SIU
SOCIETÀ ITALIANA
DI UROLOGIA
FONDATA NEL 1908

SIU UPDATES

ASCO GU

ASCO GENITOURINARY CANCER SYMPOSIUM

PROSTATE CANCER, Radiotherapy

SIU UPDATES
ASCO GU
ASCO GENITOURINARY CANCER SYMPOSIUM

ADVANCES in RADIOTHERAPY for PROSTATE CANCER

Alberto Bossi
Radiotherapy and Oncology
Gustave Roussy, Villejuif, France

PROSTATE CANCER, Radiotherapy

IGRT

RT + ADT: short vs long

RT +/- ABI/ENZA

PROSTATE CANCER, Radiotherapy

SIU UPDATES
ASCO GU
ASCO GENITOURINARY CANCER SYMPOSIUM

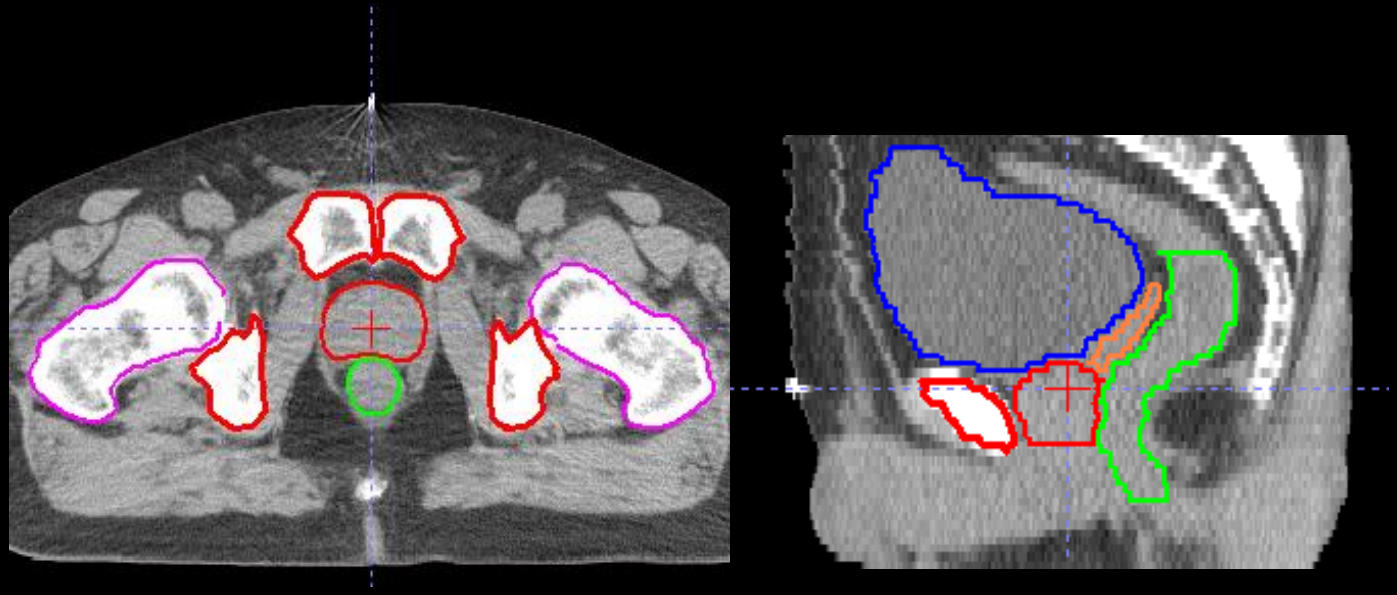
DAILY vs WEEKLY PCa IGRT: a PHASE III RCT

R. de Crevoisier [a], M. A. Bayar [b,c], P. Pommier [d], X. Muracciole [e], F. Pêne [f], P. Dudouet [g], I. Latorzeff [h], V. Beckendorf [i], J.-M. Bachaud [j], A. Laplanche [b], S. Supiot [k], B. Chauvet [l], T.-D. Nguyen [m], A. Bossi [n], G. Créhange [o], J.L. Lagrange [p]

Department of Radiotherapy, Centre Eugène Marquis,

Setup Error and Organ Motion

22 Treatment CT scans Aligned to Skin Marks



In-room CT-linear accelerator combination

courtesy of R. de Crevoisier, L. Dong, MDACC

Prostate and Seminal Vesicles movements during irradiation

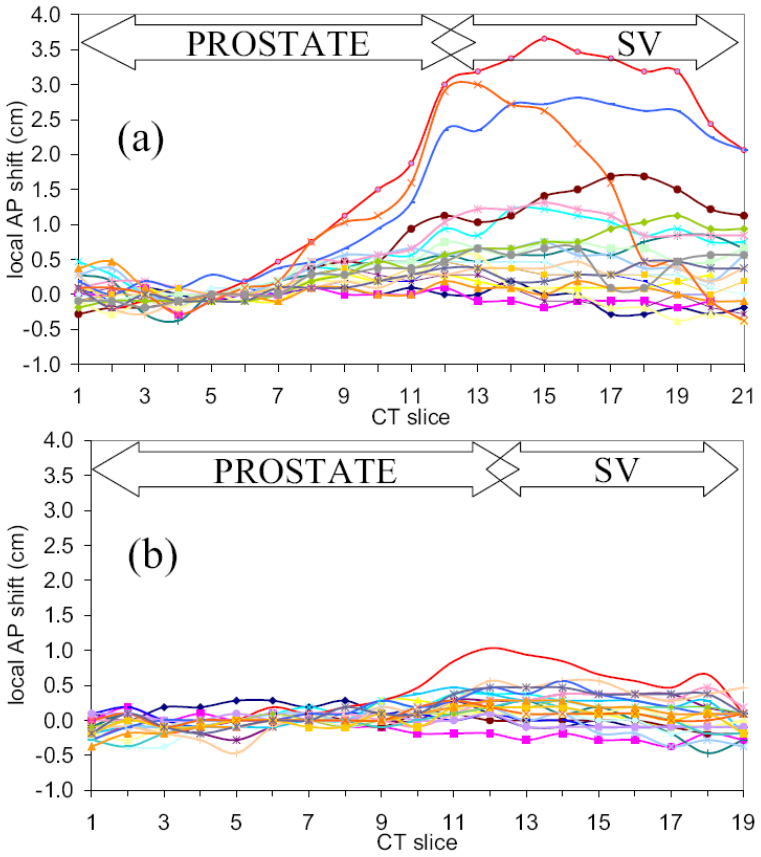


Fig. 3. Results of the local anteroposterior registration for all the daily computed tomographic images for 2 patients. (a) Patient 1: the prostate is in slices 1–13, and the seminal vesicles (SVs) are in slices 12–21. (b) Patient 2: the prostate is in slices 1–12, and the SVs are in slices 11–19. The anterior direction is positive.

Court, IJROBP, 2005

Image Guidance Technologies for Prostate Radiotherapy (1)

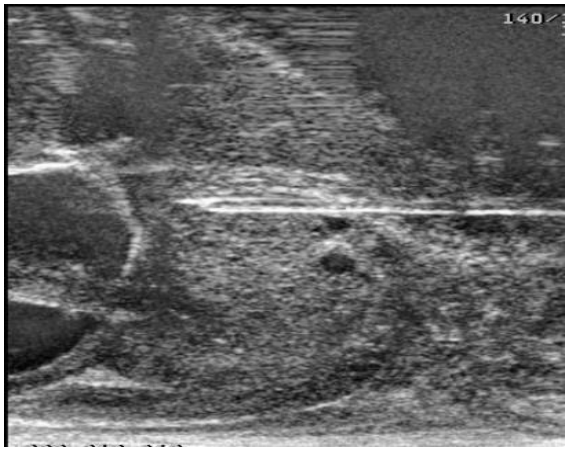
Technology	Quality of Alignement	Intrafraction Correction	Comments
Skin marks with weekly portals	Low	No	Baseline
Projected MV/kV x-rays	Medium	Possible	Bone is not a good surrogate
CT on rails for bone alignement	Medium	No	Time consuming
Ultrasound for prostate alignement	Medium / Good	Possible	Interobserver variation
Cone Beam CT	Medium / Good	Possible	Image quality challenging
Tomotherapy	Medium / High	Possible	Image resolution challenging

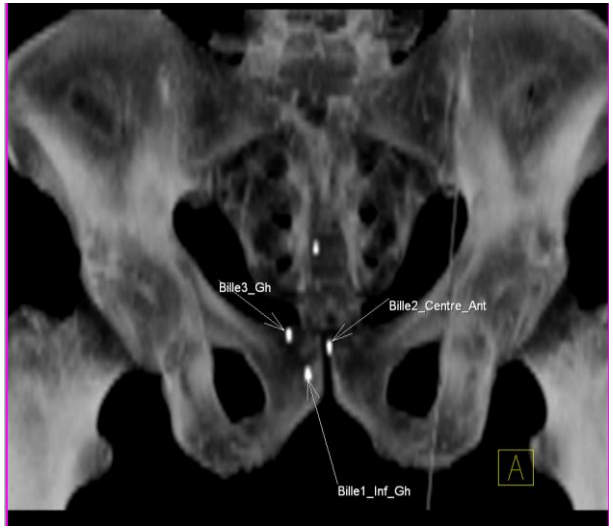
Image Guidance Technologies for Prostate Radiotherapy (2)

