal of Urology, 2021
[7]Devos et al, European Urology, 2022

Key neoadjuvant RCTs with other neoadjuvant agents

	ADT + Abi (24 weeks)[1]	ADT + Abi + Cabazitaxel (24 weeks)[1]	ADT (24 weeks)[2]	ADT + Abi (24 weeks)[2]	ADT + Doc (24 weeks)[2]	ADT + Apa (12 weeks)[3]	Enoblituzumab (6 weeks)[4]
pCR	9.1%	5.4%	0%	19%	17%	0%	0%
MRD	36.4%	37.8%	2%	13%	11%	/	/
R1	30.3%	13.5%	24%	19%	21%	16%	31%
pN1	18.2%	32.4%	17%	19%	7%	16%	13%

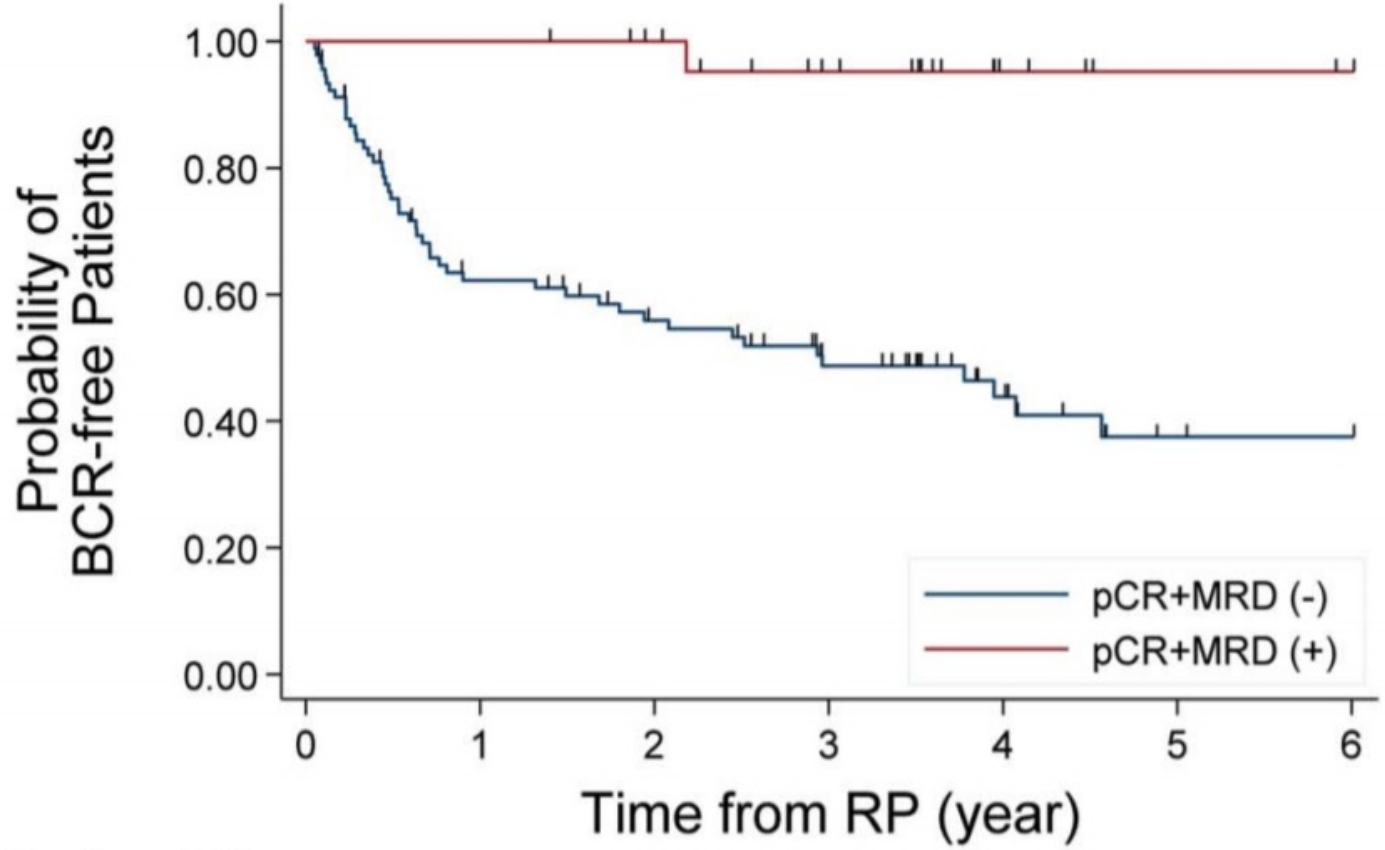
[1]ACDC-RP trial (Fleshner et al. Clin Cancer Res; 2023)
[2]Zhuang et al. Front Pharmacol; 2023
[3]NEAR trial (Lee et al. Prostate Cancer Prostatic Dis; 2022)
[4]Shenderov et al. Nat Med; 2023

Pathological response correlated with outcome?

N = 117

Neoadjuvant Enzalutamide and/or abiraterone

PSA relapse following neo-adjuvant hormonal treatment



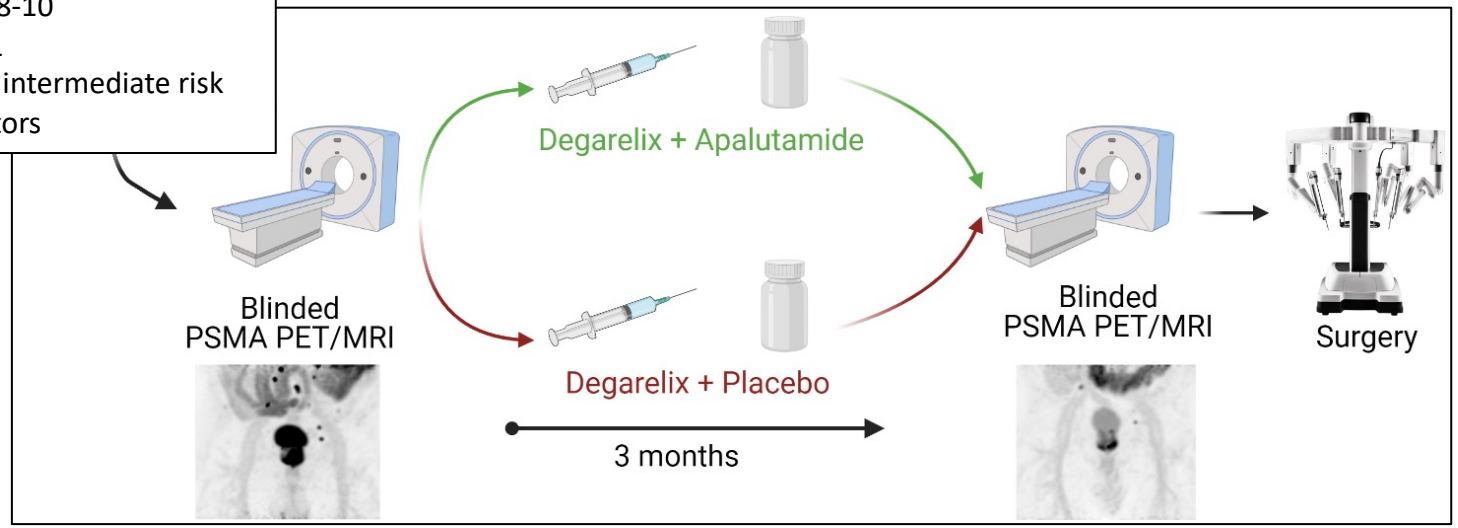
Number at risk							
pCR+MRD (-)	92	52	42	30	17	8	7
pCR+MRD (+)	25	25	22	16	7	4	3

