Standard indications of Radiotherapy associated with systemic treatment in prostate cancer

Present

- Association between Androgen Deprivation Therapy and RadioTherapy

Future

- Drugs already used for Metastatic Castration Resistant Prostate Cancer: Can be used concurrently with RT? Can they increase the therapeutic index at the time of primary treatment?
- Immunotherapy
- Radiosensitizers

Radiotherapy and Hormone Therapy Rationale

- Androgen deprivation has been shown to downregulate expression of vascular endothelial growth factor, causing apoptosis of endothelial cells and consequently decreased vascularization

- ADT may have a role in at least a transient “normalization” of tumour vascularization not only by reducing leaky immature tumour vessels, but also by causing the death of perivascular cells and thus causing decreased interstitial pressure

- Milosevic *et al.* they were the first authors to prove clinically that ADT increases prostate cancer oxygenation

- Systemically, ADT may prevent the dissemination of micrometastasis because of inhibition of DNA synthesis and cell proliferation, and an increased apoptotic ratio

- There is also some evidence of a tumoricidal immune system response triggered by androgen suppression

Jain RK. Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. *Science* 2005;307:58–62.9
Milosevic M, Chung P, Parker C, *et al.* Androgen withdrawal in patients reduces prostate cancer hypoxia: implications for disease progression and radiation response. *Cancer Res* 2007;67:6022–5.
Roden AC, Moser MT, Tri SD, *et al.* Augmentation of T cell levels and responses induced by androgen deprivation. *J Immunol* 2004;173:6098–108

ADT and Radiotherapy

- Prostate cancer was identified in the 1940s as a tumor driven by the androgen axis
- Although it was used initially for men with metastatic disease, in vivo data suggested that the combination of ADT before radiation resulted in better tumor eradication than radiation alone
- A succession of subsequent randomized studies have built a compelling case for the benefit from the addition of ADT to radiation for men with intermediate-risk and high-risk prostate cancer, although questions remain about the duration of ADT and associated toxicities
- Trials have focused both on radiation alone versus radiation in combination with androgen suppression as well as the optimal duration of hormonal therapy with the radiation. These have generally supported the use of ADT and radiation in combination
- A meta-analysis of prospective trials of androgen deprivation in non metastatic prostate cancer showed a 30% reduction in the relative risk of prostate cancer-specific mortality and a 14% reduction in the relative risk of all-cause mortality with the use of ADT

Nguyen PL, Je Y, Schutz FAB, et al. Association of androgen deprivation therapy with cardiovascular death in patients with prostate cancer: a meta-analysis of randomized trials. JAMA. 2011;306:2359-2366

ADT and Radiotherapy

- **NeoAdjuvant**

  ***Additive Effect*:**
  suppression of the growth of the prostate cancer cells:
  Dosimetric Benefit

- **Concomitant**

  ***Over-Additive Effect*:**
  stimulates and increases apoptosis promoted by radiotherapy:
  Local Benefit

- **Adjuvant**

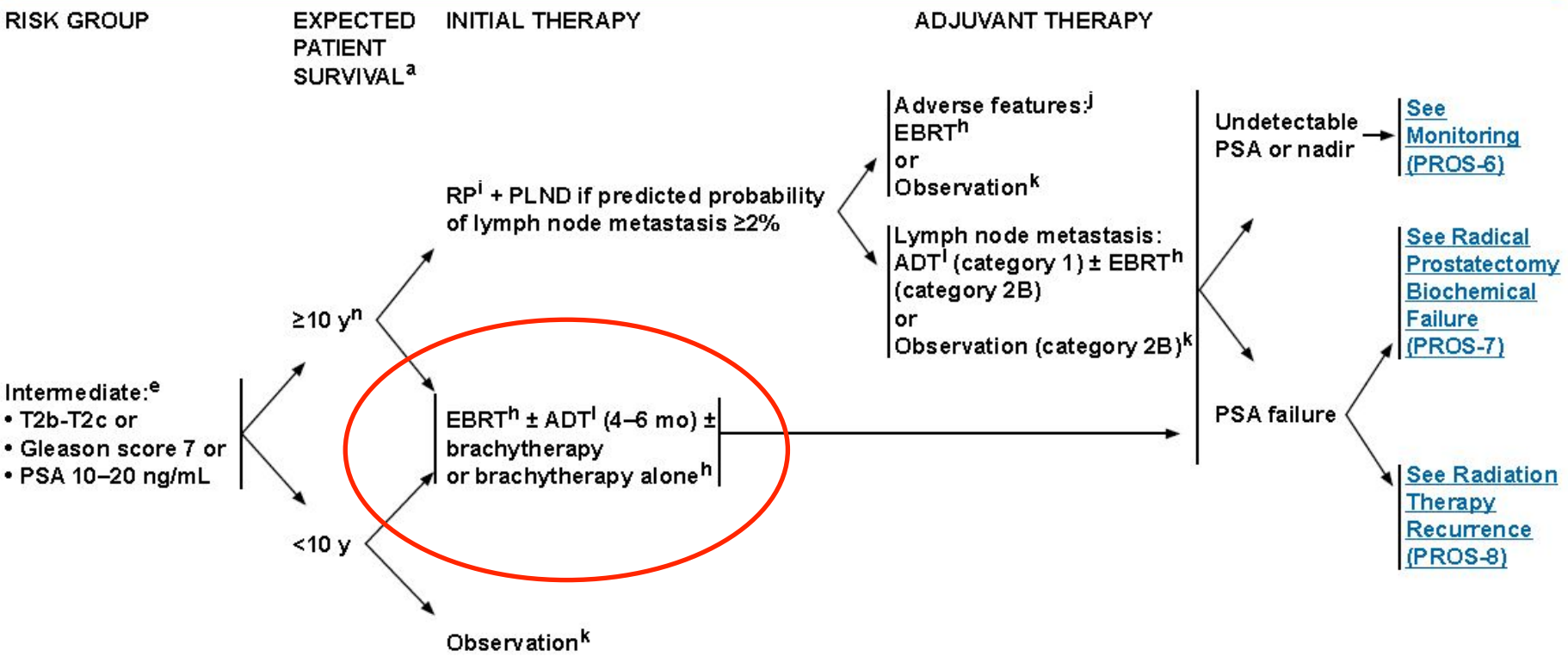
  ***Cooperative Effect*:**
  inhibits any residual quiescent clones :
  Local and Sistemic Benefit

Moule RN, Hoskin PJ, Surg Oncol, 2009

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2015
Prostate Cancer

NCCN Guidelines Index
Prostate Table of Contents
Discussion



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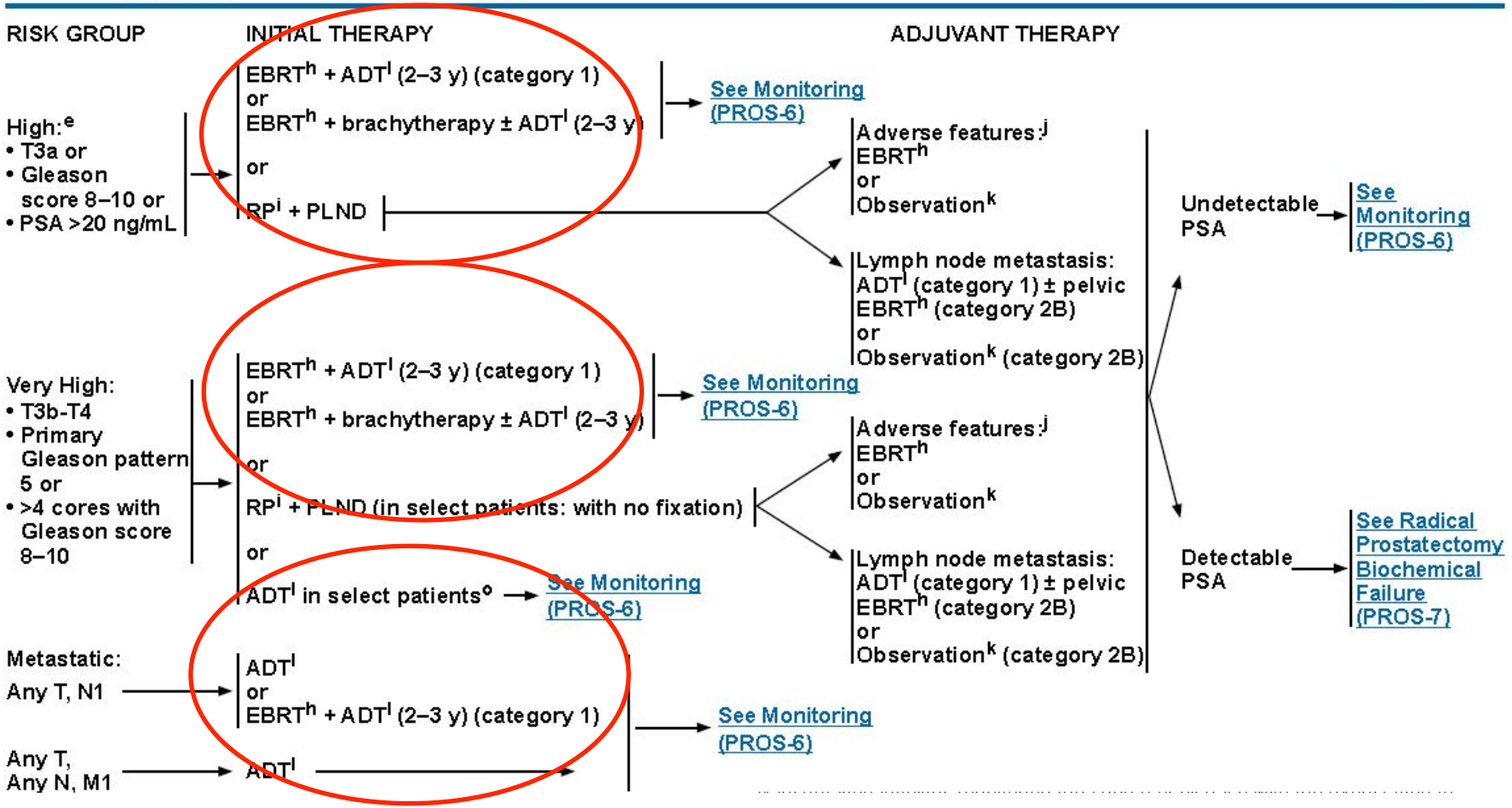