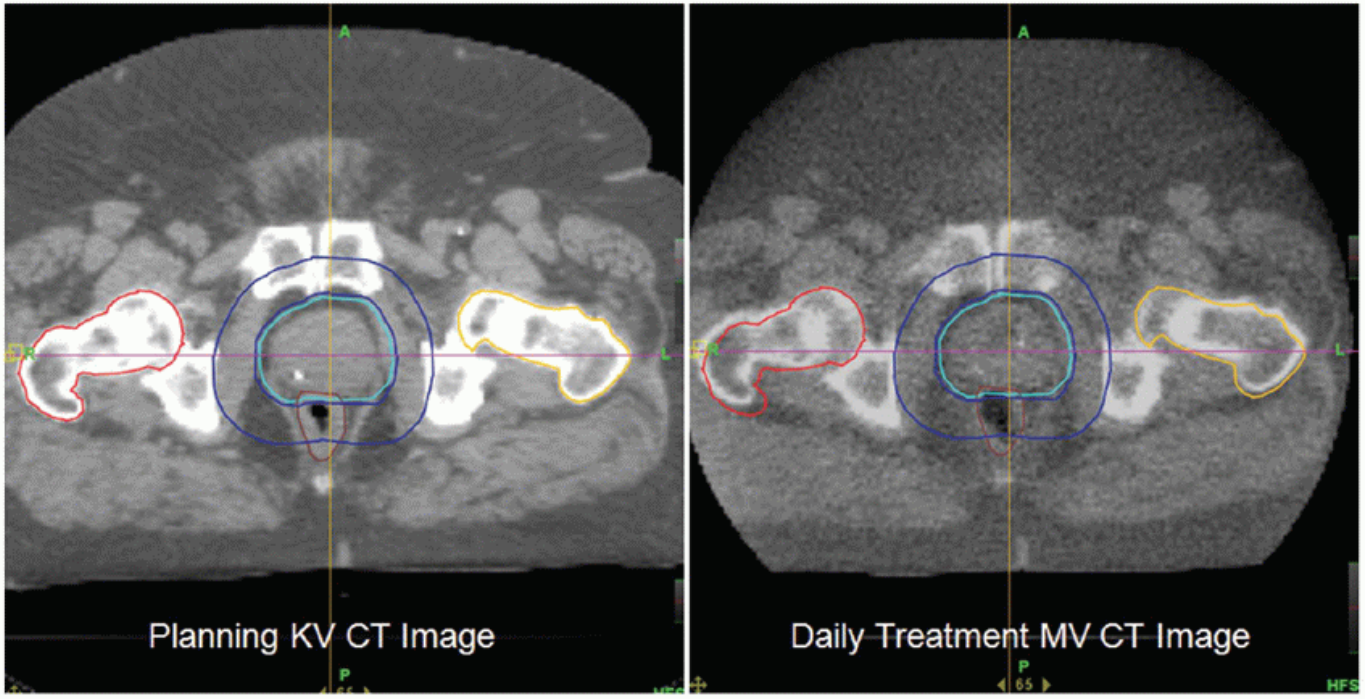
Technology	Quality of Alignement	Intrafraction Correction	Comments
Implanted Markers with AP-LL x-rays	High	Possible	No SV alignement Time consuming
CBCT+Implanted Markers	High	Possible	Image quality challenging
Ultrasound + Implanted Markers	High	Yes	Interobserver variation
Implanted Electromagnetic Transponder	High	Yes	No SV alignement
Real-Time in room MRI	High	Yes	Not currently available (?)

PROTOCOL for INTRAPROSTATIC FIDUCIAL MARKERS

- all prostate IMRT (and Brachy HDR + IMRT)
- 7 / 10 days before planning Scanner/IRM
- implantation of 3/4 gold seeds (2 at the base, and apex)
- 10 – 15 min...





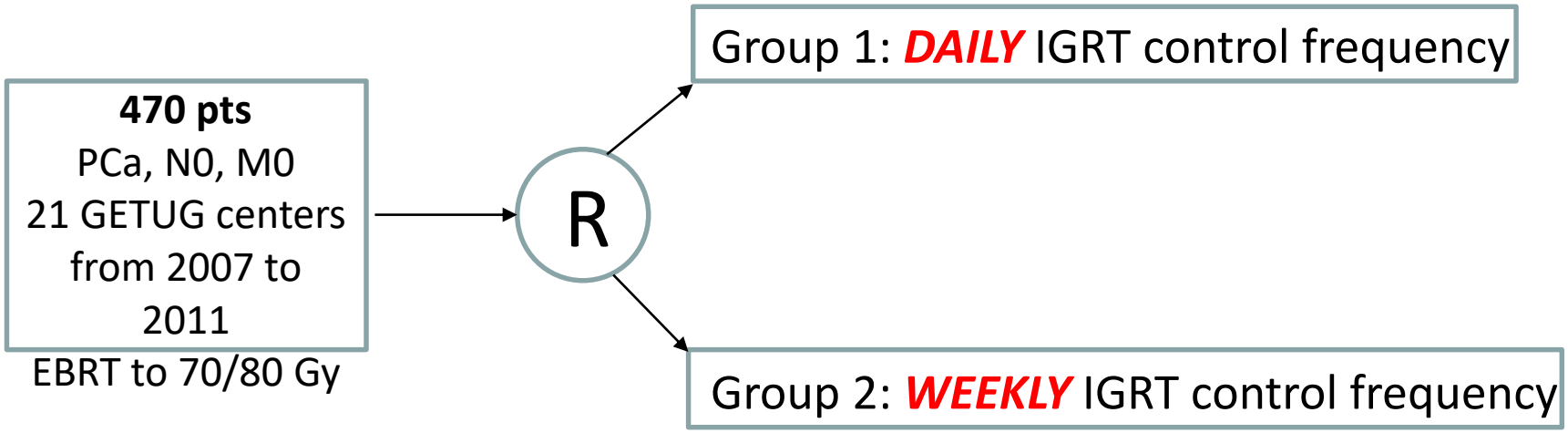


IGR, 2008

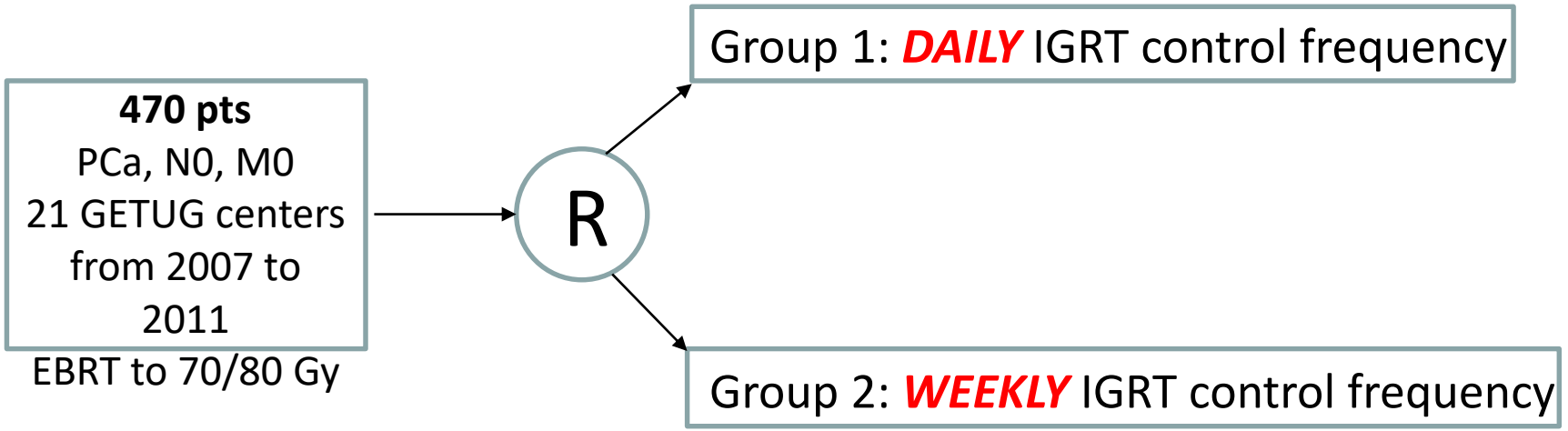
Background

The optimal frequency of prostate cancer image-guided radiation therapy (IGRT) has not yet been clearly identified. This study sought to compare the safety and efficacy of daily versus weekly IGRT.