McKay et al., Journal of Urology, 2021

ARNEO trial

A double-blind, placebo controlled randomized phase II trial of neoadjuvant degarelix with or without apalutamide prior to radical prostatectomy for high-risk prostate cancer

High-risk PCa, M0:
- cT3-4
- PSA>20
- GS 8-10
- cN1
- 2-3 intermediate risk factors



- All patients were followed-up 3-monthly until PSA >0.2 ng/ml
- No patient received adjuvant RT or ADT
- At PSA >0.2 ng/ml, patients received a PSMA PET/CT
- Type of salvage treatment was decided at MDT meeting

Primary endpoint:

Difference in % Minimal Residual Disease (<0.25ml)

Secondary endpoints:

- Tumor downstaging, PSA kinetics, toxicity, QoL, biomakers for pathological response
- BCR-free survival at 3 years follow-up

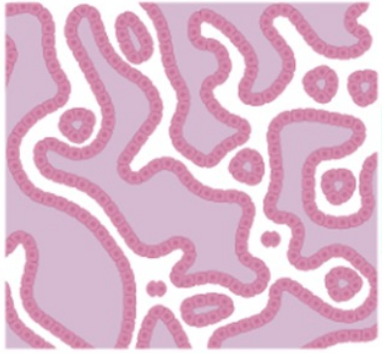
Devos G, …, Joniau S. European Urology, 2023

Results: Baseline patient characteristics

Baseline characteristics: Degarelix + Placebo (n=44)

Median	11.2 ng/ml
PSA <10	20 (45%)
PSA 10-20	14 (32%)
PSA >20	10 (23%)

≤cT2	12 (27%)
cT3a	20 (46%)
cT3b	7 (16%)
cT4	5 (11%)
cN1	5 (11%)

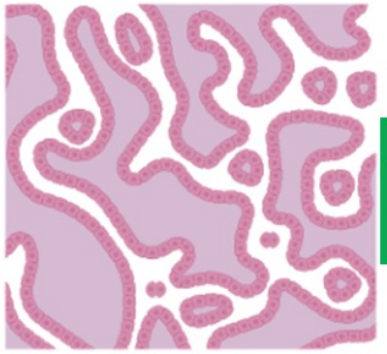


ISUP ≤ 3	13 (29%)
ISUP 4	17 (39%)
ISUP 5	14 (32%)

Baseline characteristics: Degarelix + Apalutamide (n=45)

Median	12.6 ng/ml
PSA <10	20 (44%)
PSA 10-20	14 (31%)
PSA >20	11 (25%)

≤cT2	12 (26%)
cT3a	18 (40%)
cT3b	12 (27%)
cT4	3 (7%)
cN1	7 (16%)

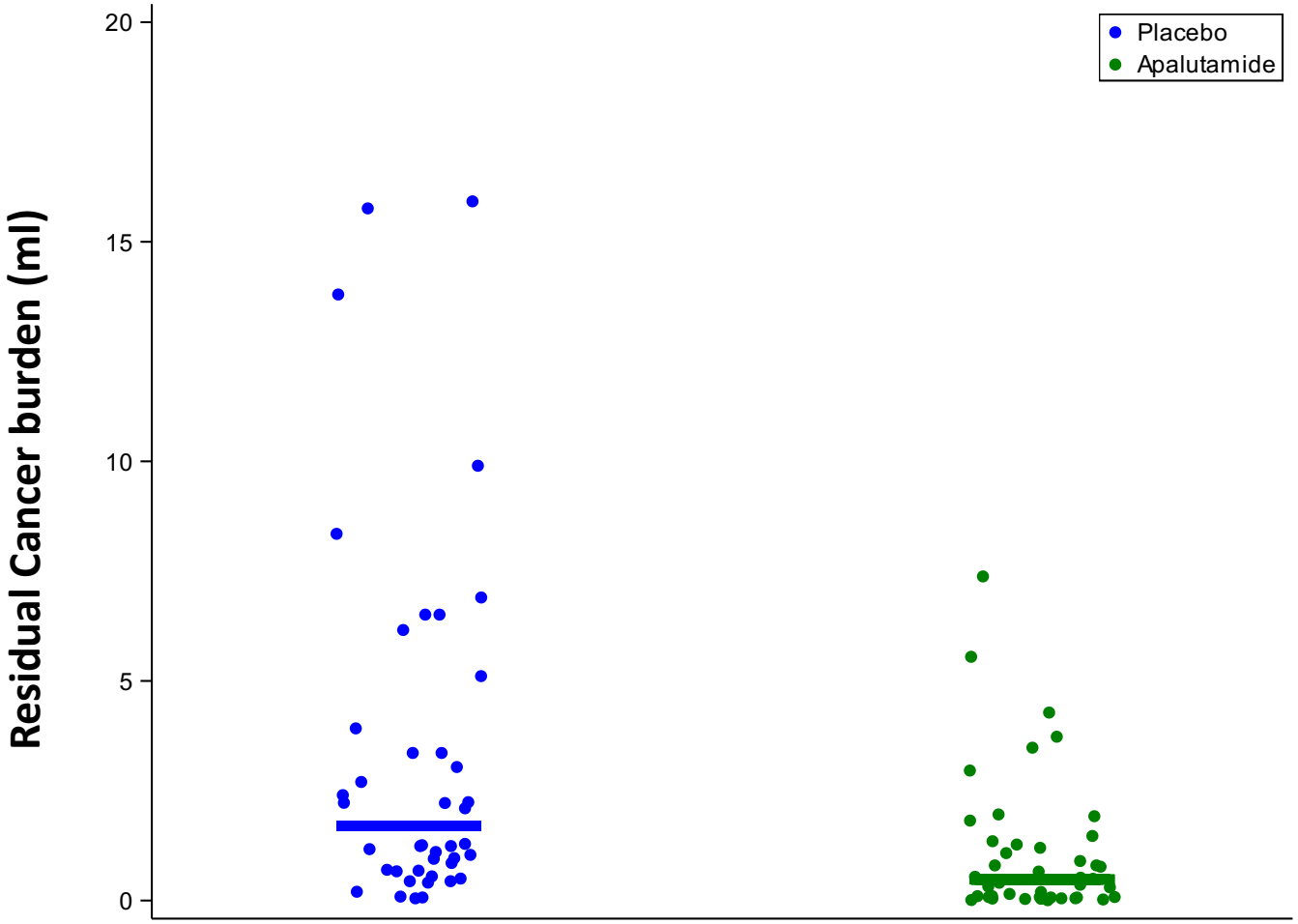


ISUP ≤ 3	16 (35%)
ISUP 4	10 (22%)
ISUP 5	19 (43%)