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NCCN Guidelines Version 1.2015
Prostate Cancer

- **Low risk** (≤ T2a and Gleason score ≤ 3+3 and PSA < 10 ng/mL) : **no ADT**
- **Intermediate risk** (T2b-c and/or Gleason score ≥ 7 and/or PSA 10-20 ng/mL): **short term ADT (4-6 months) + EBRT**
- **High risk** (T3a or Gleason 8-10 or PSA > 20 ng/mL) and Very High risk (T3b-T4 or Primary Gleason score 5 or > 4 cores with Gleason score 8-10): **long term ADT (2-3 years) + EBRT**

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Prostate Cancer

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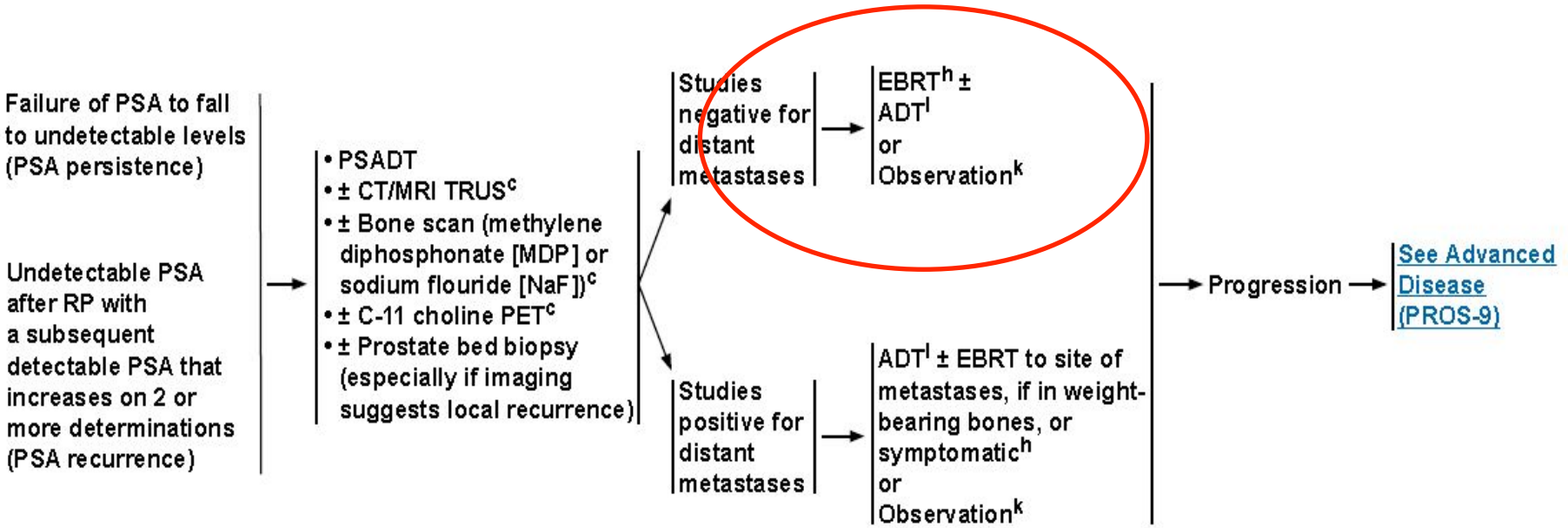
Discussion

RADICAL PROSTATECTOMY BIOCHEMICAL FAILURE



Clinical studies
Localized and Locally advanced

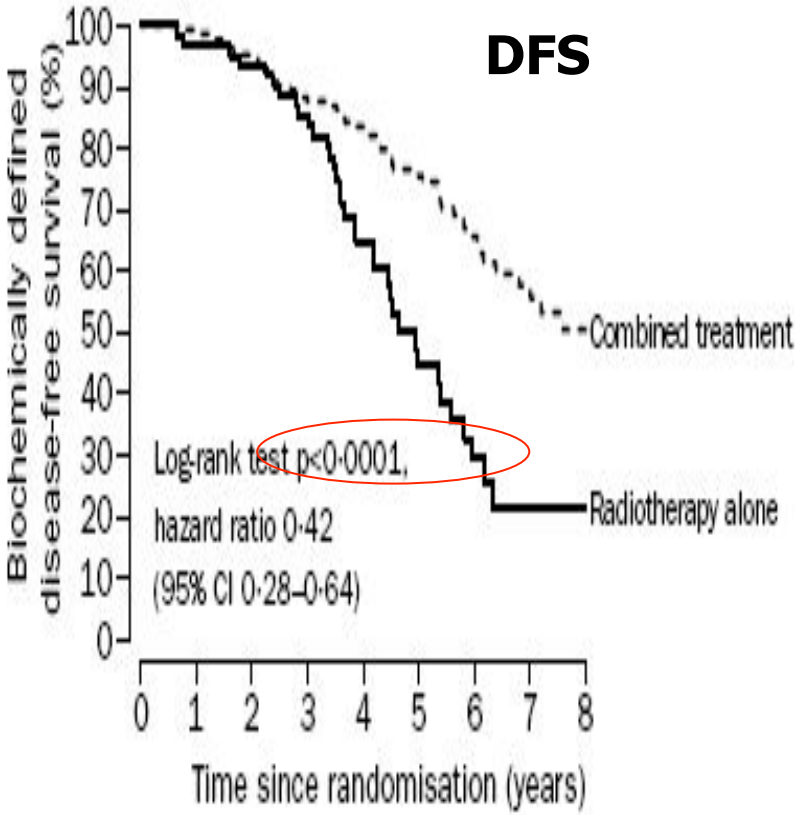
QUESTION	STUDY	DISEASE STAGE (%)	GLEASON SCORE (%)	NO.	MEDIAN FOLLOW-UP, y	TREATMENT ARMS	OVERALL SURVIVAL, %	PROSTATE CANCER-SPECIFIC MORTALITY, %
Localized disease: RT vs RT + ADT	TROG 96.01[119]	T2b (26), T2c (34), T3,T4 (40), N0M0	≤6 (44), 7 (38), ≥8 (17)	818	10.6	RT 66 Gy	10 y, 57.5	10 y, 22
						RT + 3 mo ADT	10 y, 63.3*	10 y, 18.9*
						RT + 6 mo ADT	10 y, 70.8	10 y, 11.4
	DFCI 95-096[115]	T1b (2), T1c (46), T2a (23), T2b (30), N0M0	≤6 (28), 7 (58), ≥8 (15)	206	7.6	RT 67 Gy	8 y, 61	8 y, 12
						RT + 6 mo ADT	8 y, 74	8 y, 3
	RTOG 94-08[105]	T1 (49), T2 (51), N0M0	≤6 (62), 7 (28), ≥8 (9)	1979	9.1	RT 66.6 Gy	10 y, 57	10 y, 8
						RT + 4 mo ADT	10 y, 62	10 y, 4
Locally advanced disease: RT vs RT + ADT	RTOG 86-10[120]	T2 (30), T3,T4 (70), N0 (92), N1 (8), M0	≤6 (30), ≥7 (70)	471	12.6	RT 65-70 Gy	10 y, 34	10 y, 36
						RT + 4 mo ADT	10 y, 43*	10 y, 23
	EORTC 22863[121]	T1 (1), T2 (10), T3 (80), T4 (9) N0 (89), M0	≤6 (62), 7 (28), ≥8 (9)	415	9.1	RT 70 Gy	10 y, 39.8	10 y, 30.4
						RT + 36 mo ADT	10 y, 58.1	10 y, 10.3
Locally advanced disease: ADT vs RT + ADT	SPCG-7[2]	T1 (2), T2 (19), T3 (78), N0M0	NA	875	7.6	ADT	10 y, 61	10 y, 24
						ADT + RT 70 Gy	10 y, 70	10 y, 12
	PR.3/PRO7[3]	T2 (13), T3 (83), T4 (4), NXM0	≤7 (81), 8-10 (18)	1205	6	ADT	7 y, 66	7 y, 19
						ADT + RT 65-69 Gy	7 y, 74	7 y, 9

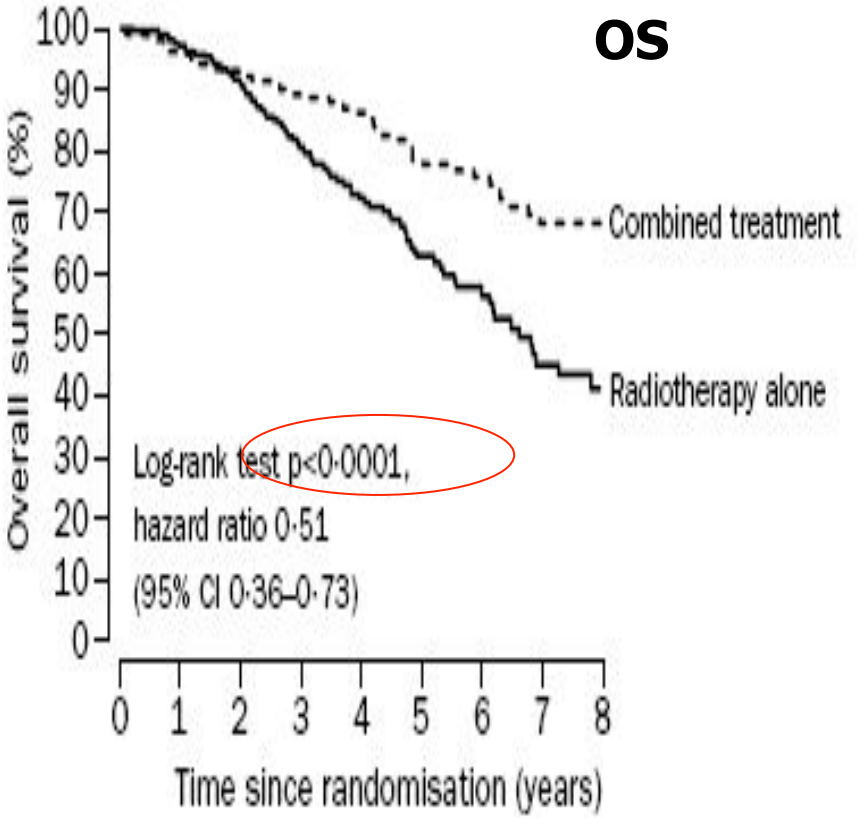
Martin NE, D'Amico AV. Progress and controversies: Radiation therapy for prostate cancer. CA Cancer J Clin. 2014 Sep 18