De Crevoisier, 2018

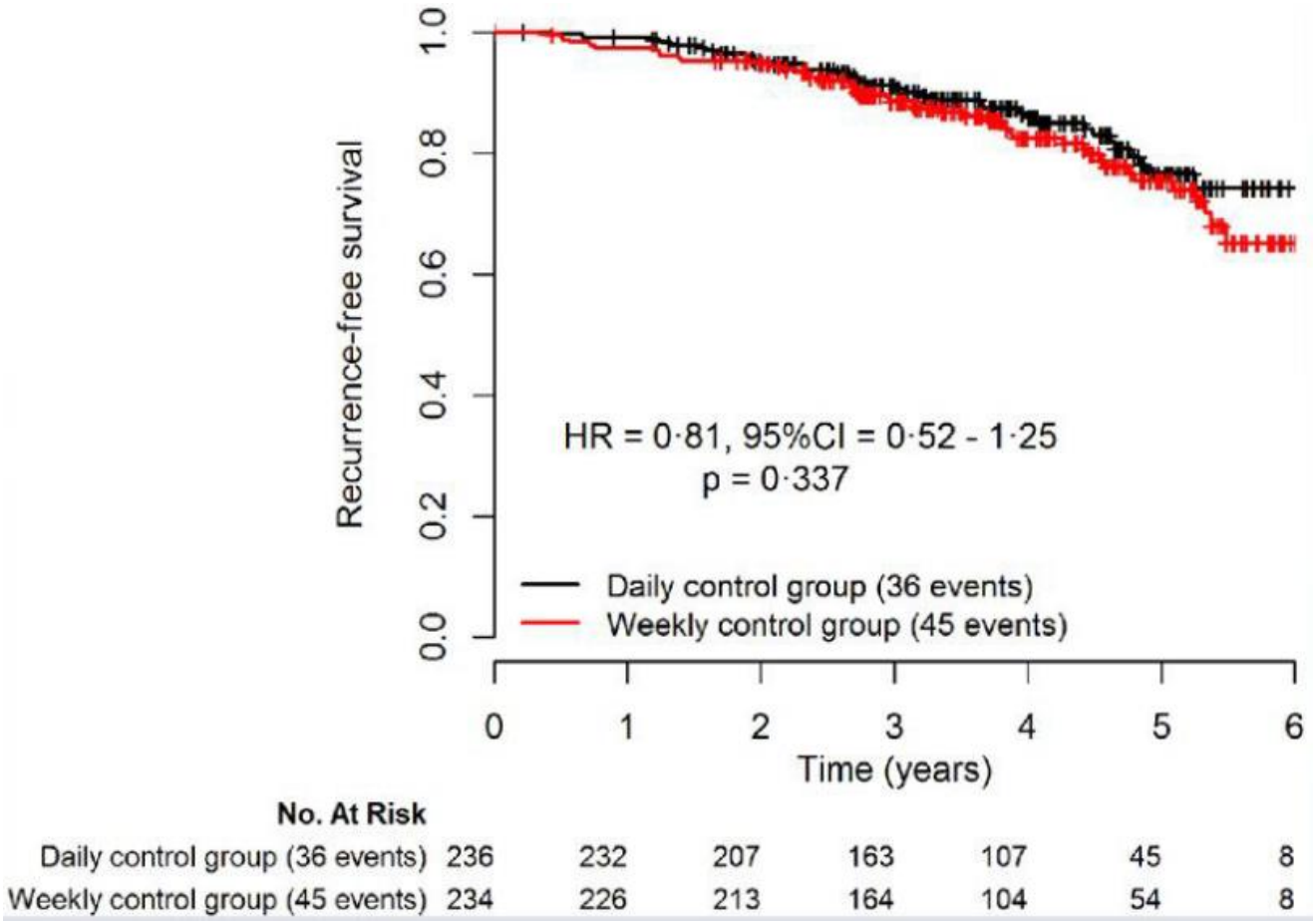


De Crevoisier, 2018

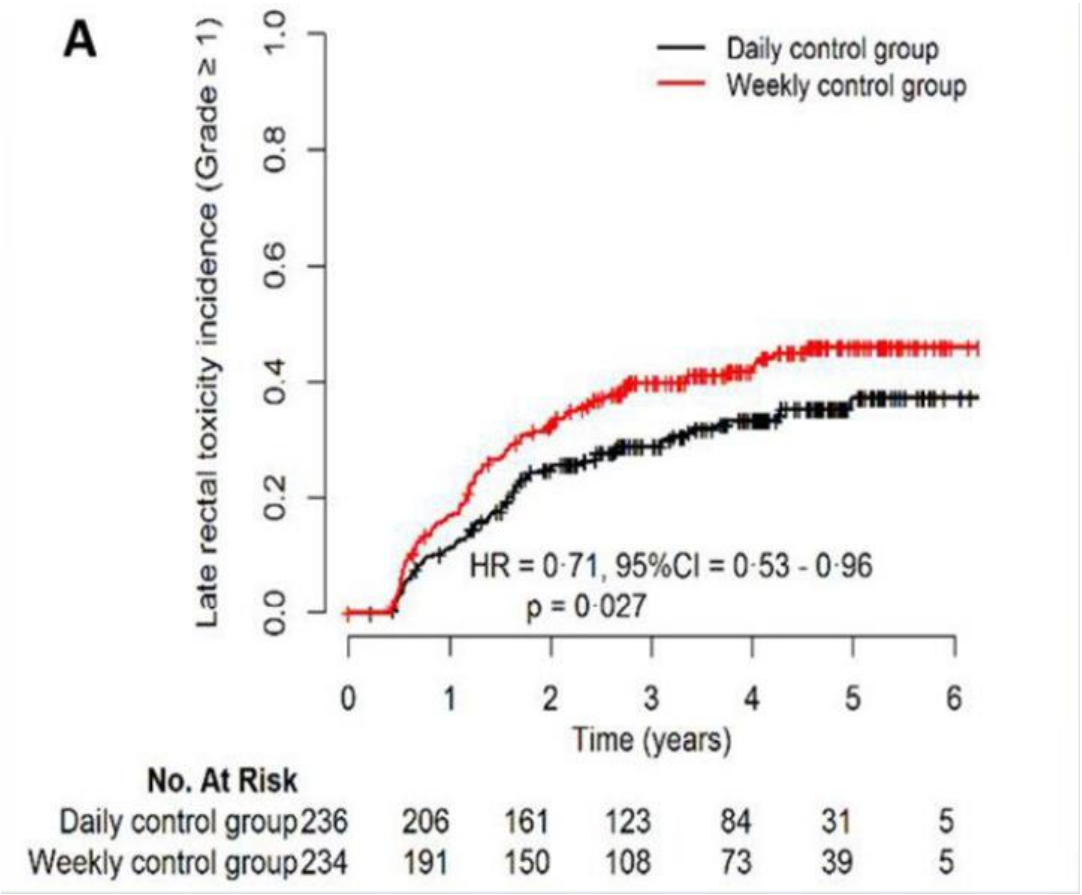


The primary outcome was 5-year recurrence-free survival (RFS). Secondary outcomes included overall survival (OS) and toxicity (CTCAE V.3.0).