± 25% PSA >20 **± 75% ≥ cT3a** **10-15% cN1** **± 65% ≥ ISUP 4**

Devos G, …, Joniau S. European Urology, 2023

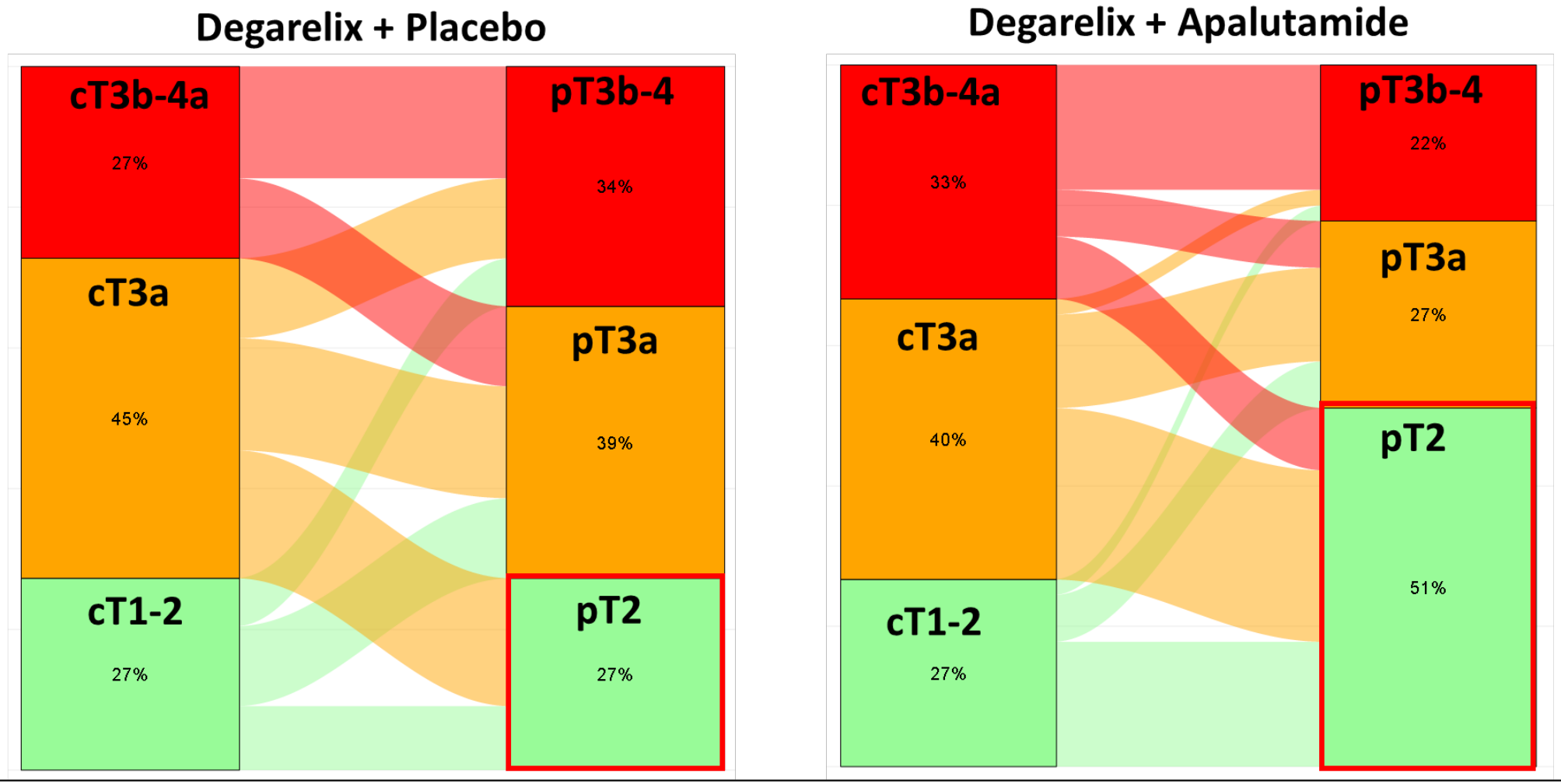
Primary endpoint: Minimal residual disease



Minimal residual disease (<0.25ml): 38% in the apalutamide arm vs. 9% in the placebo arm. P=0.002, RR 4.2

Devos G, …, Joniau S. European Urology, 2023

Impact on Tumor downstaging



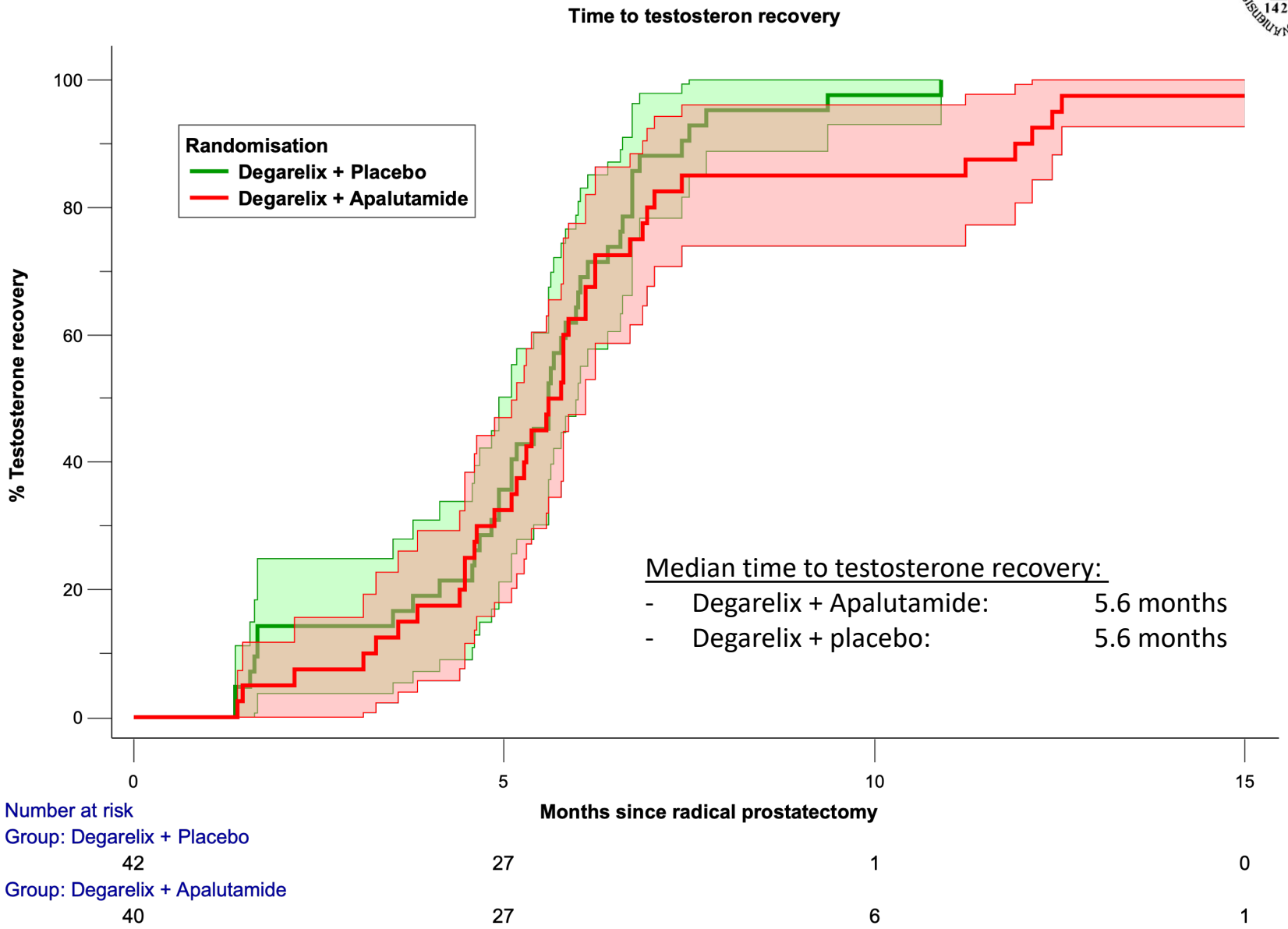
Downstaging to pT2-disease was significantly more frequent in the apalutamide arm (**51% vs. 27%, p=0.03**).