Articles

Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomised trial

Michel Bolla, Laurence Collette, Léo Blank, Padraig Warde, Jean Bernard Dubois, René-Olivier Mirimanoff, Guy Storme, Jacques Bernier, Abraham Kuten, Cora Sternberg, Johan Mattelaer, José Lopez Torecilla, J Rafael Pfeffer, Carmel Lino Cutajar, Alfredo Zurlo, Marianne Pierart

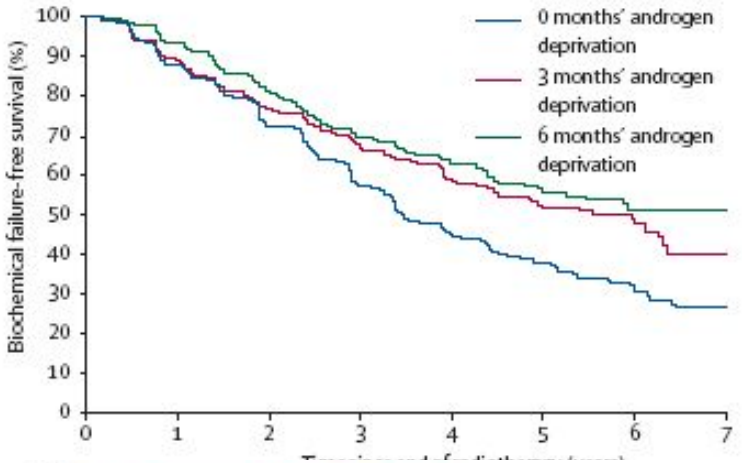


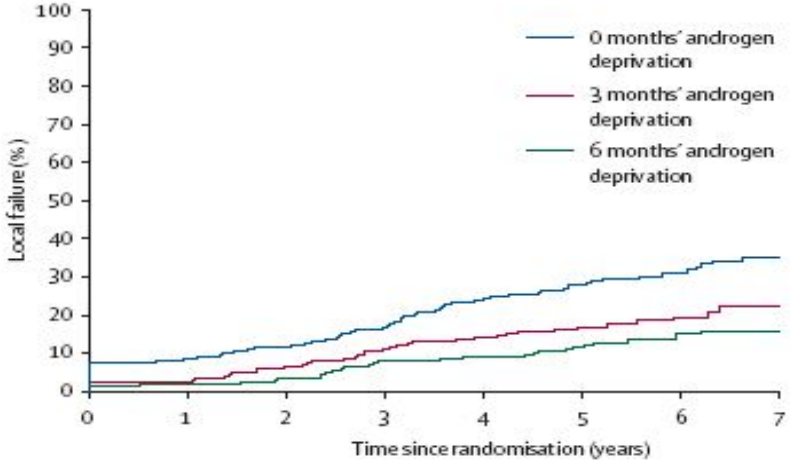


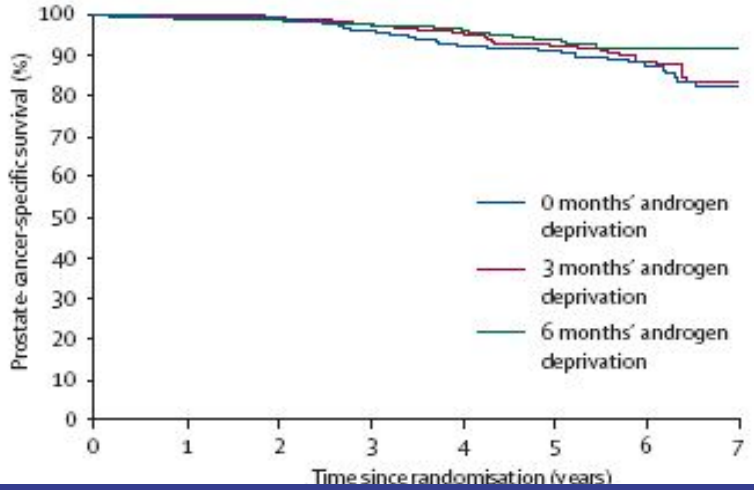
T1-T4, N0-1, RT pelvis + prostate 70 Gy, HT for 3 years

Short-term androgen deprivation and radiotherapy for locally advanced prostate cancer: results from the Trans-Tasman Radiation Oncology Group 96.01 randomised controlled trial

James W Denham, Allison Steigler, David S Lamb, David Joseph, Hedy Mameghan, Sandra Turner, John Matthews, Ian Franklin, Chris Atkinson, John North, Michael Poulsen, David Christie, Nigel A Spry, Keen-Hun Tai, Chris Wynne, Gillian Duchesne, Olga Kovacev, Catherine D'Este







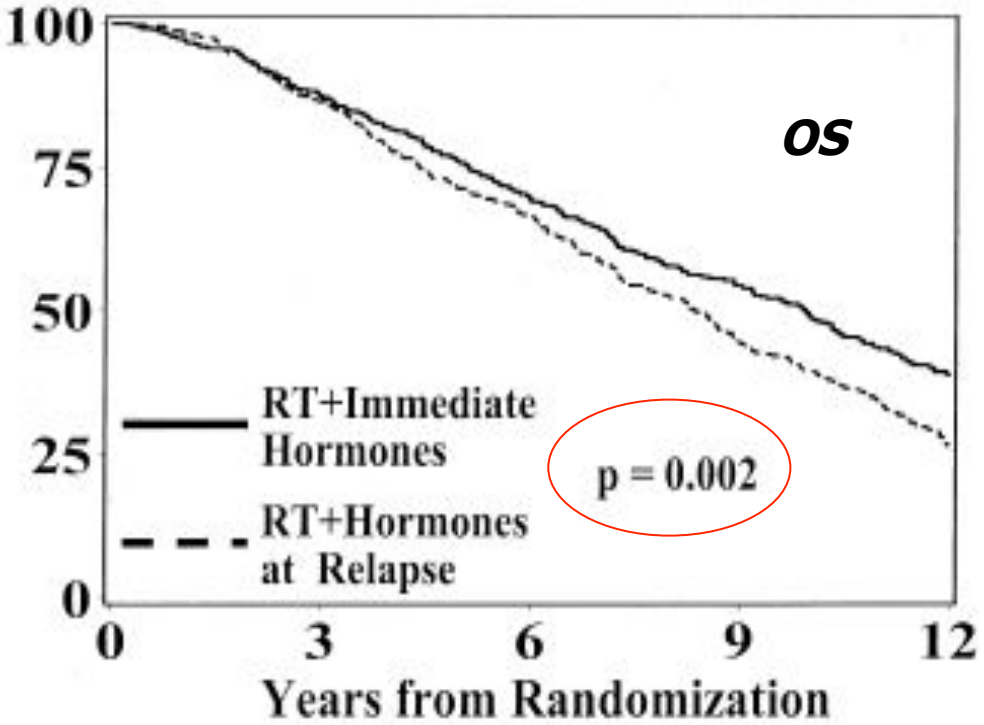
- **3 months'** androgen deprivation reduced **biochemical failure**, increased **disease-free survival**
- **6 months'** androgen deprivation augmented these effects and also improved **cancer-specific survival**.

Denham, Lancet 2005

CLINICAL INVESTIGATION Prostate

ANDROGEN SUPPRESSION ADJUVANT TO DEFINITIVE RADIOTHERAPY IN PROSTATE CARCINOMA—LONG-TERM RESULTS OF PHASE III RTOG 85-31

MILJENKO V. PILEPICH, M.D.,* KATHRYN WINTER, M.S.,† COLLEEN A. LAWTON, M.D.,‡ ROBERT E. KRISCH, M.D.,§ HARVEY B. WOLKOV, M.D.,‖ BENJAMIN MOVSAS, M.D.,¶ EUGEN B. HUG, M.D.,# SUCHA O. ASBELL, M.D.,** AND DAVID GRIGNON, M.D.††



OS, 10-years, → **49% vs 39%**
Local Failure, 10 years → **23% vs 38%**

prostatic and pelvic RT + adjuvant LHRH

vs.