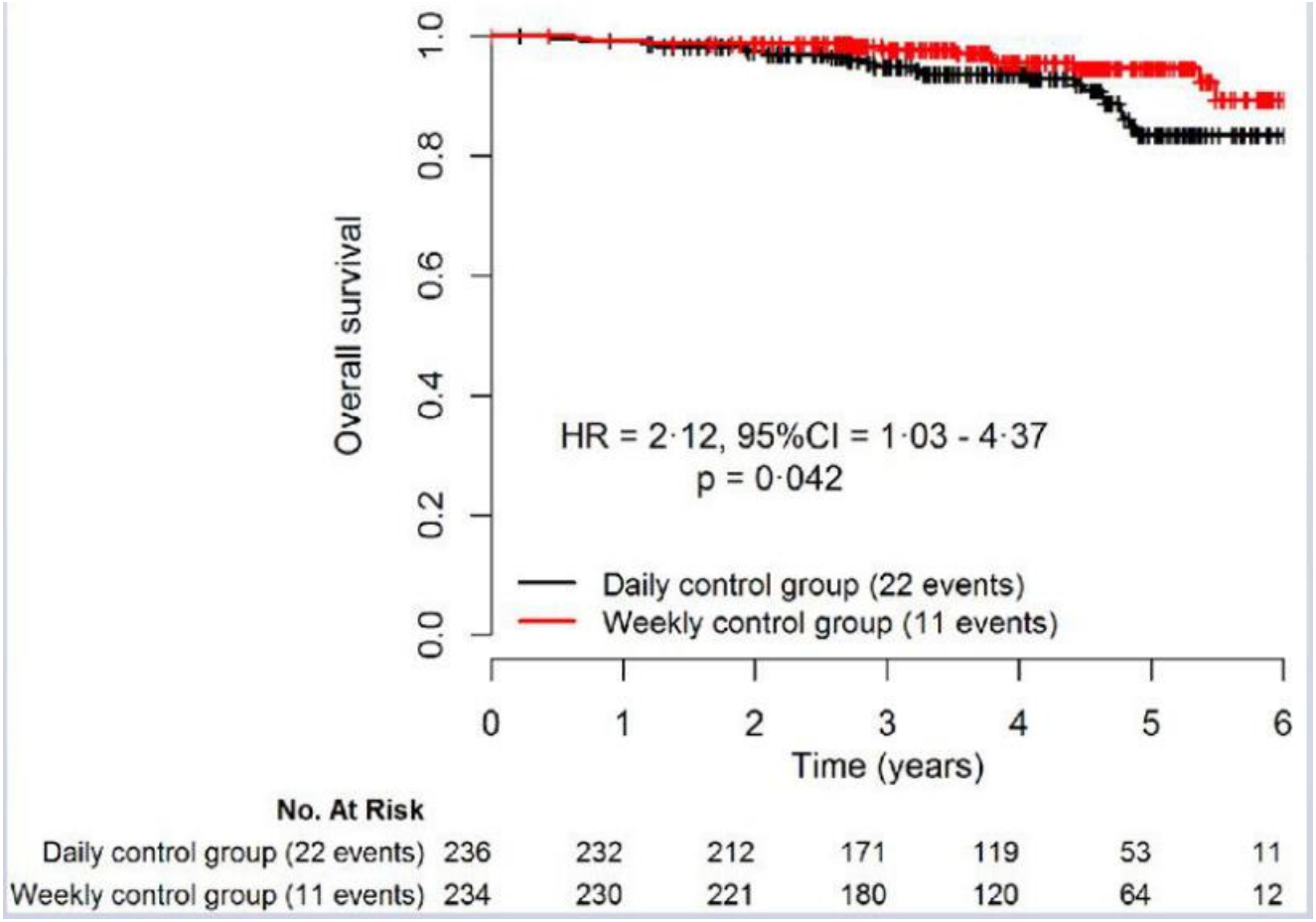
De Crevoisier, 2018



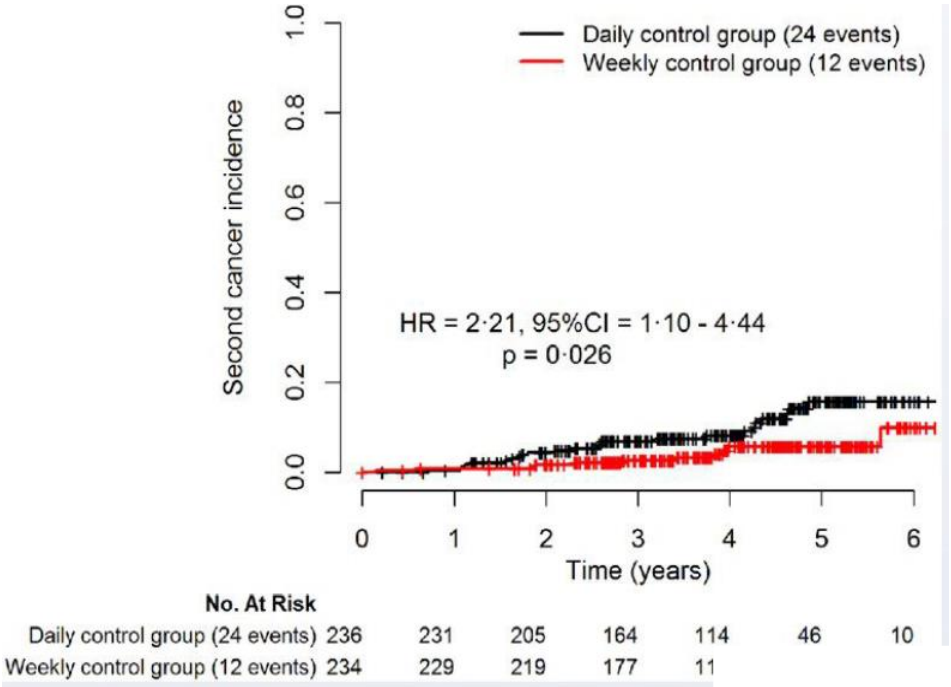
De Crevoisier, 2018



De Crevoisier, 2018

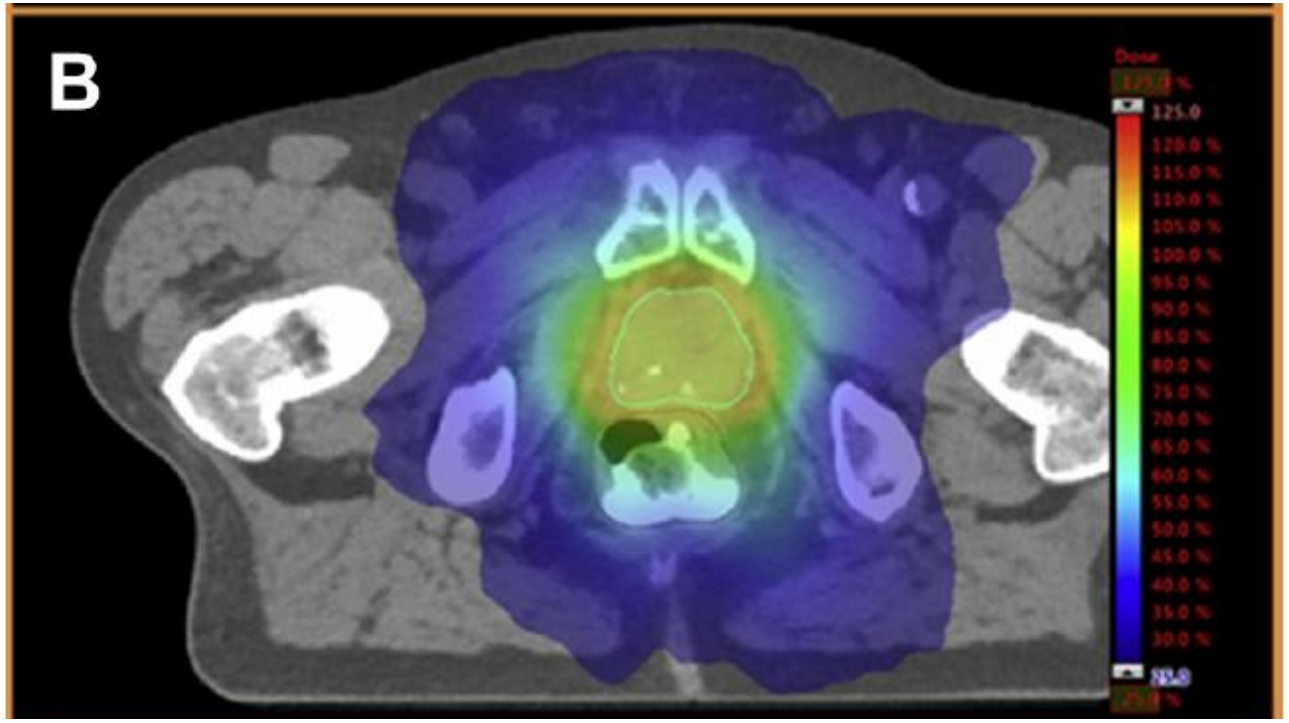


De Crevoisier, 2018



Second cancers occurred within a median of 31 months following randomization, located in the pelvis in only 18% of cases.

De Crevoisier, 2018



Second cancers occurred within a median of 31 months following randomization, located in the pelvis in only 18% of cases.