Devos G, …, Joniau S. European Urology, 2023

Unpublished data

Interim results ARNEO (cfr. UROOnco23)

Testosterone recovery

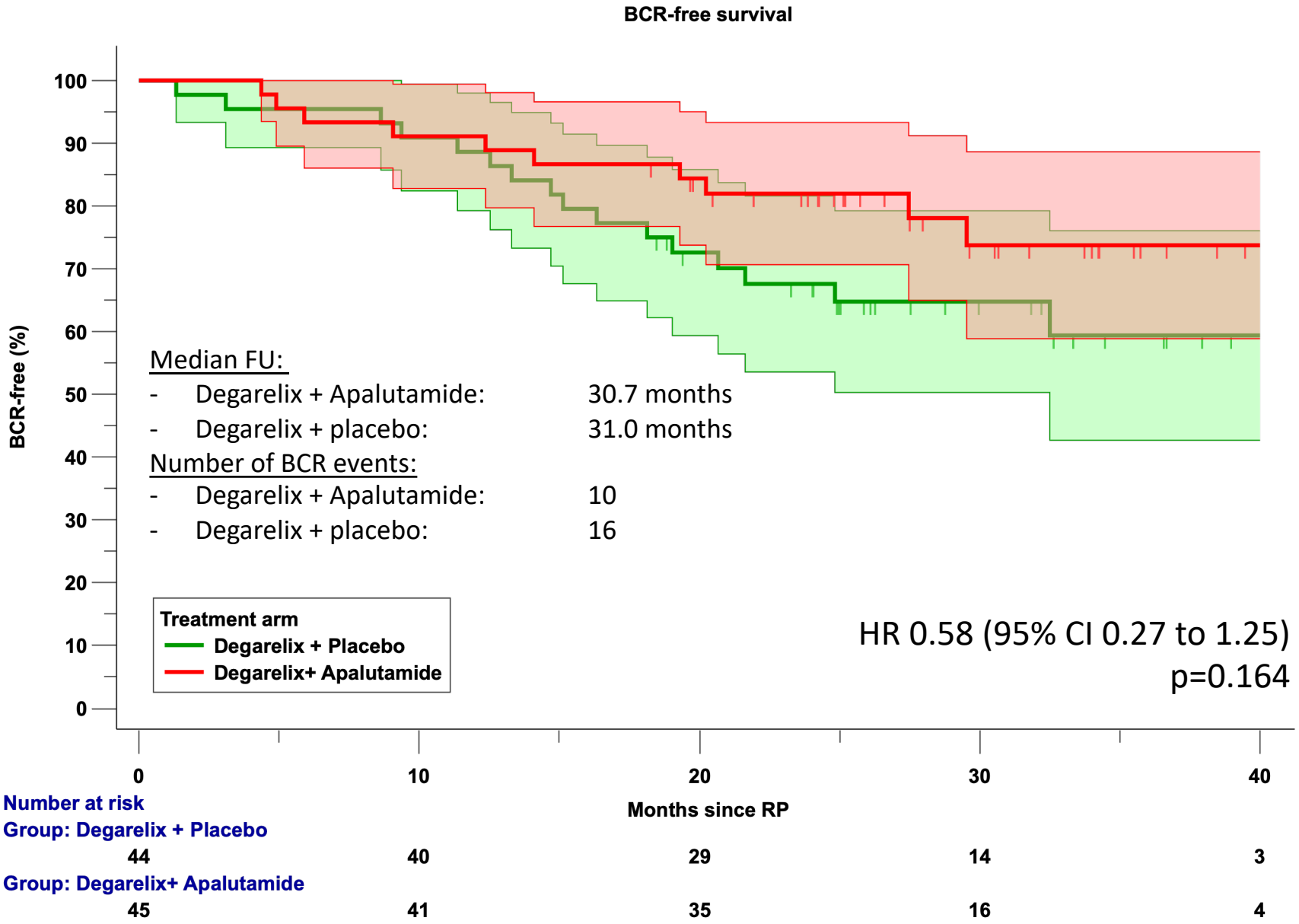


Median time to testosterone recovery:

- Degarelix + Apalutamide: 5.6 months
- Degarelix + placebo: 5.6 months

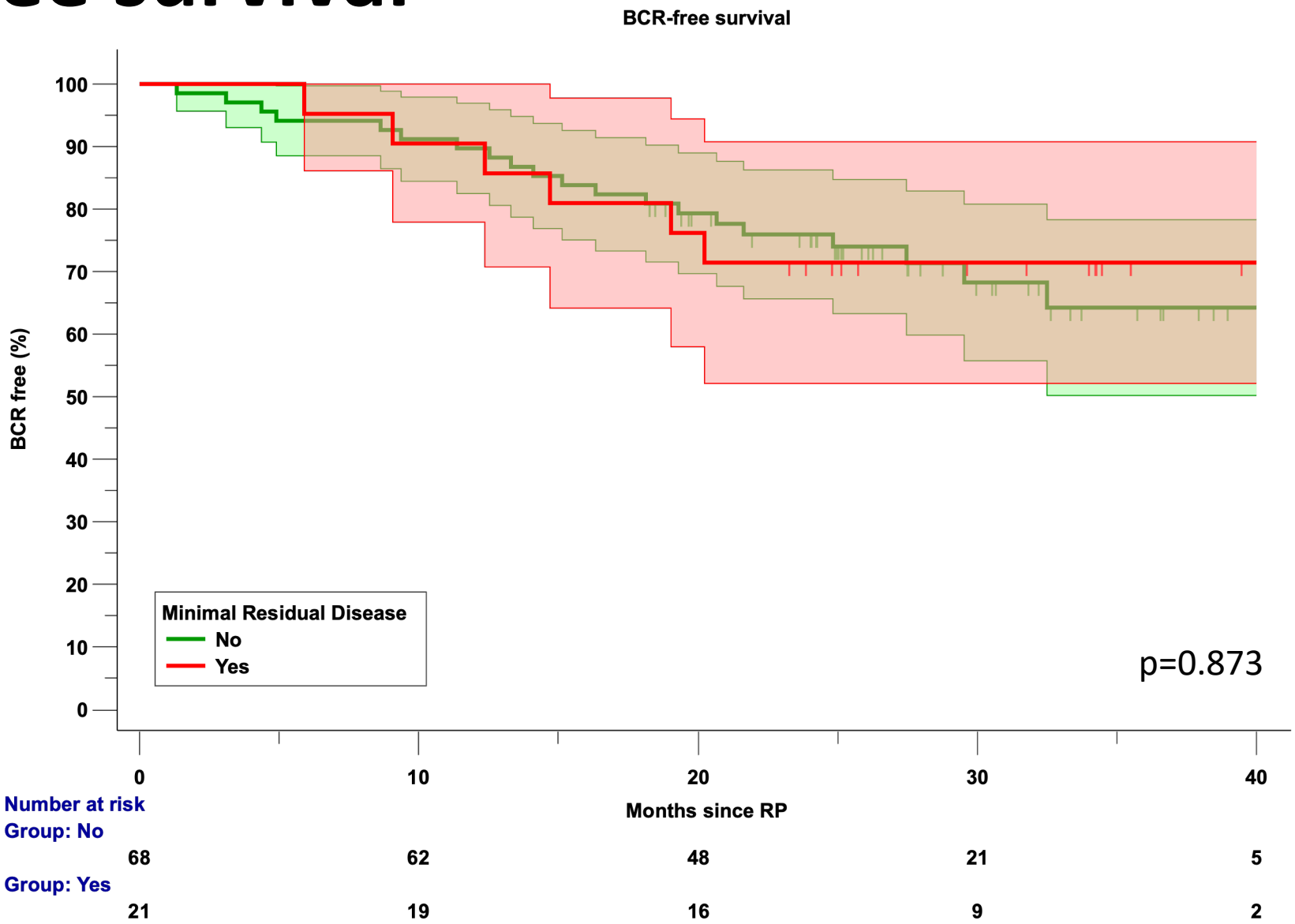
Unpublished data

BCR-free survival (interim ARNEO)