RT alone plus HT at time of relapse

-HT started during the last week of RT and continued indefinitely or until signs of progression.
- >= T3 or N+

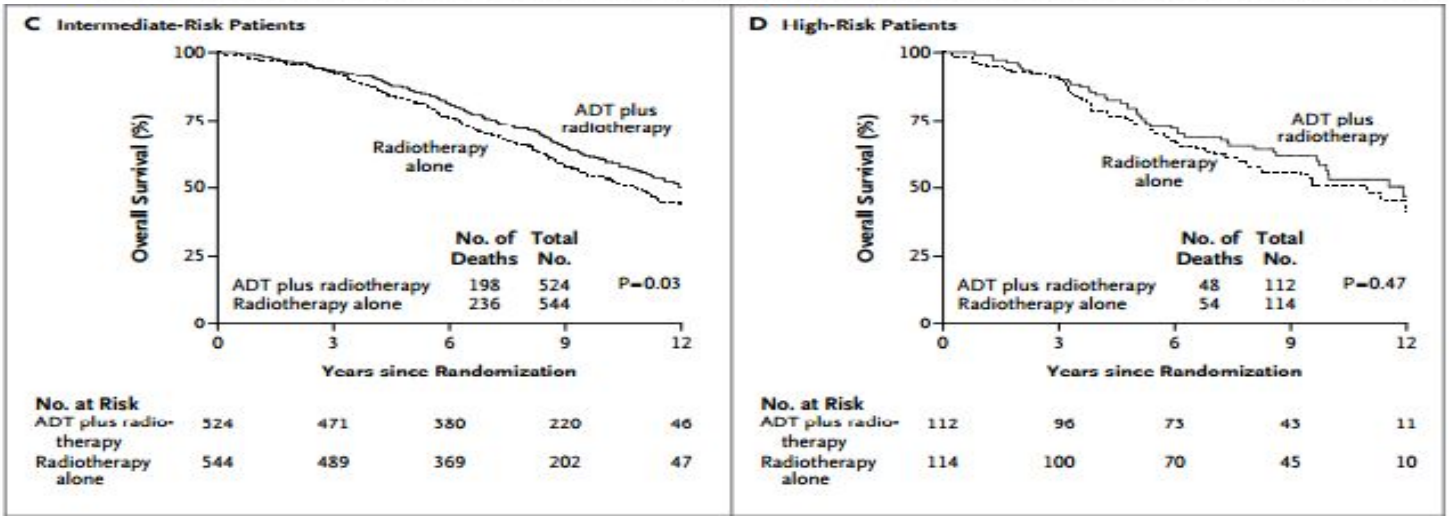
Pilepich, IJROBP, 2005

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 14, 2011 VOL. 365 NO. 2

Radiotherapy and Short-Term Androgen Deprivation for Localized Prostate Cancer

Christopher U. Jones, M.D., Daniel Hunt, Ph.D., David G. McGowan, M.B., Ch.B., Mahul B. Amin, M.D., Michael P. Chetner, M.D., Deborah W. Bruner, R.N., Ph.D., Mark H. Leibenhaut, M.D., Siraj M. Husain, M.D., Marvin Rotman, M.D., Luis Souhami, M.D., Howard M. Sandler, M.D., and William U. Shipley, M.D.

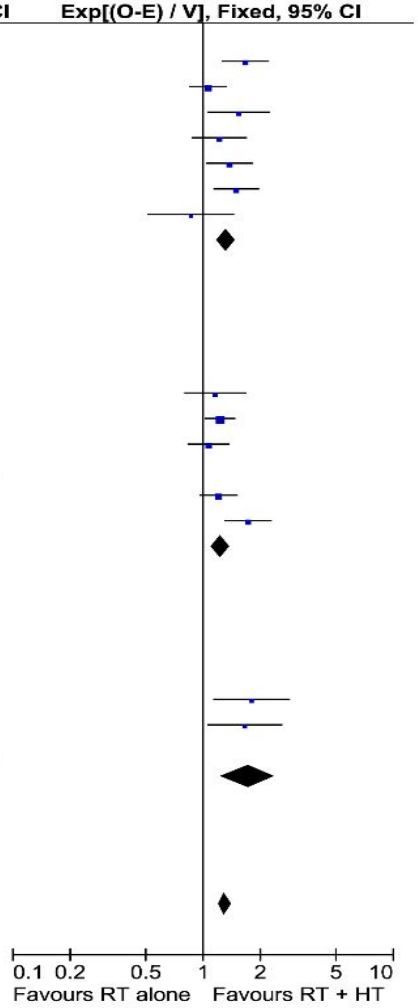


Among patients with stage T1b, T1c, T2a, or T2b prostate adenocarcinoma and a PSA level of 20 ng per milliliter or less, the use of short-term **ADT for 4 months before and during radiotherapy** was associated with significantly decreased disease-specific mortality and increased overall survival

N ENGL J MED 365;2 NEJM.ORG JULY 14, 2011

Radiotherapy Alone versus Radiotherapy Plus Hormone Therapy: Overall survival

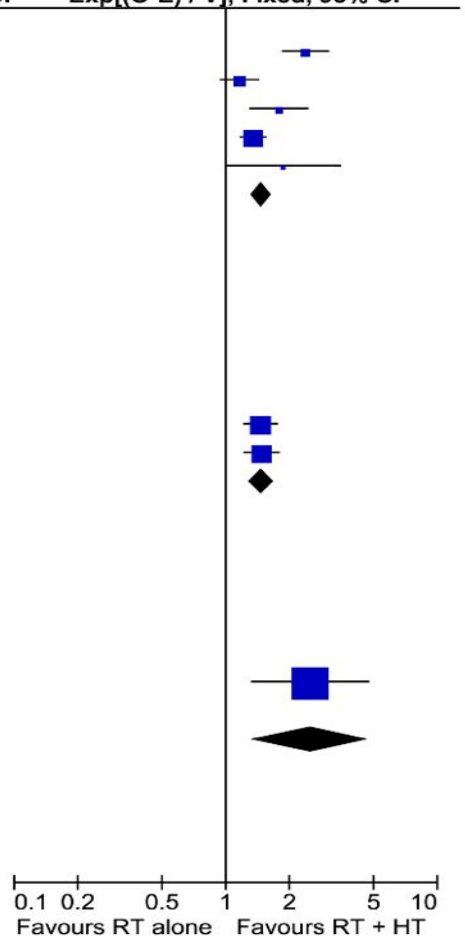
Study or Subgroup	RT alone Events	RT alone Total	RT + HT Events	RT + HT Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
1.1.1 Radiotherapy alone v radiotherapy and adjuvant hormone therapy								
EORTC 22863	112	208	80	207	23.84	46.67	7.2%	1.67 [1.25, 2.22]
EPC 23-25_localised	146	527	143	538	4.47	72.24	11.2%	1.06 [0.84, 1.34]
EPC23-25_locally advanced	61	144	49	161	11.71	27.17	4.2%	1.54 [1.06, 2.24]
RTOG 85-31_Gleason 2-6	77	129	64	125	6.95	34.95	5.4%	1.22 [0.88, 1.70]
RTOG 85-31_Gleason 7	104	160	91	172	15.51	48.53	7.5%	1.38 [1.04, 1.82]
RTOG 85-31_Gleason 8-10	107	137	94	139	20.05	50.04	7.8%	1.49 [1.13, 1.97]
Zagars	27	40	29	38	-2.07	13.98	2.2%	0.86 [0.51, 1.46]
Subtotal (95% CI)		**1345**		**1380**			**45.5%**	**1.32 [1.17, 1.47]**
Total events	634		550					
Heterogeneity: Chi² = 10.13, df = 6 (P = 0.12); I² = 41%								
Test for overall effect: Z = 4.70 (P < 0.00001)								
1.1.2 Radiotherapy alone v neoadjuvant hormone therapy and radiotherapy								
Jones_high risk	56	114	53	112	4.04	27.23	4.2%	1.16 [0.80, 1.69]
Jones_intermediate risk	250	544	204	524	23.25	112.33	17.4%	1.23 [1.02, 1.48]
Jones_low risk	120	334	116	351	3.99	58.98	9.1%	1.07 [0.83, 1.38]
L-101	0	0	0	0	0	0		Not estimable
RTOG 8610	154	232	129	224	13.03	70.2	10.9%	1.20 [0.95, 1.52]
TROG 96.01	115	270	78	267	25.35	46.48	7.2%	1.73 [1.29, 2.30]
Subtotal (95% CI)		**1494**		**1478**			**48.9%**	**1.25 [1.12, 1.39]**
Total events	695		580					
Heterogeneity: Chi² = 6.53, df = 4 (P = 0.16); I² = 39%								
Test for overall effect: Z = 3.92 (P < 0.0001)								
1.1.3 Radiotherapy alone v neoadjuvant, concomitant and adjuvant hormone therapy + radiotherapy								
D'Amico	44	104	30	102	10.48	17.84	2.8%	1.80 [1.13, 2.86]
Granfors	0	46	0	45	9.33	18.5	2.9%	1.66 [1.05, 2.61]
L-101	0	0	0	0	0	0		Not estimable
Subtotal (95% CI)		**150**		**147**			**5.6%**	**1.72 [1.25, 2.39]**
Total events	44		30					
Heterogeneity: Chi² = 0.06, df = 1 (P = 0.80); I² = 0%								
Test for overall effect: Z = 3.29 (P = 0.001)								
Total (95% CI)		**2989**		**3005**			**100.0%**	**1.30 [1.20, 1.41]**
Total events	1373		1160					
Heterogeneity: Chi² = 20.21, df = 13 (P = 0.09); I² = 36%								
Test for overall effect: Z = 6.69 (P < 0.00001)								
Test for subgroup differences: Chi² = 3.48, df = 2 (P = 0.18), I² = 42.6%								



M. Schmidt-Hansen , P. Hoskin , P. Kirkbride , E. Hasler , N. Bromham, Hormone and Radiotherapy versus Hormone or Radiotherapy Alone for Non-metastatic Prostate Cancer: A Systematic Review with Meta-analyses ,Clinical Oncology Volume 26, Issue 10, October 2014, Pages e21–e46

Radiotherapy Alone versus Radiotherapy Plus Hormone Therapy: Disease-free Survival

Study or Subgroup	RT alone Events	RT alone Total	RT + HT Events	RT + HT Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
1.2.1 Radiotherapy alone v radiotherapy and adjuvant hormone therapy								
EORTC 22863	145	208	94	207	49.47	57.03	15.9%	2.38 [1.84, 3.09]
EPC 23-25_localised	175	527	165	538	12.81	84.93	23.7%	1.16 [0.94, 1.44]
EPC23-25_locally advanced	86	144	66	161	21.65	37.34	10.4%	1.79 [1.30, 2.46]
RTOG 85-31	360	468	322	477	50.72	169.97	47.3%	1.35 [1.16, 1.57]
Zagars	25	40	16	38	6.12	9.76	2.7%	1.87 [1.00, 3.51]
Subtotal (95% CI)		**1387**		**1421**			**100.0%**	**1.48 [1.33, 1.64]**
Total events	791		663					
Heterogeneity: Chi² = 21.18, df = 4 (P = 0.0003); I² = 81%								
Test for overall effect: Z = 7.43 (P < 0.00001)								
1.2.2 Radiotherapy alone v neoadjuvant hormone therapy and radiotherapy								
Jones	0	0	0	0	0	0		Not estimable
L-101	0	0	0	0	0	0		Not estimable
RTOG 8610	224	232	199	224	39.94	105.38	51.5%	1.46 [1.21, 1.77]
TROG 96.01	236	270	171	267	38.74	99.15	48.5%	1.48 [1.21, 1.80]
Subtotal (95% CI)		**502**		**491**			**100.0%**	**1.47 [1.28, 1.68]**
Total events	460		370					
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.93); I² = 0%								
Test for overall effect: Z = 5.50 (P < 0.00001)								
1.2.3 Radiotherapy alone v neoadjuvant, concomitant and adjuvant hormone therapy + radiotherapy								
D'Amico	0	0	0	0	0	0		Not estimable
Granfors	28	46	14	45	8.58	9.33	100.0%	2.51 [1.32, 4.76]
L-101	0	0	0	0	0	0		Not estimable
Subtotal (95% CI)		**46**		**45**			**100.0%**	**2.51 [1.32, 4.76]**
Total events	28		14					
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.81 (P = 0.005)								