De Crevoisier, 2018

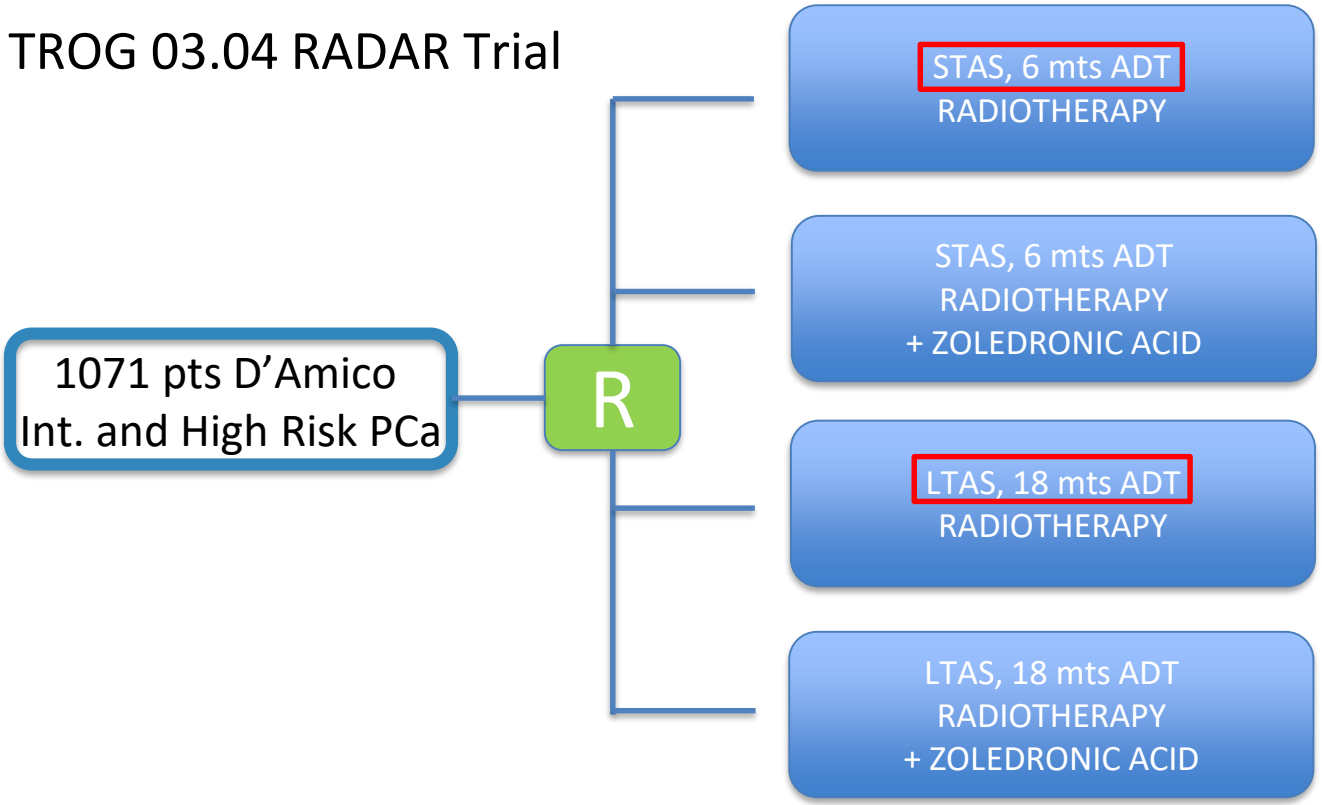
PROSTATE CANCER, Radiotherapy

SIU UPDATES
ASCO GU
ASCO GENITOURINARY CANCER SYMPOSIUM

TEN YEARS RESULTS of theTROG 03-04 RADAR TRIAL

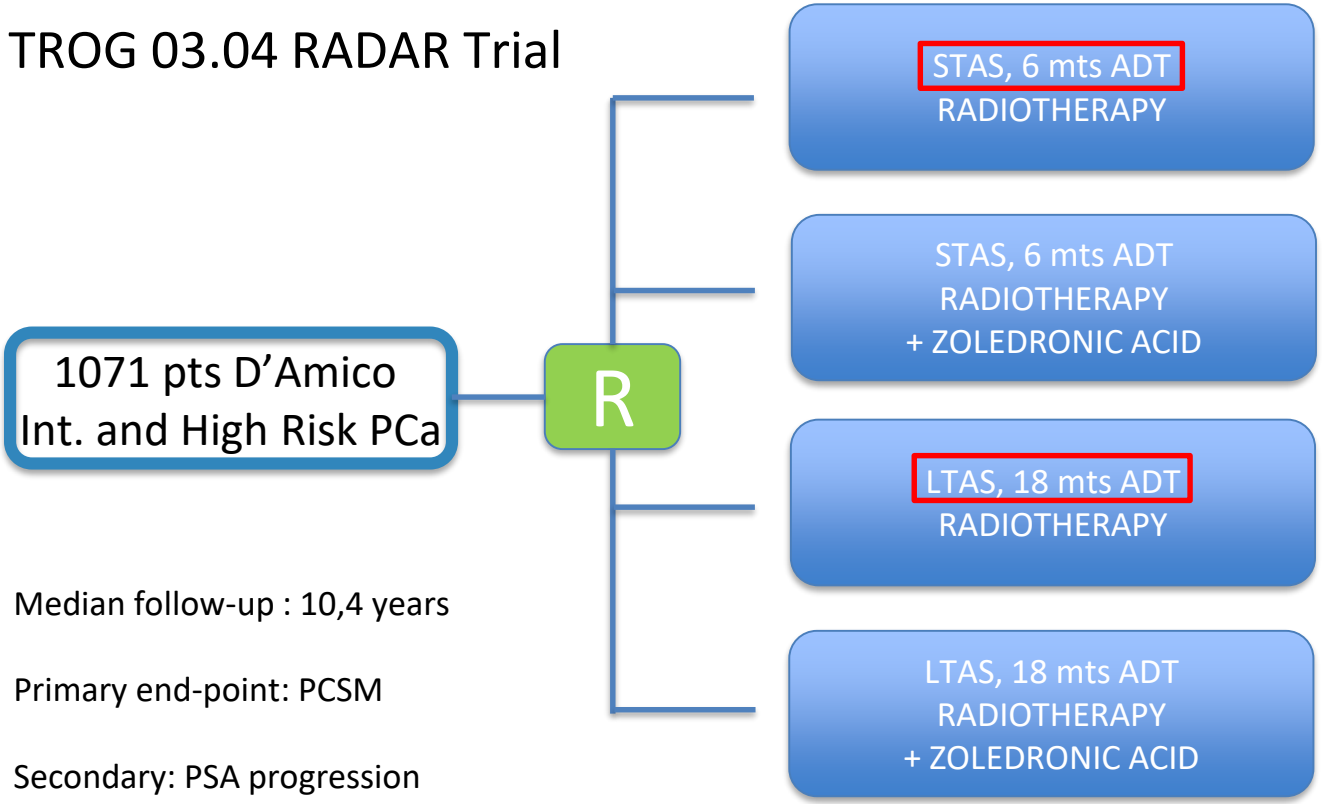
D. Joseph on behalf of the TROG group

TROG 03.04 RADAR Trial



Denham et al, Lancet Oncol 2012

TROG 03.04 RADAR Trial



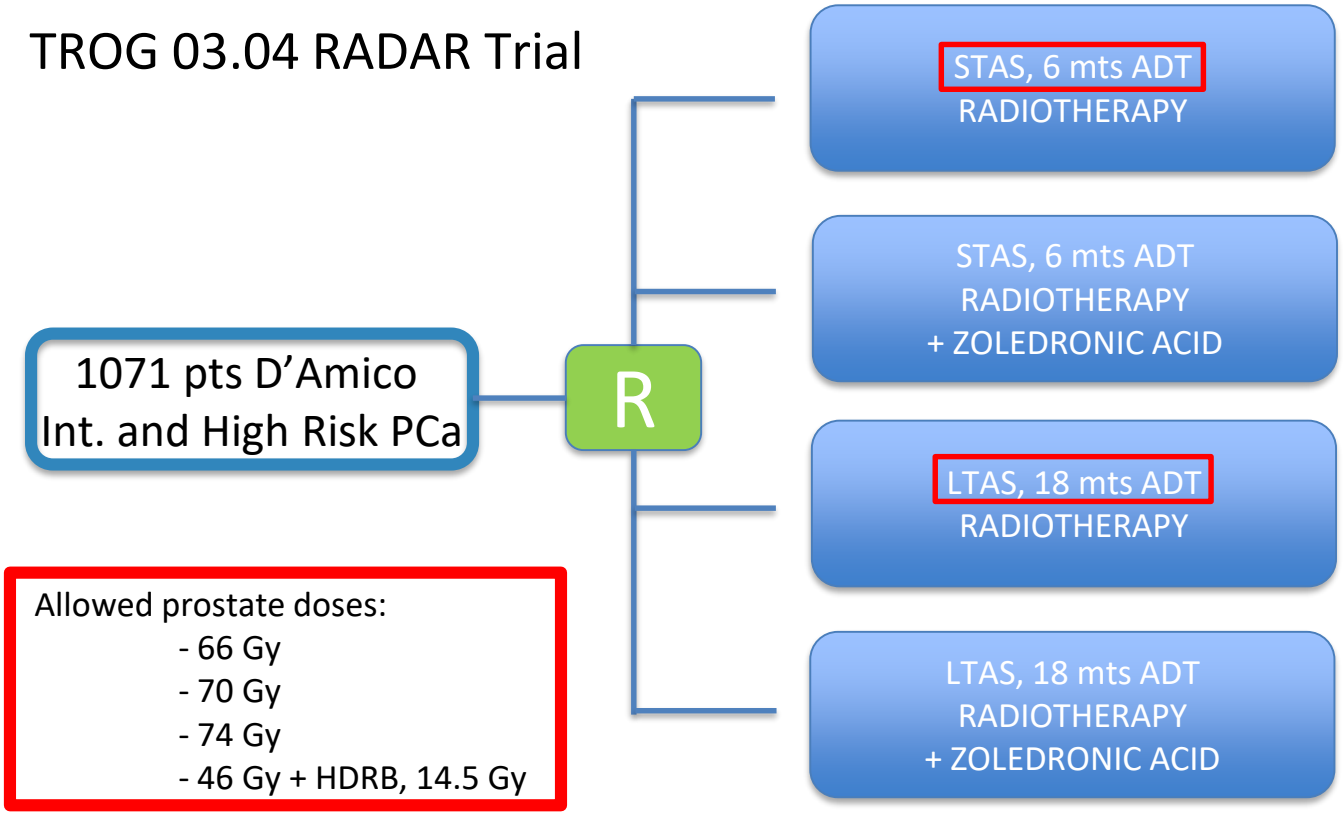
Median follow-up : 10,4 years

Primary end-point: PCSM

Secondary: PSA progression
OS, PR Toxicity and QoL
time to castration-resistance

Denham et al, Lancet Oncol 2012

TROG 03.04 RADAR Trial



Denham et al, Lancet Oncol 2012

18 versus 6 months ADT for Int to High risk PCa

- 30 % reduction in PCSM
- 29 % decrease in Distant Progression
- 35 % decrease in PSA Progression