Unpublished data

BCR-free survival



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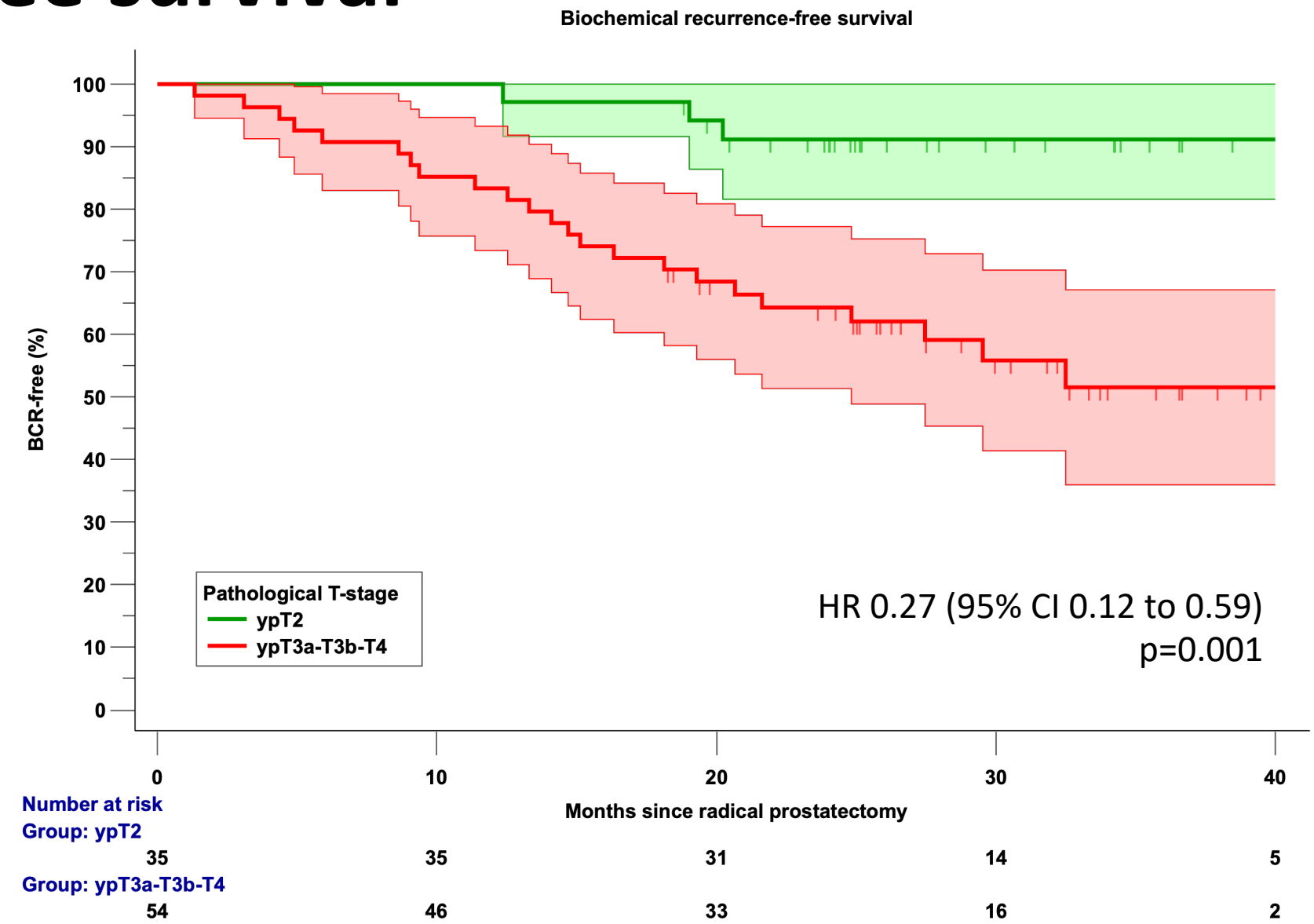
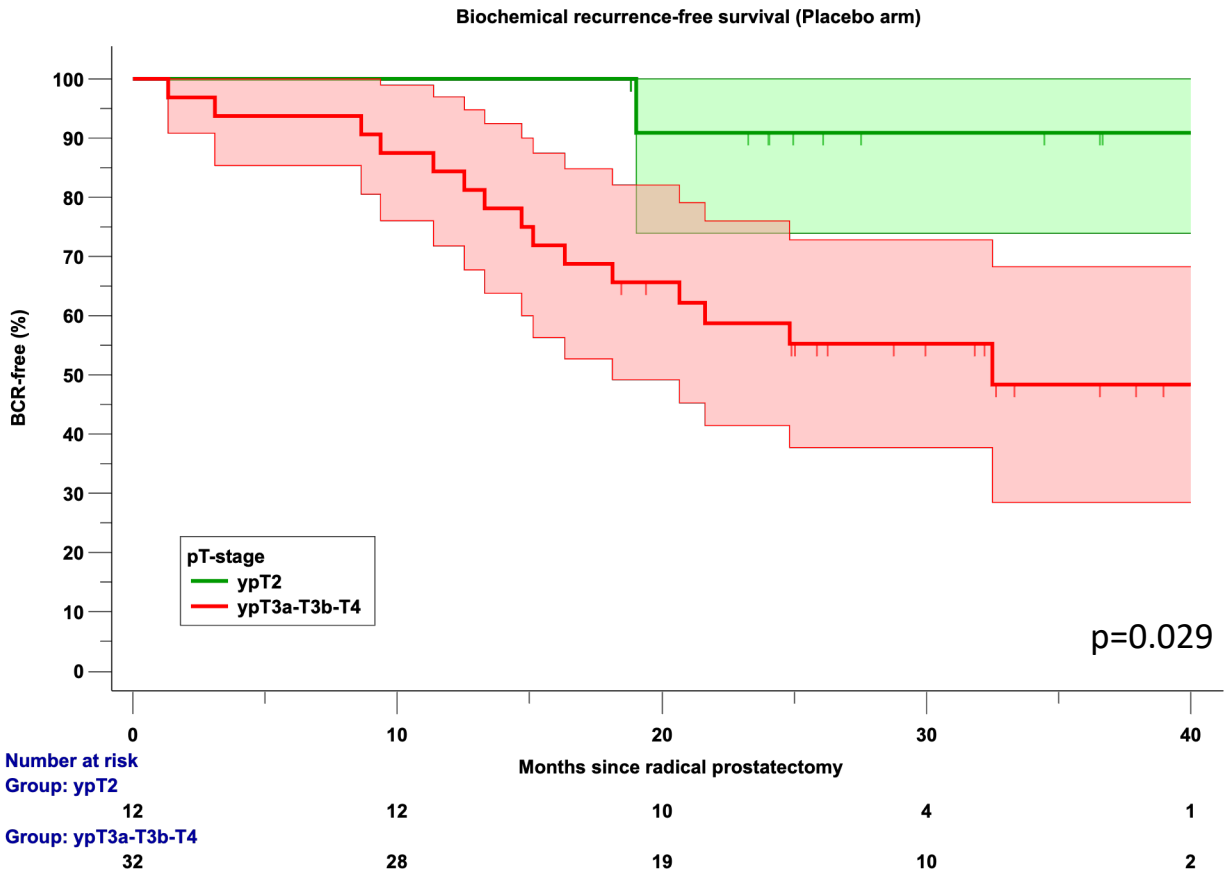
BCR-free survival