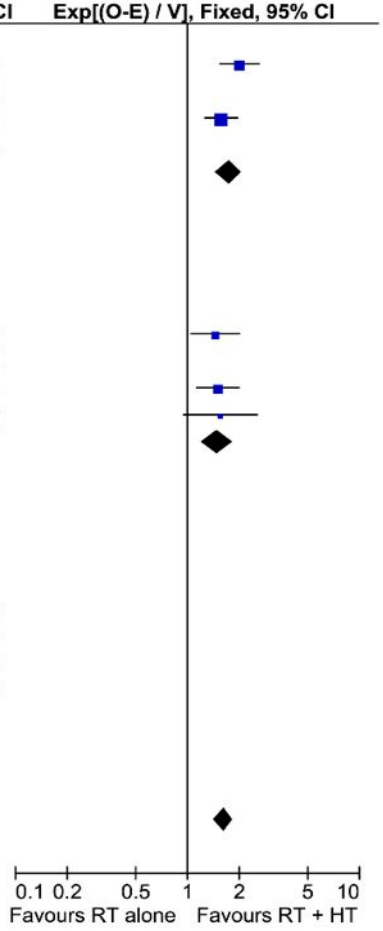


Test for subgroup differences: Chi² = 2.59, df = 2 (P = 0.27), I² = 22.7%

M. Schmidt-Hansen , P. Hoskin , P. Kirkbride , E. Hasler , N. Bromham, Hormone and Radiotherapy versus Hormone or Radiotherapy Alone for Non-metastatic Prostate Cancer: A Systematic Review with Meta-analyses ,Clinical Oncology Volume 26, Issue 10, October 2014, Pages e21–e46

Radiotherapy Alone versus Radiotherapy Plus Hormone Therapy: Distant metastasis-free survival

Study or Subgroup	RT alone Events	RT alone Total	RT + HT Events	RT + HT Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
1.3.1 Radiotherapy alone v radiotherapy and adjuvant hormone therapy								
EORTC 22863	0	208	0	207	36.96	53.32	23.9%	2.00 [1.53, 2.62]
EPC 23-25	0	0	0	0	0	0		Not estimable
RTOG 85-31	183	468	128	477	33.76	75.32	33.8%	1.57 [1.25, 1.96]
Zagars	0	0	0	0	0	0		Not estimable
Subtotal (95% CI)		**676**		**684**			**57.7%**	**1.73 [1.46, 2.06]**
Total events	183		128					
Heterogeneity: Chi² = 1.87, df = 1 (P = 0.17); I² = 47%								
Test for overall effect: Z = 6.24 (P < 0.00001)								
1.3.2 Radiotherapy alone v neoadjuvant hormone therapy and radiotherapy								
Jones	79	992	59	987	12.55	33.78	15.1%	1.45 [1.03, 2.03]
L-101	0	0	0	0	0	0		Not estimable
RTOG 8610	109	232	78	224	18.53	45.47	20.4%	1.50 [1.12, 2.01]
TROG 96.01	36	270	26	267	6.61	15.1	6.8%	1.55 [0.94, 2.57]
Subtotal (95% CI)		**1494**		**1478**			**42.3%**	**1.49 [1.22, 1.82]**
Total events	224		163					
Heterogeneity: Chi² = 0.05, df = 2 (P = 0.97); I² = 0%								
Test for overall effect: Z = 3.88 (P = 0.0001)								
1.3.3 Radiotherapy alone v neoadjuvant, concomitant and adjuvant hormone therapy + radiotherapy								
D'Amico	0	0	0	0	0	0		Not estimable
Granfors	0	0	0	0	0	0		Not estimable
L-101	0	0	0	0	0	0		Not estimable
Subtotal (95% CI)		**0**		**0**				**Not estimable**
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
Total (95% CI)		**2170**		**2162**			**100.0%**	**1.63 [1.43, 1.85]**
Total events	407		291					
Heterogeneity: Chi² = 3.15, df = 4 (P = 0.53); I² = 0%								
Test for overall effect: Z = 7.26 (P < 0.00001)								
Test for subgroup differences: Chi² = 1.23, df = 1 (P = 0.27), I² = 18.6%								



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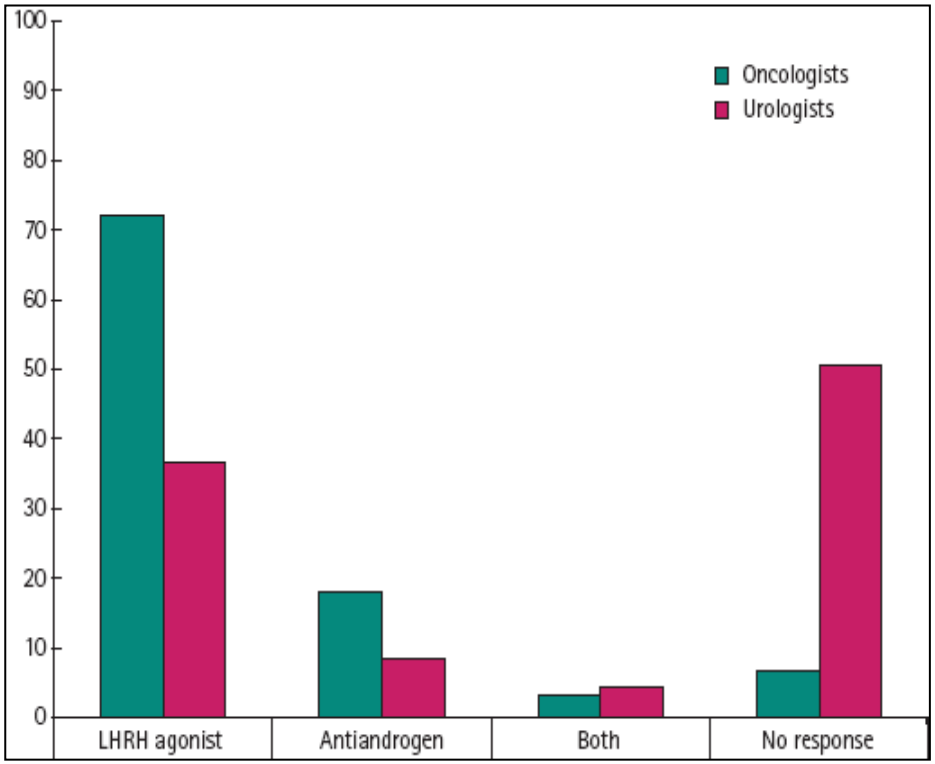
What kind of ADT



Payne, BJU 2007

What kind of ADT?

- GnRH agonists (Leuprolide and Goserelin)
  - Both agents are expensive
  - May initially result in an increase in testosterone
- GnRH antagonist (Degarelix)
  - Similar cost issues without an increase in testosterone
  - Monthly injections

- Anti-androgens which block the effects of testosterone. (Blocks binding of DHT to androgen receptors.)

- 5-α reductase inhibitor (enhances intracellular androgen blockade)

- Combination therapies.

- Orchiectomy. Cost effective if ADT for 6 months or more.

Single-Therapy Androgen Suppression in Men with Advanced Prostate Cancer: A Systematic Review and Meta-Analysis

- 24 RCT involving 6600 patients, (1966 - 1998)
- Results
  - LHRHa are equivalent to orchiectomy (10 trials, n=1908, HR-1.262, 95% CI, 0.915-1.386).
  - There was no difference in OS among the LHRH analogues
    - Leuprolide (hazard ratio, 1.0994 [CI, 0.207 to 5.835])
    - Buserelin (hazard ratio, 1.1315 [CI, 0.533 to 2.404])
    - Goserelin (hazard ratio, 1.1172 [CI, 0.898 to 1.390]).
  - Non steroidal antiandrogens are associated with lower OS (8 trials, 2717 patients, HR 1.2158 [CI, 0.988 to 1.496]).
  - Treatment withdrawals are less frequent with LHRHa (0% to 4%) than with non steroidal antiandrogens (4% to 10%).

Ann.Intern.Med. 2000 Apr 4;132(7):566-77

Is combined androgen blockade better than castration alone?