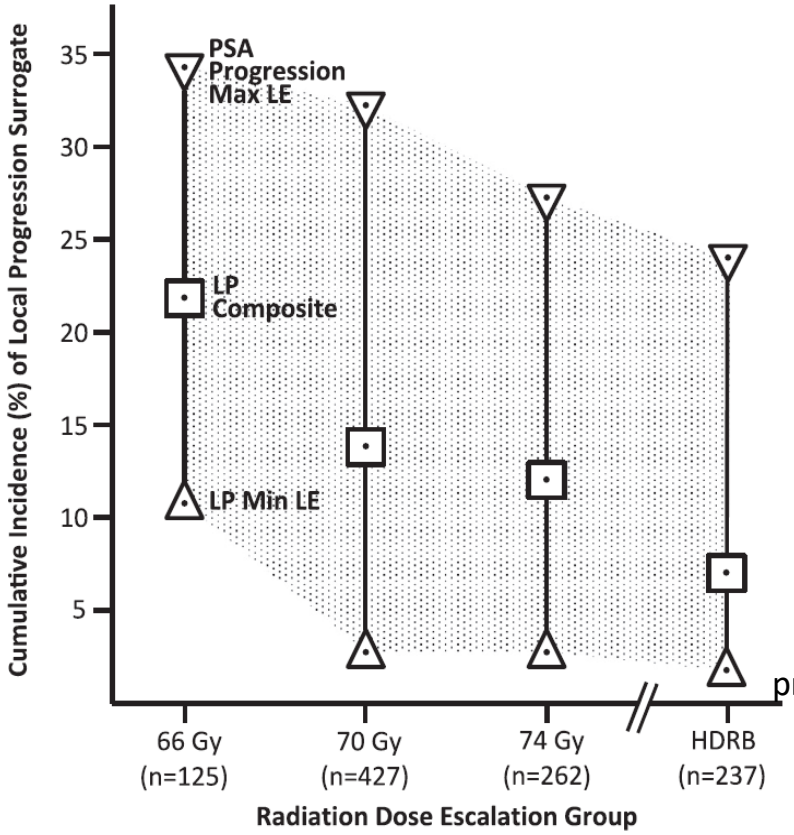
TROG 03.04 RADAR Trial

18 versus 6 months ADT for Int to High risk PCa

- 30 % reduction in PCSM
- 29 % decrease in Distant Progression
- 35 % decrease in PSA Progression

- time to castration-resistant state was decreased with a HR = 0.63 (p = 0,004)
- NO difference in OS
- NO difference in PR Toxicity or QoL
- any significant impact with the addition of Zoledronic acid

TROG 03.04 RADAR Trial



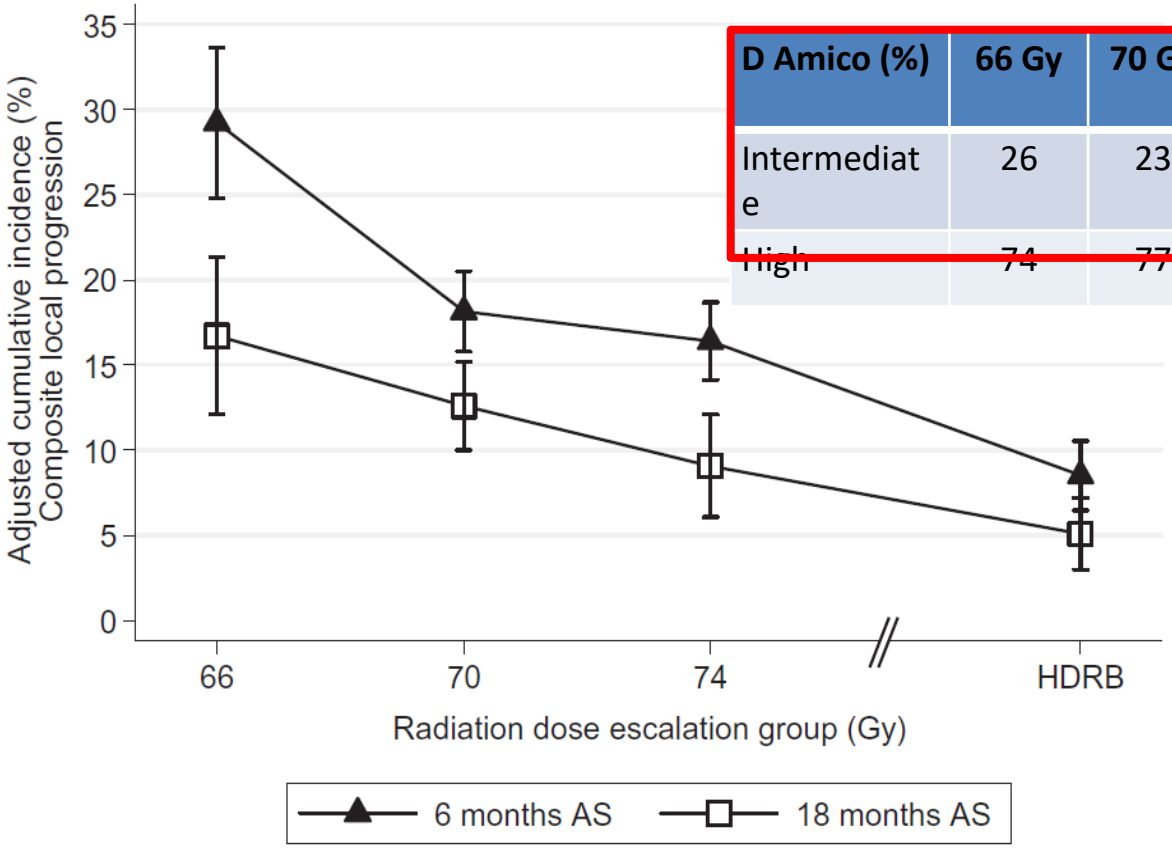
Cumulative incidence estimates in the four radiation dose escalation groups at 6,5 years post-randomisation for 3 potential surrogate endpoints for local prostatic progression

Local Progression Surrogates:

- PSA progression
- Clinically detected Local progression
- PSA DT

TROG 03.04 RADAR Trial

Denham et al, R&O, 2015



D Amico (%)	66 Gy	70 Gy	74 Gy	HDR B
Intermediate	26	23	22	8
High	74	77	78	92

TROG 03.04 RADAR Trial

Denham et al, R&O, 2015

	0 Gy	74 Gy	HDR B
	23	22	8
	77	78	92

Adjusted cumulative incidence (%)
Composite local progression

35
30
25
20
15
10
5
0

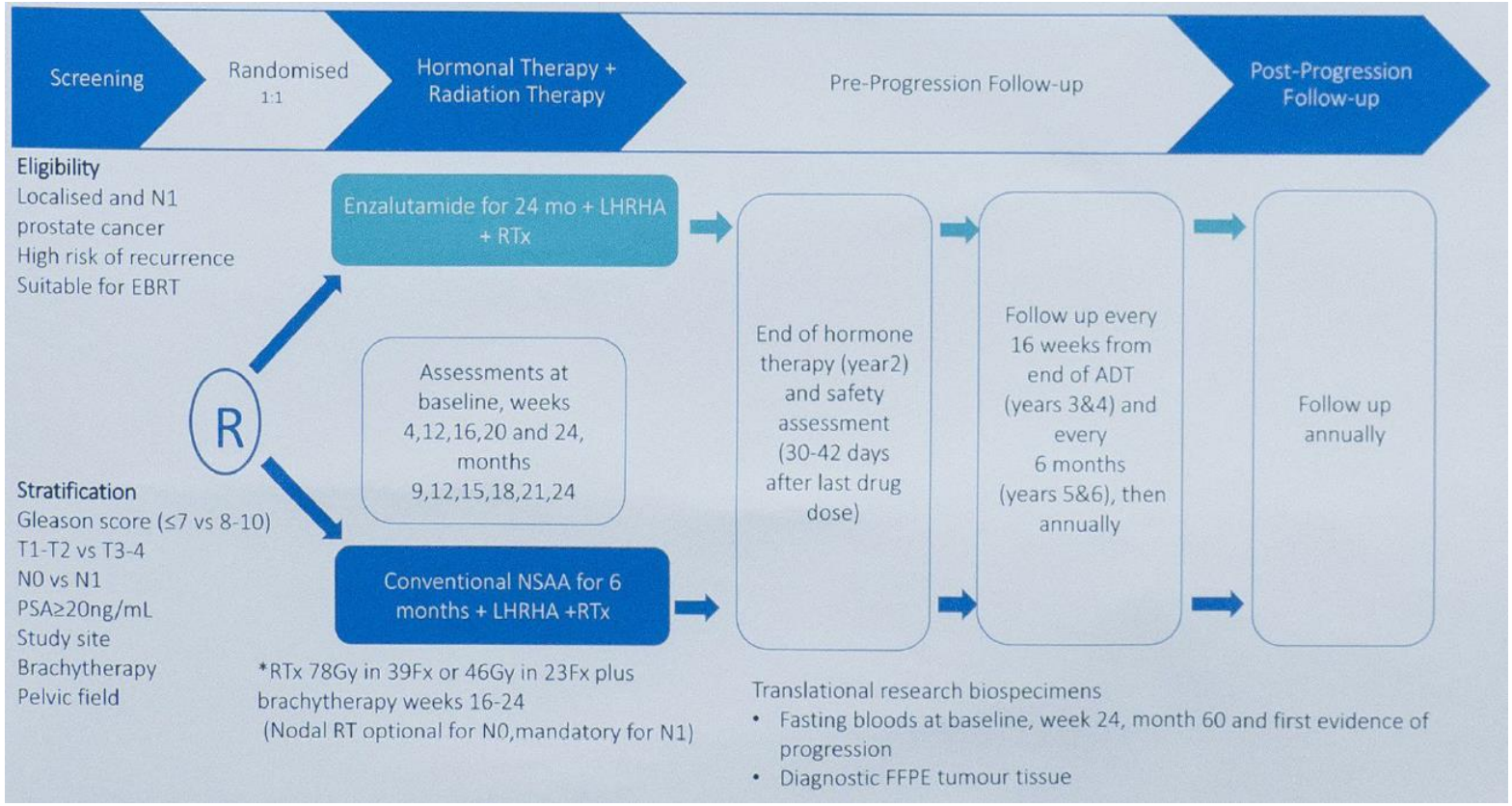
TROG 03.04 RAD

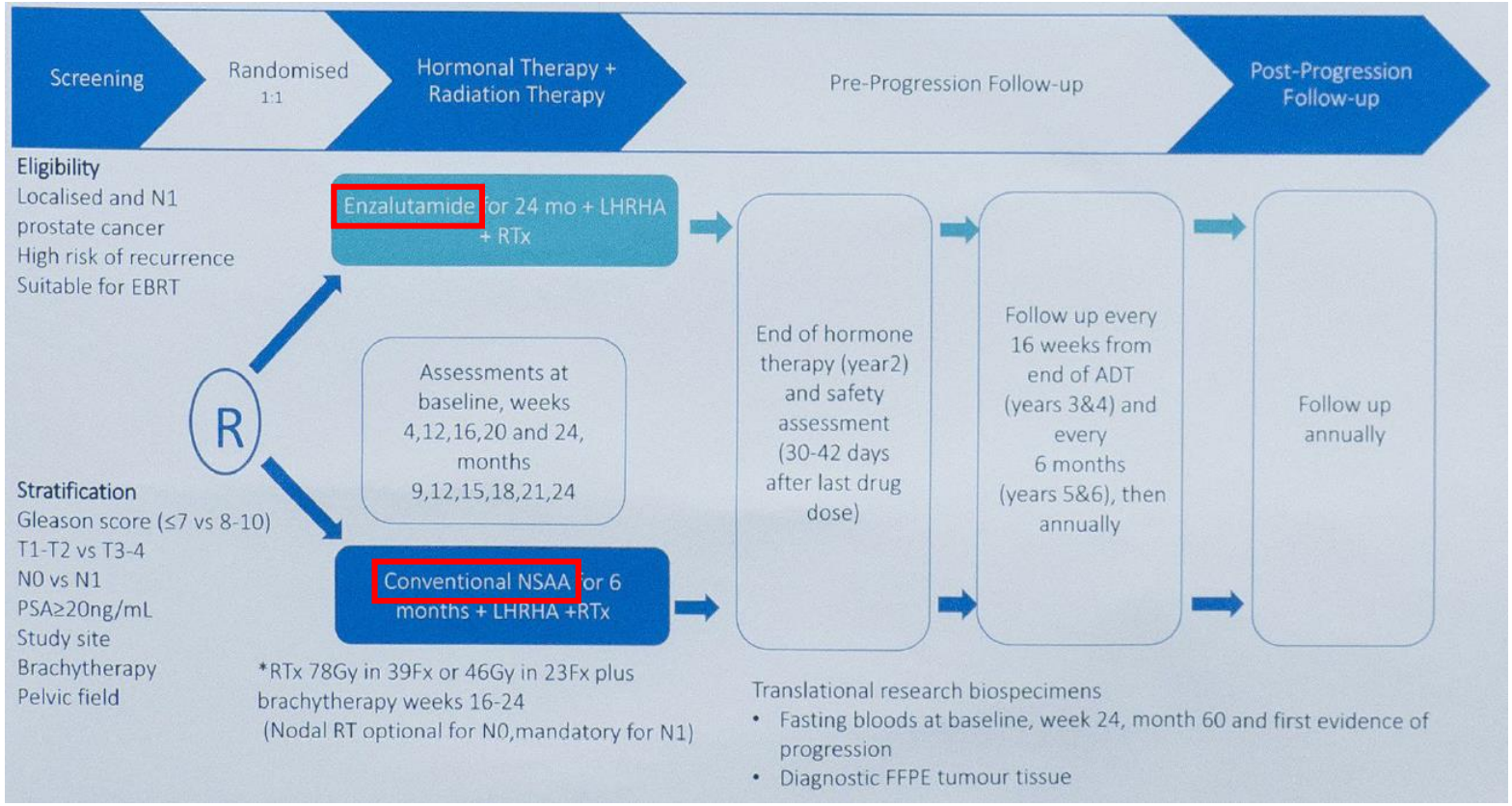
et al, R&O, 2015

PROSTATE CANCER, Radiotherapy

ENZARAD, ANZUP 13-03. HIGH RISK LOCALIZED PCa, ADT +/- ENZALUTAMIDE: A PHASE III TRIAL

S. Williams on behalf of the ANZUP Trial Group


Screening
Randomised
1:1
Hormonal Therapy + Radiation Therapy
Pre-Progression Follow-up
Post-Progression Follow-up
Eligibility
Localised and N1 prostate cancer
High risk of recurrence
Suitable for EBRT
R
Stratification
Gleason score (≤7 vs 8-10)
T1-T2 vs T3-4
N0 vs N1
PSA≥20ng/mL
Study site
Brachytherapy
Pelvic field
Enzalutamide for 24 mo + LHRHA + RTx
Conventional NSAA for 6 months + LHRHA +RTx
Assessments at baseline, weeks 4,12,16,20 and 24, months 9,12,15,18,21,24
End of hormone therapy (year2) and safety assessment (30-42 days after last drug dose)
Follow up every 16 weeks from end of ADT (years 3&4) and every 6 months (years 5&6), then annually
Follow up annually
*RTx 78Gy in 39Fx or 46Gy in 23Fx plus brachytherapy weeks 16-24
(Nodal RT optional for N0,mandatory for N1)
Translational research biospecimens
• Fasting bloods at baseline, week 24, month 60 and first evidence of progression
• Diagnostic FFPE tumour tissue


Screening
Randomised
1:1
Hormonal Therapy + Radiation Therapy
Pre-Progression Follow-up
Post-Progression Follow-up
Eligibility
Localised and N1 prostate cancer
High risk of recurrence
Suitable for EBRT
Enzalutamide for 24 mo + LHRHA + RTx
R
Assessments at baseline, weeks 4,12,16,20 and 24, months 9,12,15,18,21,24
Conventional NSAA for 6 months + LHRHA +RTx
Stratification
Gleason score (≤7 vs 8-10)
T1-T2 vs T3-4
N0 vs N1
PSA≥20ng/mL
Study site
Brachytherapy
Pelvic field
*RTx 78Gy in 39Fx or 46Gy in 23Fx plus brachytherapy weeks 16-24
(Nodal RT optional for N0,mandatory for N1)
End of hormone therapy (year2) and safety assessment (30-42 days after last drug dose)
Follow up every 16 weeks from end of ADT (years 3&4) and every 6 months (years 5&6), then annually
Follow up annually
Translational research biospecimens
• Fasting bloods at baseline, week 24, month 60 and first evidence of progression
• Diagnostic FFPE tumour tissue