Unpublished data

BCR-free survival

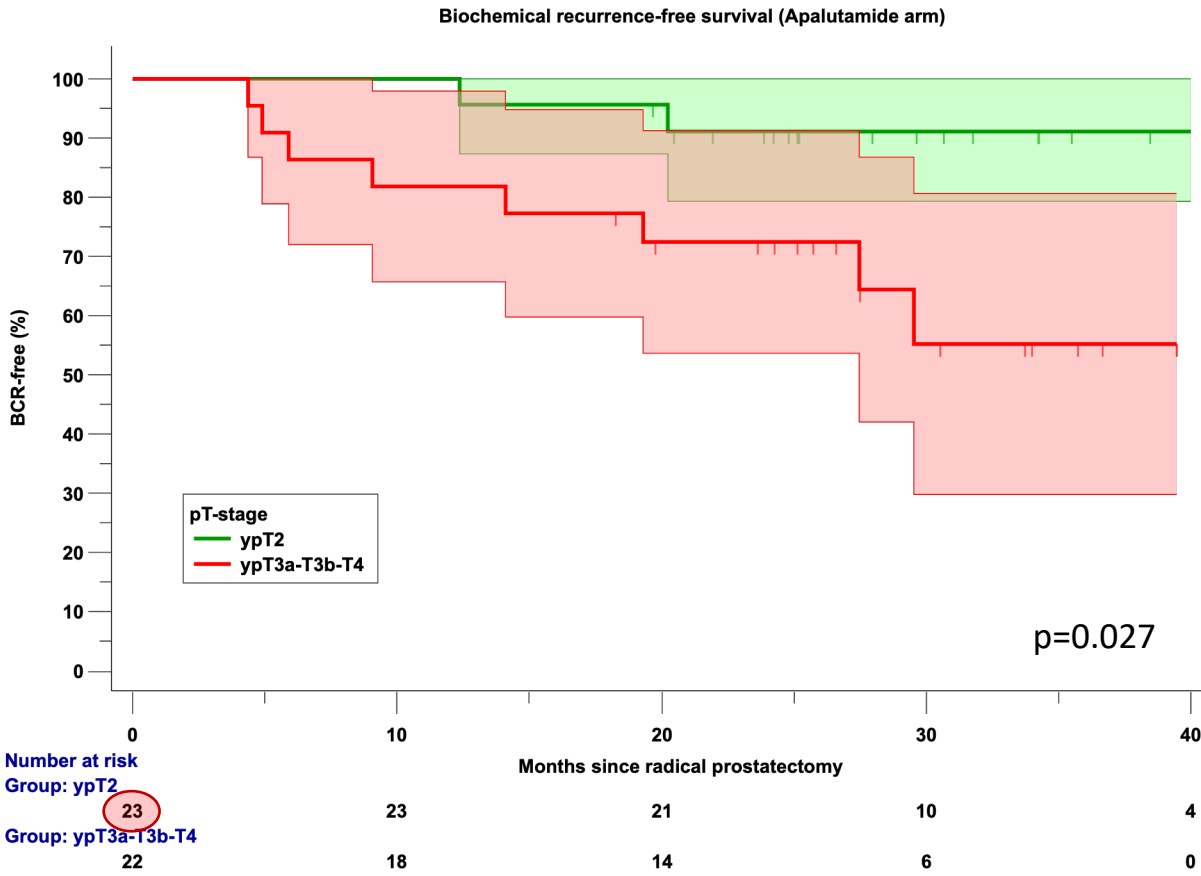
Placebo arm



Number at risk

Group: ypT2				
12	12	10	4	1
Group: ypT3a-T3b-T4				
32	28	19	10	2

Apalutamide arm



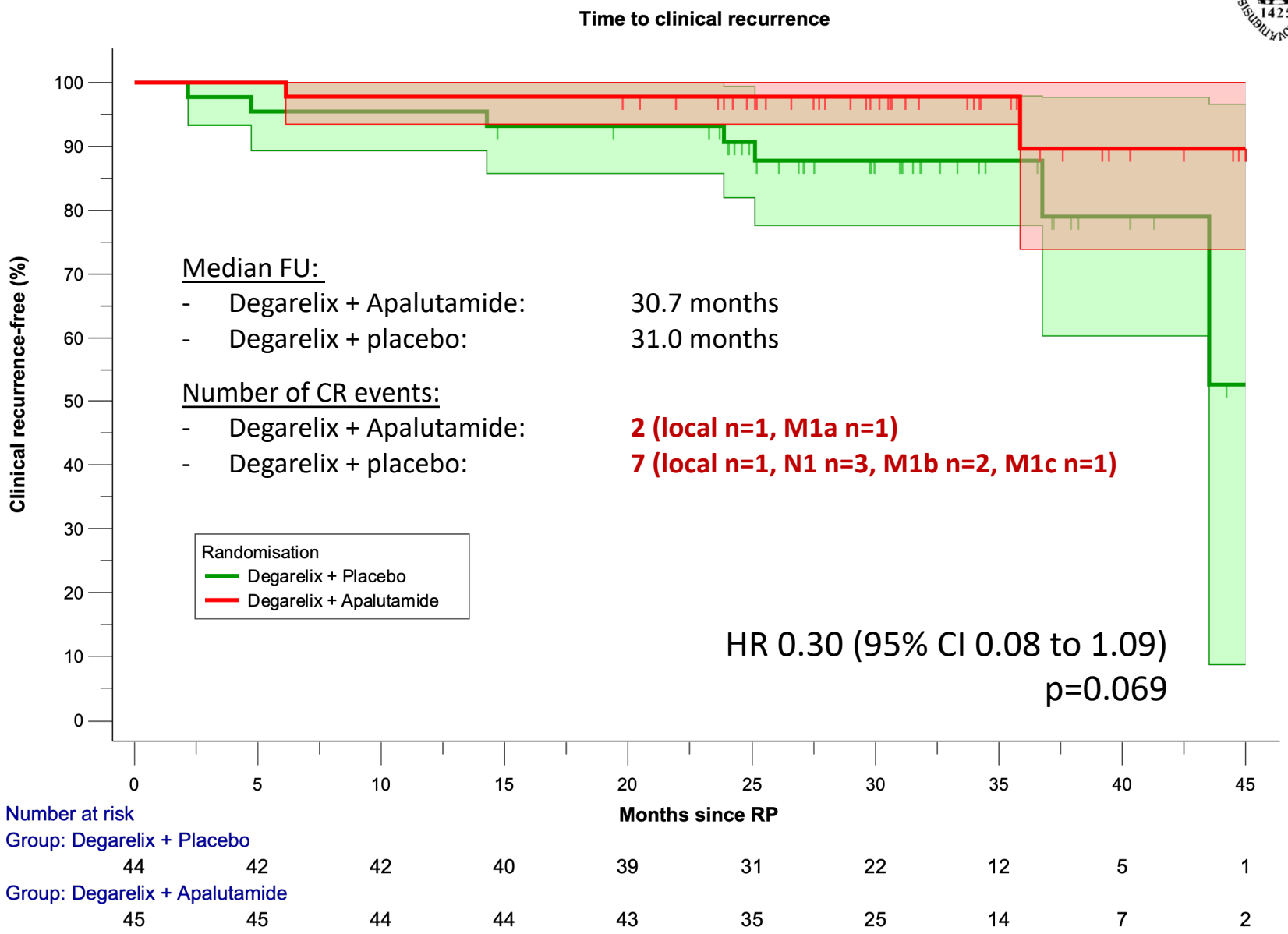
Number at risk

Group: ypT2				
23	23	21	10	4
Group: ypT3a-T3b-T4				
22	18	14	6	0

Unpublished data

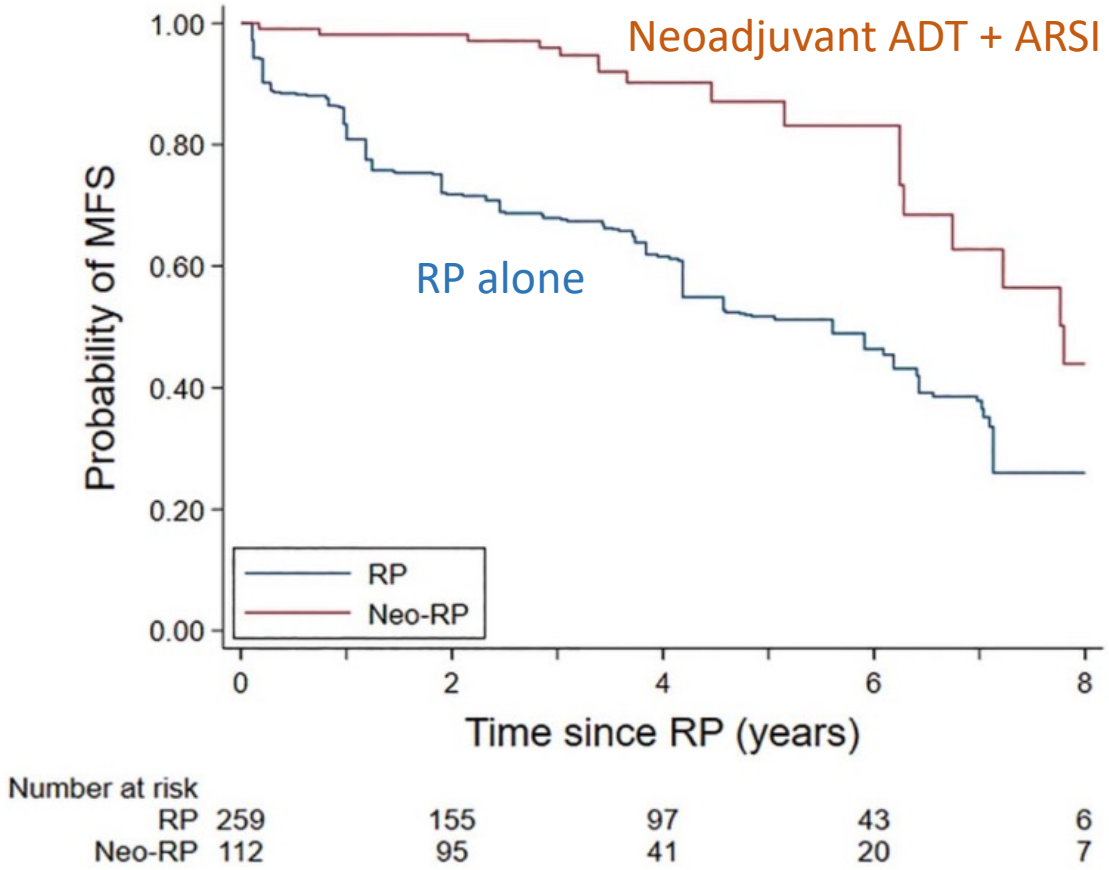
rPFS-free survival

All radiographic progression was PSMA PET/CT detected



Long-term oncological outcomes?

Characteristic	Neo-RP		RP	
No. pts	112		259	
Median yrs age (range)	61	(45–75)	62	(42–75)
No. White race (%)	101	(90)	237	(92)
No. yr of RP (%):				
2010–2013	49	(44)	167	(65)
2014–2016	63	(56)	92	(36)
No. biopsy Gleason score (%):				
7	28	(25)	125	(48)
8	32	(29)	71	(27)
9-10	52	(46)	63	(24)
No. clinical T stage (%):				
T1	38	(34)	198	(76)
T2	49	(44)	39	(15)
T3	25	(22)	13	(5)
Unknown	-		9	(4)
Median ng/ml PSA at diagnosis (IQR)	7.0 (4.6–13.9)		6.9 (4.8–9.9)	
No. ng/ml PSA at diagnosis (%):				
<10	71	(63)	191	(74)
10–20	25	(22)	42	(16)
≥20	16	(14)	19	(7)
Unknown	-		7	(3)



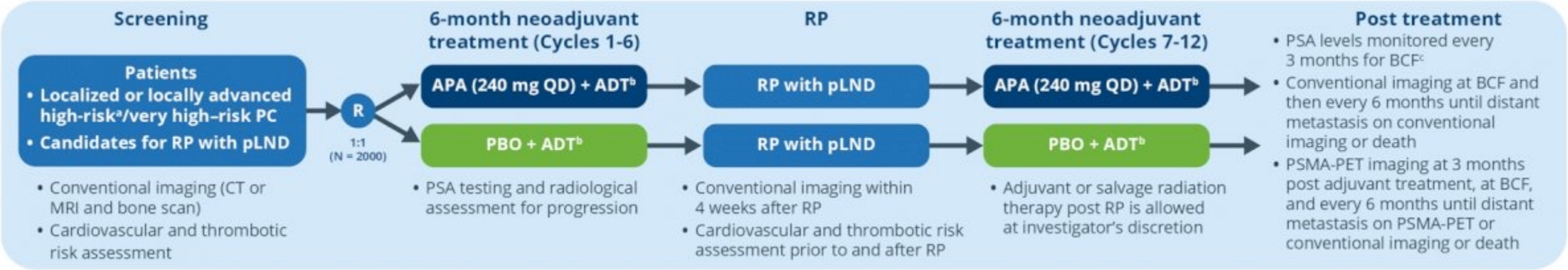
Ravi P, et al. J Urol 2022

What do the EAU guidelines tell us?

Recommendations	Strength rating