- N=1387 patients (Orch + Flutamide group-700, Orch + Placebo group-687)
- Patients receiving flutamide had greater rates of diarrhea and anemia.
- There was no significant difference between the two groups in overall survival (P=0.14).
- HR for flutamide as compared with placebo was 0.91 (90 % CI-0.81-1.01).
- Flutamide was not associated with enhanced benefit in patients with minimal disease.
- ***Conclusions:*** **The addition of flutamide to bilateral orchiectomy does not result in a clinically meaningful improvement in survival among patients with metastatic prostate cancer.**

N Engl J Med. **1998** Oct 8;339(15):1036-42

Selection of Hormonal Agents

- Androgen deprivation therapy, either through chemical castration or, far more rarely, through orchiectomy, is one reasonable standard
- Gonadotrophin-releasing hormone (GnRH) agonists, including leuprorelin and goserelin, have been the primary medical castration therapies in the Western World
- A GnRH antagonist has been gaining momentum in the first-line setting because clinical trial data suggest that it results in more rapid reduction of testosterone and therefore do not require a short course of androgen receptor antagonists
- One potential disadvantage of degarelix is the requirement for monthly administration
- 3-monthly administration is particularly indicated as it coincides with the initial follow-up visits recommended by the guidelines*

Channing J. Paller, MD, and Emmanuel S. Antonarakis, MD
Management of Biochemically Recurrent Prostate Cancer After Local Therapy: Evolving Standards of Care and New Directions
Clinical Advances in Hematology & Oncology Volume 11, Issue 1 January 2013

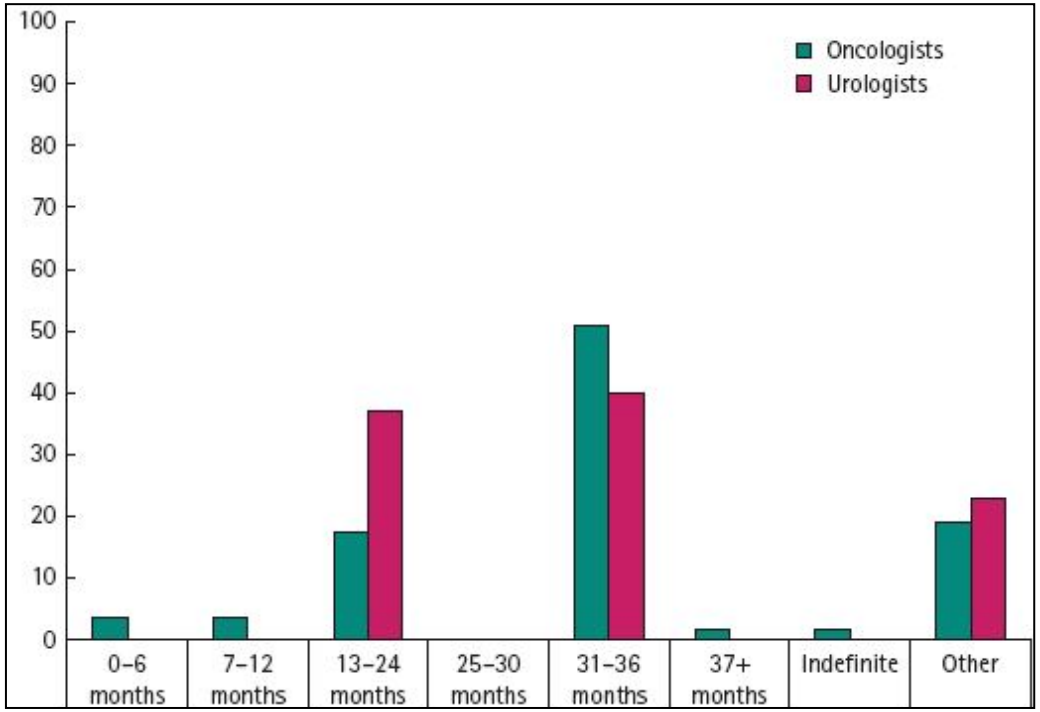
Selection of Hormonal Agents

- Long-term experience and availability of easy to use GnRH agonists, makes the latter the preferred approach in many practices

- The different products have practical differences that need to be considered in everyday practice including *:
  - Storage temperature
  - whether a drug is ready for immediate use or requires reconstitution
  - whether a drug is given by subcutaneous or intramuscular injection.
  - It is important to follow the directions carefully for using a particular drug to avoid any misuse

*EAU Guidelines 2014

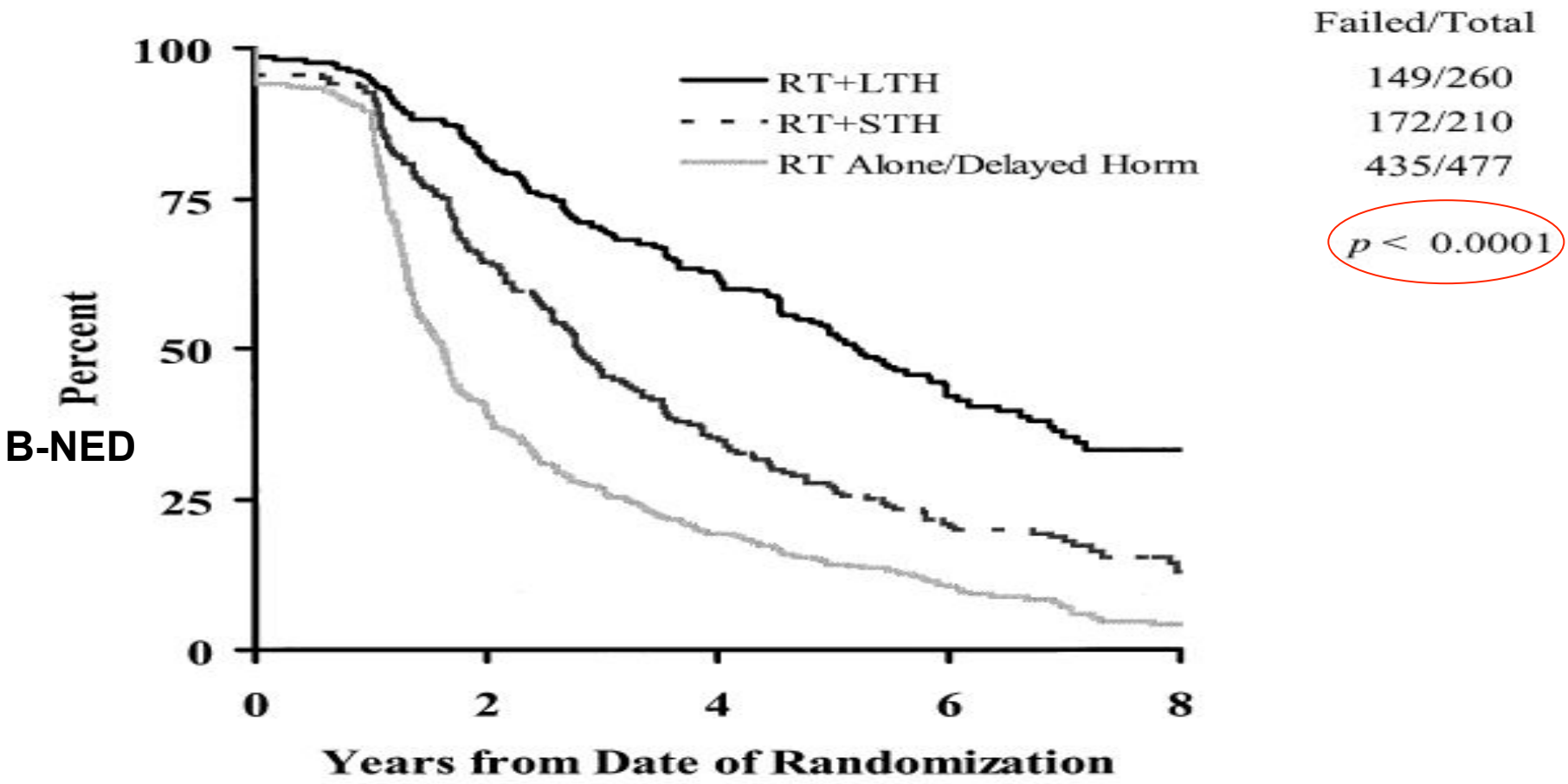
Duration?



Duration of adjuvant HT combined with RT

Payne, BJU 2007

RTOG Trial 86-10 vs. RTOG 85-31



Adjuvant long-term HT compared to short-term HT resulted in statistically significant improvements in bNED control, DMF, and CSF rates.

Horwitz EM, IJROBP, 2001

RTOG Trial 86-10 vs. RTOG 85-31

Arm I: RT alone
Arm II: Long term HT (RTOG 85-31)
Arm III: Short term HT (RTOG 86-10)

Endpoint	Arm	Number of failures/ total number of patients	8-year actuarial rates	Significance
Overall survival	Arm I	210/441	44%	
	Arm II	105/280	50%	$p = 0.20$
	Arm III	74/152	47%	
Cause-specific failure	Arm I	85/441	23%	
	Arm II	30/280	15%	$p = 0.0015$
	Arm III	39/152	28%	
bNED control	Arm I	377/415	14%*	
	Arm II	149/260	52%*	$p < 0.0001$
	Arm III	122/152	28%*	
Distant metastases failure	Arm I	150/441	39%	
	Arm II	49/280	24%	$p < 0.0001$
	Arm III	57/152	38%	

Horwitz EM, IJROBP, 2001

ASTRO 2014

Zapatero (DART 01/05 Study)	Nabid (PCS IV Study)
355 patients with intermediate- or high-risk prostate cancer treated with high-dose radiation therapy of at least 76 Gy and randomized to short-duration ADT (4 months before and during radiation only) or long-duration ADT (4 months before and during radiation and 24 months afterward) With a median follow-up of 63 months, relative to short-duration ADT, **long-duration ADT was associated with better 5-year rates** of : •biochemical disease–free survival according to the Phoenix definition (89.8% vs. 81.3%) •overall survival (94.8% vs. 86.1%) •and metastasis-free survival (93.6% vs. 83.4%) *Dr. Lawton, the press briefing moderator, said:* *But what we have yet to show is … do you really need the hormone therapy if you use dose escalation? And the answer is yes."*	561 men with high-risk prostate cancer treated with radiation therapy (44 Gy to the whole pelvis and 70 Gy to the prostate) and randomized to 18 months or 36 months of ADT With a median follow-up of 84 months, patients who had received ADT for 18 months were more likely to have recovery of testosterone values into the normal range (55.7% vs. 44.9%, *P* = .01) and had a shorter median time to recovery (47.2 vs. 73.2 months, *P* less than .001). They had a significantly better scores on 18 of 30 items on the European Organization for Research and Treatment of Cancer's global quality of life questionnaire (EORTC 30) (*P* less than .01 for each) and on 10 of 25 items on the related Prostate Module (PR 25) (*P* less than .01 for each). The investigators expect to be able to publish final efficacy and quality of life results next year. *Dr. Lawton noted that the definition of long-duration ADT has varied by world region, and has typically been 28 months in the United States and 36 months in Europe*

Docetaxel and RT

Table 11 Prospective clinical trials evaluating concurrent external beam radiation therapy and taxane-based chemotherapy for high-risk prostate cancer