Specific Objectives (Endpoints)

Primary objective (endpoint):

Overall survival (death from any cause)

Secondary objectives (endpoints):

1) Cause specific survival (prostate cancer, and other causes)
2) PSA progression-free survival (Phoenix criteria)
3) Clinical progression free survival
4) Time to subsequent hormonal therapy (restarting ADT)
5)Time to castration-resistant disease (PCWG2 criteria)
6) Metastasis-free survival
7) Adverse events (CTCAE v4.03)
8) Health-related quality of life (EORTC QLQC-30 & PR-25, EQ-5D-5L)
9) Health outcomes relative to costs (incremental cost effectiveness ratio)

Study Progress 07 February 2018

	Accrual	Sites Open/ Planned
Australia and New Zealand	455	44/44
Ireland	66	6/6
United Kingdom	98	11/11
United States	93	2/2
Europe	2	4/13
Total	714	67/76

PROSTATE CANCER, Radiotherapy

SIU UPDATES
ASCO GU
ASCO GENITOURINARY CANCER SYMPOSIUM

PHASE II TRIAL of RT for INT - HIGH RISK PCa +/- up-front ABI or ENZA …

Dana-Farber/Harvard Cancer Center Prostate Cancer Program,
Beth Israel Deaconess Medical Center and Dana Farber Cancer Institute

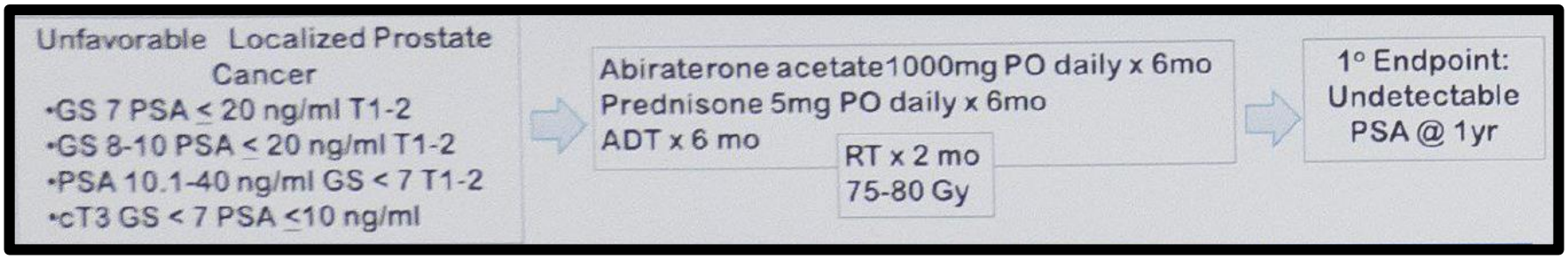
-Duke Cancer Institute Departments of Radiation Oncology, Medicine, and Biostatistics
MD Anderson Cancer Center, Departments of Radiation Oncology and Medicine

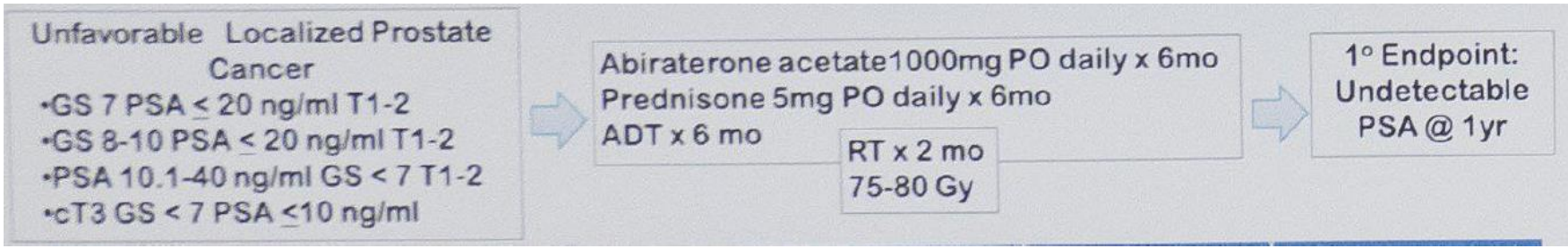
Phase III RCT of RT +/- ADT

	Number of patients	Characteristics	Hormone therapy	Results
RTOG 85-31[1]	977	T3/N+	Goserelin	OS, *P* < 0.004
EORTC 22861[2]	415	T1-2, G3 T3-4	Goserelin, **3 years** (AA, 1 month)	OS, *P* < 0.001
RTOG 92-02[3]	1,514	T2c-4, N0 PSA < 150 ng/mL	4 months TAB Goserelin, **2 years**	Gleason 8-10 OS, *P* = 0.04
RTOG 94-13[4]	1,292	T1c-4, PSA ≤ 100 ng/dL, risk N+ >15%	PORT vs. WPRT, NHT vs. AHT	WPRT+ NHT, better PFS

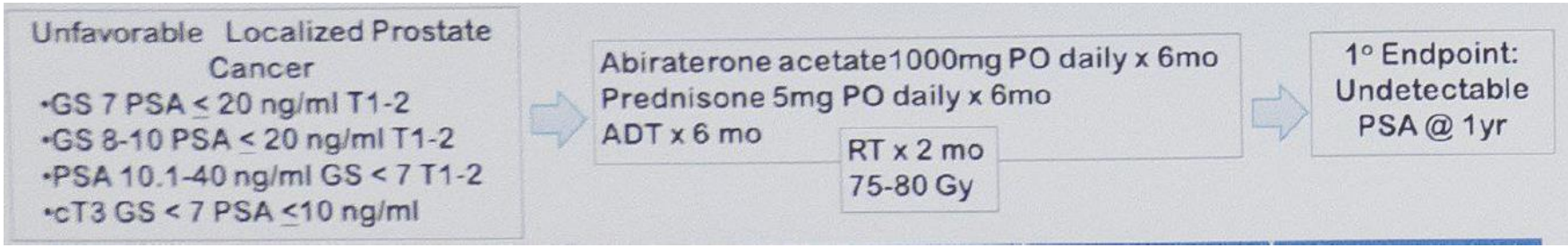
OS: overall survival; AA: antiandrogen; TAB: total androgen blockade; PORT: prostate-only RT; WPRT: whole-pelvic RT; NHT: neoadjuvant hormone therapy; PFS: progression-free survival

[1]Pilepich MV, et al. Proc Am Soc Clin Oncol 2003;22 (abstract n. 1530); [2]Bolla M, et al. Lancet 2002;360:103-8; [3]Hanks GE, et al. J Clin Oncol 2003;21:3972-78; [4]Roach M, et al. J Clin Oncol 2003;21:1904-11


Unfavorable Localized Prostate Cancer
•GS 7 PSA ≤ 20 ng/ml T1-2
•GS 8-10 PSA ≤ 20 ng/ml T1-2
•PSA 10.1-40 ng/ml GS < 7 T1-2
•cT3 GS < 7 PSA ≤10 ng/ml
Abiraterone acetate1000mg PO daily x 6mo
Prednisone 5mg PO daily x 6mo
ADT x 6 mo
RT x 2 mo
75-80 Gy
1° Endpoint:
Undetectable
PSA @ 1yr



open label phase II study of enzalutamide for 6 months as neo- and adjuvant treatment for intermediate risk PCa patients (NCCN criteria) receiving RT.



33 pts…

open label phase II study of enzalutamide for 6 months as neo- and adjuvant treatment for intermediate risk PCa patients (NCCN criteria) receiving RT.

47 pts….

CONCLUSIONS

In men with high risk intermediate or limited high risk PC, utilizing short-term ADT/AAP with definitive RT shows

1) high rate of testosterone recovery and good quality of life and
2) excellent PSA and disease control at 1 and 2 years with no relapses to date.

CONCLUSIONS

In men with high risk intermediate or limited high risk PC, utilizing short-term ADT/AAP with definitive RT shows

1) high rate of testosterone recovery and good quality of life and
2) excellent PSA and disease control at 1 and 2 years with no relapses to date.

Results

1.Using the endpoint of PSA nadir after 6 months of therapy, enzalutamide monotherapy was associated with an excellent PSA response, in line with that achieved with LHRH analogs in the same patient population

2.The treatment was well tolerated with the major side affects attributed to enzalutamide being fatigue, breast pain and hypertension

3.As expected, enzalutamide treatment was associated with higher androgen levels

CONCLUSIONS

In men with high risk intermediate or limited high risk PC, utilizing short-term ADT/AAP with definitive RT shows

1) high rate of testosterone recovery and good quality of life and
2) excellent PSA and disease control at 1 and 2 years with no relapses to date.

Conclusion

These findings warrant randomized trial of LHRH analogs versus enzalutamide as adjuvant treatment with radiation for intermediate risk prostate cancer

GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

…thank you for your attention