No active treatment modality has shown superiority over any other active management options or deferred active treatment in terms of overall- and PCa-specific survival for clinically localised low/intermediate-risk disease.	Strong
Offer a watchful waiting policy to asymptomatic patients with clinically localised disease and with a life expectancy < 10 years (based on co-morbidities and age).	Strong
Inform patients that all local treatments have side effects.	Strong
Surgical treatment	
Radical prostatectomy can be safely delayed for at least 3 months from diagnosis in any risk category.	Weak
Inform patients that no surgical approach (open-, laparoscopic- or robotic radical prostatectomy) has clearly shown superiority in terms of functional or oncological results.	Weak
When a lymph node dissection (LND) is deemed necessary based on a nomogram, perform an extended LND template for optimal staging.	Strong
Consider avoiding nerve-sparing surgery when there is a risk of ipsilateral extra-capsular extension (based on cT stage, ISUP grade, magnetic resonance imaging, or with this information combined in a nomogram).	Weak
Do not offer neoadjuvant androgen deprivation therapy before surgery.	Strong

Pathological response correlated with outcome?

PROTEUS trial



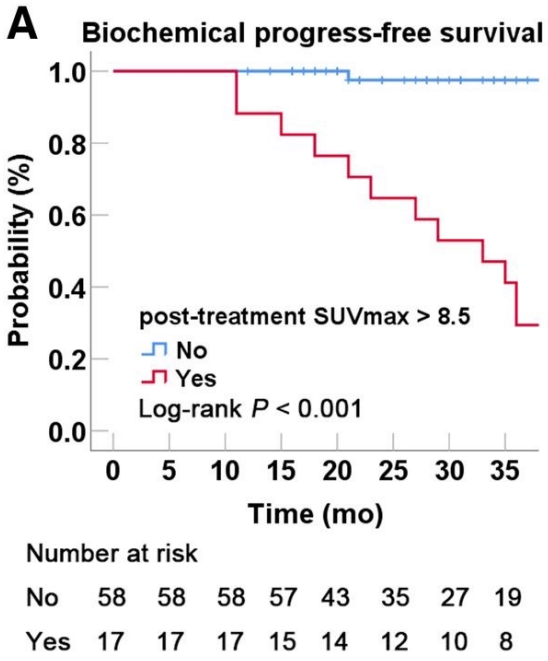
Dual Primary endpoint: Pathological complete response and Metastasis-free survival.