Study	Design	N patients	EBRT technique	EBRT dosage (Gy)	Taxane drug	Taxane dosage (mg/m^2)	ADT duration (months)	Toxicity scoring system	Highest acute GU toxicity §	Highest acute GI toxicity §	Highest late toxicity §	Biochemical recurrence	Follow-up, median (months)
Kumar [14]	Phase I	22	3D-CRT	70.2	Docetaxel	5 (n=3), 8 (n=3), 12 (n=3), 16 (n=5), 20 (n=6), 25(n=2)	None	CTC v2.0, RTOG †	Grade 2 Frequency/ urgency (n=8)	Grade 3 Diarrhea (n=2)	Urinary Retention (n=1)	5/8	8
Sanfilippo [23]	Phase VII	22	3D-CRT	63 (n=3), 66.6 (n=7), 70.2 (n=4), 73.8 (n=8)	Paclitaxel	30	9	CTC v2.0	Grade 2 Frequency/ urgency (n=4)	Grade 3 Diarrhea (n=4)	Grade 1 Frequency (n=2)	6/22	38
Perrotti [15]	Phase VII	20	IMRT	72	Docetaxel	20	None	CTC, RTOG †	Grade 2 Frequency (n=7)	Grade 2 Diarrhea (n=8)	none	3/20	11.7
Bolla [16]	Phase II	50	3D-CRT (n=45), IMRT (n=5)	70	Docetaxel	20	<36 (n=6), 36 (n=43), >36 (n=1)	CTC v2.0, RTOG †	Grade 3 Dysuria (n=2)	Grade 4 Proctitis (n=1)	Grade 3 Proctitis (n=1)	NR ‡	54
Hussain [24]	Phase I	59	3D-CRT	70.2 (n=29), 64.8 (n=30)*	Paclitaxel	40 (n=10), 50 (n=31), 60 (n=18)	4 (n=29), 24 (n=30)	CTC v2.0	Grade 2 Frequency/ urgency/ Incontinence (n=5)	Grade 3 Diarrhea (n=9)	NA	13/29, 11/30*	76.3, 74.9*
Chen [25]	Phase I	18	IMRT	78	Docetaxel	10 (n=9), 15 (n=6), 20 (n=3)	24	CTCAE v3.0	Grade 2 Frequency (n=2)	Grade 3 Diarrhea (n=2)	NA	3/18	26
Present series	Phase II	35	IMRT	80 (n=17), 70 (n=18)*	Docetaxel	30 mg (n=8), 40 mg (n=27)	24	CTCAE v3.0	Grade 3 Urinary retention (n=1)	Grade 3 Diarrhea (n=2)	Grade 2 urinary Retention (n=2)	6/17, 8/18*	63

3D-CRT = three-dimensional conformal radiation therapy; *ADT* = androgen deprivation therapy; *CTC* = Common Toxicity Criteria of the National Cancer Institute; *CTCAE* = Common Terminology Criteria for Adverse Events of the National Cancer Institute; *EBRT* = external beam radiation therapy; *GI* = gastrointestinal symptoms; *GU* = genitourinary symptoms; *IMRT* = intensity-modulated radiation therapy; *NA* = not assessed; *NR* = not reported; *RTOG* = Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer toxicity criteria.
*Patients with previous radical prostatectomy; † late toxicity; ‡ clinical disease-free survival was 66.72% at 5 years; § when two or more events, only the most common was reported.

Guttilla et al. Radiation Oncology 2014, 9:24

A New Paradigm for the Treatment of High-Risk Prostate Cancer: Radiosensitization with Docetaxel

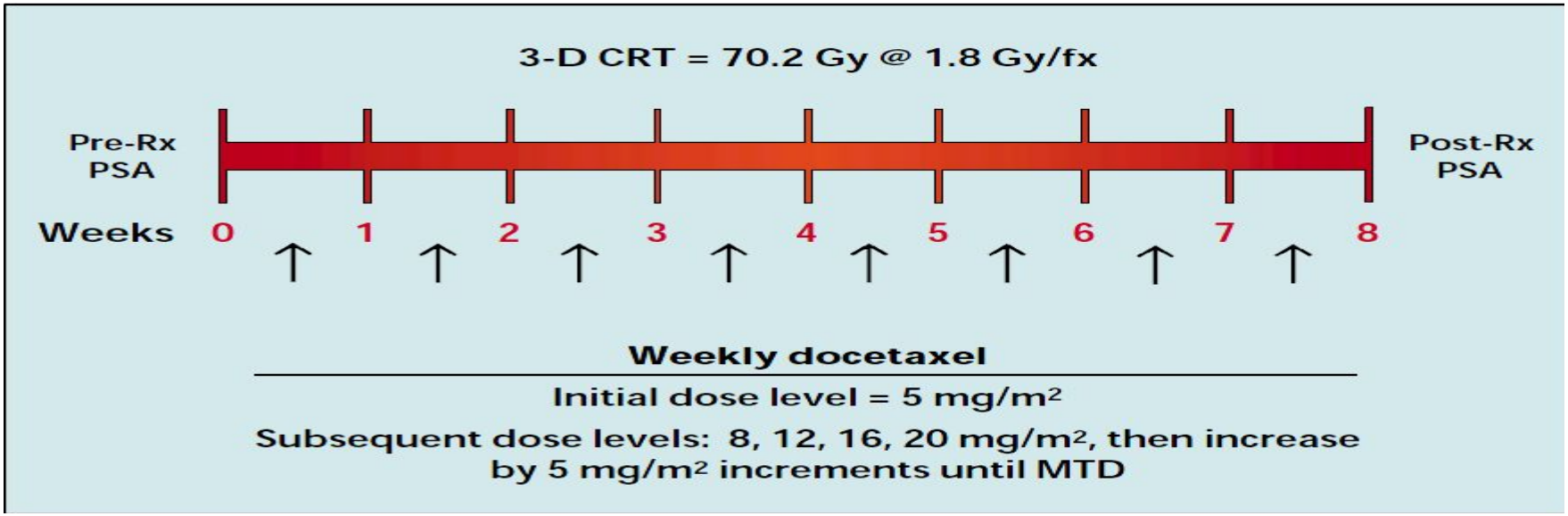
Parvesh Kumar, MD

Docetaxel, when combined with RT, has been demonstrated to increase radioresponsiveness by a factor of 2.5- to 3.0-fold in vitro; and murine MCa-K tumors treated with docetaxel plus radiation had a 3-fold increase in tumor cure.

[Rev Urol. *2003;5(suppl 3):S71–S77*]

Phase I Trial of Weekly Docetaxel With Concurrent Three-Dimensional Conformal Radiation Therapy in the Treatment of Unfavorable Localized Adenocarcinoma of the Prostate

Parvesh Kumar, Michael Perrotti, Robert Weiss, Mary Todd, Susan Goodin, Kenneth Cummings, and Robert S. DiPaola



Conclusion

Concurrent weekly docetaxel in conjunction with 3-D CRT is well tolerated with acceptable toxicity. The MTD of weekly docetaxel was determined to be 20 mg/ m2 with concurrent 3-D CRT.

J Clin Oncol 22:1909-1915. 2004

Original article

Phase I/II trial of docetaxel and concurrent radiation therapy in localized high risk prostate cancer (AGUSG 03-10)

Michael Perrotti, M.D.[a,b,*], Todd Doyle, M.D.[c], Parvesh Kumar, M.D.[c], Daryl McLeod, B.A.[b], William Badger, M.D.[b], Susan Prater, M.S.[b], Michael Moran, M.D.[a,b], Stuart Rosenberg, M.D.[a,b], Cora Bonatsos, M.D.[d], Carrie Kreitner, R.N.[d], Ralf Kiehl, M.D.[c], Theodore Chang, M.D.[a,b], Michael Kolodziej, M.D.[d]

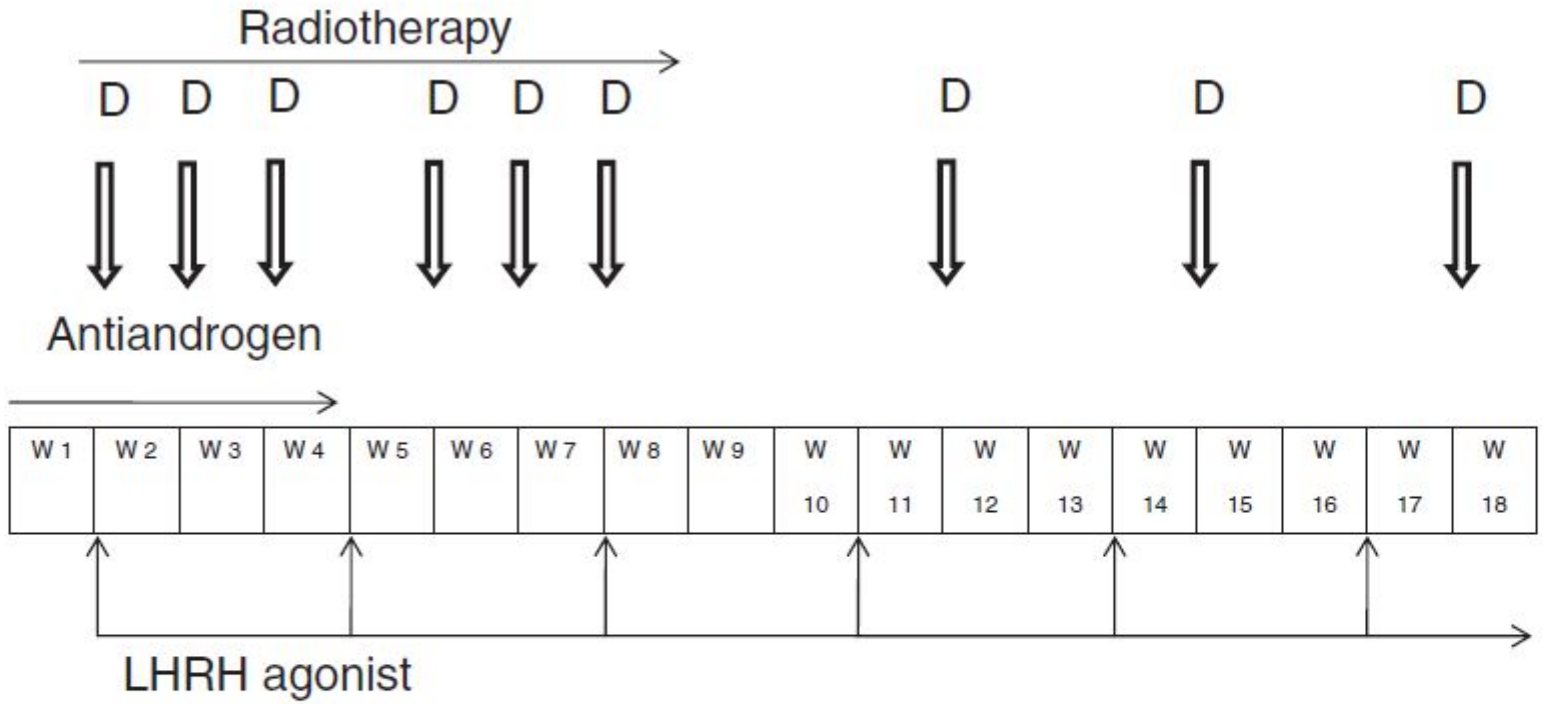
20 patients
Docetaxel administered weekly (20 mg/m2) with concurrent
intensity modulated radiation therapy (72 Gy at 1.8 Gy/fraction)
The most frequently observed toxicities were grade 2 diarrhea (40%), grade 2 fatigue (40%), grade 2 urinary frequency (35%), taste aversion (20%), grade 2 constipation (20%), and rectal bleeding (15%). No significant hematologic toxicity (grades 2–4) was encountered among the 20 patients.
At a median follow-up duration of 11.7 months, 17 patients were free of biochemical disease recurrence, and all patients are alive.