Note: ”An open-label sub-study comparing apalutamide plus ADT before and after RP with pLND with <u>standard of care treatment</u> will be initiated at selected sites upon notification by the sponsor. **“**

Clinical Trials: NCT03767244

Future perspectives

Can we predict who responds?



[^{68}Ga]PSMA PET/CT response is an independent risk factor for bPFS after neoadjuvant treatment.[1]

Variables	Favourable pathological responses			
	Univariate		Multivariate	
	OR (95% CI)	*P* value	*OR (95% CI)*	*P* value
Post-NCHT SUVmax before RP	0.209 (0.102–0.429)	<0.001	0.209 (0.102–0.429)	<0.001

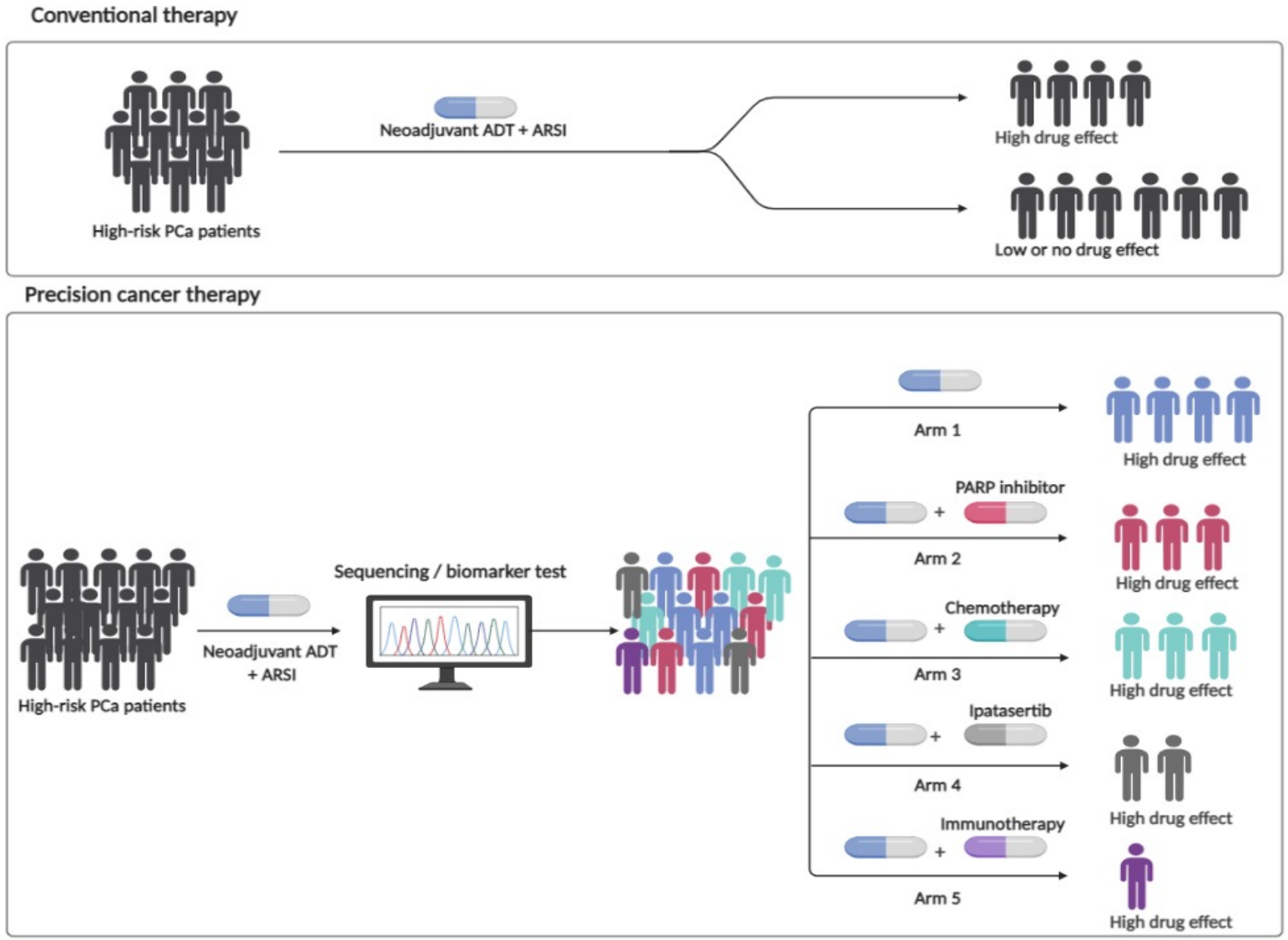
[^{68}Ga]PSMA PET/CT had a better concordance with a favourable pathological response to NCHT compared with nadir PSA and mpMRI.[2]

	Univariate HR (95% CI); p-Value	Multivariate HR (95% CI); p-Value
Treatment arm (degarelix vs. degarelix + apalutamide)	HR 1.7 (0.78-3.8); p=0.17	-
PSA response following neoadjuvant hormonal therapy (PSA ≤0.3 ng/ml vs >0.3 ng/ml)	HR 0.61 (0.28-1.36); p=0.22	-
pN-stage (pN1 vs pN0)	HR 3.5 (1.53-7.78); p=0.002	HR 0.72 (0.22-2.37); p=0.59
pT-stage (>pT2 vs. pT2)	HR 5.9 (1.78-19.8); p= 0.003	HR 0.4 (0.11-1.56); p=0.18
Positive surgical margin (Yes vs. No)	HR 5 (2.26-10.87); p=0.0001	HR 3.3 (1.38-7.85); p=0.007
PSMA PET estimated volume following neoadjuvant hormonal therapy (ml)	HR 1.23 (1.14-1.32); p<0.0001	HR 1.19 (1.07-1.31); p=0.002
Highest PSMA SUVmax following neoadjuvant hormonal therapy (SUVmax)	HR 1.12 (1.02-1.23); p=0.01	HR 0.96 (0.82-1.12); p=0.61
cN-stage on PSMA PET following neoadjuvat hormonal therapy (cN1 vs. cN0)	HR 5.8 (2.6-12.9); p<0.0001	HR 3.3 (1.06-9.3); p=0.04

PSMA PET response (in terms of estimated tumor volume and cN-stage) following neoadjuvant hormonal therapy might be used to predict PSA relapse following RP.[3]

[1]Chen M et al. J Nucl Med; 2023
[2]Ke Z et al. Eur J Nucl Med Mol Imaging; 2023
[3]ARNEO trial; unpublished!

Patient-tailored neoadjuvant therapy



Example: **G**enomic Biomarker-Selected **U**mbrella **N**eoadjuvant **S**tudy for High Risk Localized Prostate Cancer (**GUNS**) - NCT04812366

Devos et al, nature reviews urology, 2021

Conclusions

Conclusions

1. (Very-)high-risk PCa patients are at significantly elevated risk of dying from PCa.
2. Improving survival of patients with (very)high-risk PCa is an unmet need.
   - Neo-adjuvant systemic treatment prior to surgery may be a reasonable strategy to achieve this goal
     - Provided intensified systemic treatment is used
     - Provided toxicity of neo-adjuvant treatment is kept low
3. Deep pathological response may serve as a surrogate for disease-free survival. pCR, downstaging and MRD are correlated with a significantly lower risk of BCR.
4. Early results are promising, but long-term oncological outcomes are lacking.
   - Most trials use neoadjuvant ADT or ADT + NHT as standard of care arm.
   - First comparative analysis demonstrate lower MFS in high-risk PCa patients who received neo-adj treatment + surgery vs. surgery alone.
   - The fully accrued phase 3 PROTEUS trial results are eagerly awaited.
5. The future of neoadjuvant therapy is probably biomarker-driven.

QUESTIONS?