Urologic Oncology: Seminars and Original Investigations 26 (2008) 276–280

Phase II trial

Concurrent and adjuvant docetaxel with three-dimensional conformal radiation therapy plus androgen deprivation for high-risk prostate cancer: Preliminary results of a multicentre phase II trial ☆

Michel Bolla [a,*], Jean Michel Hannoun-Levi [b], Jean-Marc Ferrero [b], Philippe Maingon [c], Joëlle Buffet-Miny [d], Agnès Bougnoux [e], Jacques Bauer [f], Jean-Luc Descotes [g], Philippe Fourneret [a], Florence Jover [a], Marc Colonna [h]



Radiotherapy and Oncology 97 (2010) 312–317

Phase II trial

Concurrent and adjuvant docetaxel with three-dimensional conformal radiation therapy plus androgen deprivation for high-risk prostate cancer: Preliminary results of a multicentre phase II trial ☆

Michel Bolla [a,*], Jean Michel Hannoun-Levi [b], Jean-Marc Ferrero [b], Philippe Maingon [c], Joëlle Buffet-Miny [d], Agnès Bougnoux [e], Jacques Bauer [f], Jean-Luc Descotes [g], Philippe Fourneret [a], Florence Jover [a], Marc Colonna [h]

50 patients
70 Gy in 35 fractions,
Weekly docetaxel (20 mg/m2).
Adjuvant docetaxel for 3 cycles (60 mg/m2), every 3 weeks.
LHRH agonist for 3 years.
5 patients experienced a grade 3 toxicity, and 15 patients experienced a grade 2 toxicity.
The 5-year clinical disease-free survival was 66.72% and the 5-year survival was 92.15%.

Radiotherapy and Oncology 97 (2010) 312–317

CLINICAL INVESTIGATION Prostate

LONG-TERM RESULTS OF A PROSPECTIVE, PHASE II STUDY OF LONG-TERM ANDROGEN ABLATION, PELVIC RADIOTHERAPY, BRACHYTHERAPY BOOST, AND ADJUVANT DOCETAXEL IN PATIENTS WITH HIGH-RISK PROSTATE CANCER

Steven J. DiBiase, M.D.,* Arif Hussain, M.D.,‡ Ritesh Kataria,† Pradip Amin, M.D.,†
Sunakshi Bassi,† Nancy Dawson, M.D,§ and Young Kwok, M.D.†

Table 1. Treatment schema

Week 1 (Day 1)	Week 9	Week 13
Pelvic EBRT 45 Gy (5 weeks) LHRH agonist (2 years) Anti-androgen (4 weeks)	Brachytherapy boost (I-125–108 Gy) or (Pd-103–100 Gy)	Adjuvant docetaxel × 3 cycles (1 cycle = 35 mg/m^2 i.v., Days 1, 8, 15 Q 28 days)

Abbreviations: EBRT = external beam radiation; LHRH = luteinizing hormone-releasing hormone.

42 patients

Grade 2 and 3 acute genitourinary (GU) and gastrointestinal (GI) toxicities were 50.0% and 14.2%, respectively, with no Grade 4 toxicities noted. Grade 3 and 4 acute hematologic toxicities were 19% and 2.4%, respectively. The 5- and 7-year actuarial rates of late Grade 2 GI/GU toxicity (no Grade 3–5) was 7.7%.

Int. J. Radiation Oncology Biol. Phys., Vol. 81, No. 3, pp. 732–736, 2011

CLINICAL INVESTIGATION Prostate

LONG-TERM RESULTS OF A PROSPECTIVE, PHASE II STUDY OF LONG-TERM ANDROGEN ABLATION, PELVIC RADIOTHERAPY, BRACHYTHERAPY BOOST, AND ADJUVANT DOCETAXEL IN PATIENTS WITH HIGH-RISK PROSTATE CANCER

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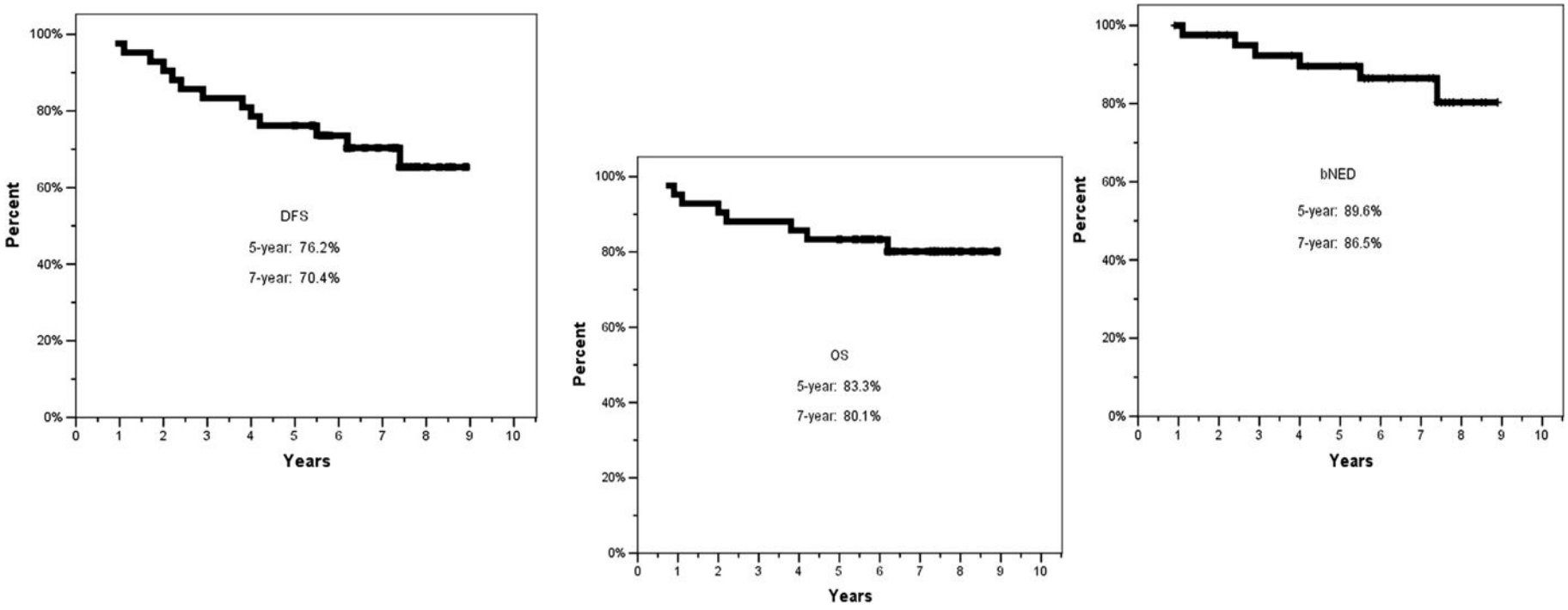


Int. J. Radiation Oncology Biol. Phys., Vol. 81, No. 3, pp. 732–736, 2011

BJUI
BJU INTERNATIONAL

Phase I study of concurrent weekly docetaxel, high–dose intensity–modulated radiation therapy (IMRT) and androgen–deprivation therapy (ADT) for high–risk prostate cancer

Ronald C. Chen*§, Julian G. Rosenman*§, Leroy G. Hoffman¶, Wing–Keung Chiu††, Andrew Z. Wang*§, Raj S. Pruthi†§, Eric M. Wallen†§, Jeffrey M. Crane††, William Y. Kim†§, W. Kimryn Rathmell†§, Paul A. Godley†§ and Young E. Whang†§

- High-risk prostate cancer treated with a LHRH(starting 2 – 3 months before IMRT and lasting 2 years), IMRT of 78 Gy to the prostate and seminal vesicles, and weekly docetaxel during RT (10, 15, and 20 mg/m 2)
- 18 patients
- One G3 diarrhoea
- At a median follow-up of 2.2 years, all patients achieved a PSA nadir of < 1 ng/mL, including 13 patients who had an undetectable PSA level. The 2-year biochemical progression-free survival was 94%.

2 012 B J U I N T E R N A T I O N A L | 110 , E 7 21 – E 7 2 6

Multimodal treatment for high-risk prostate cancer with high-dose intensity-modulated radiation therapy preceded or not by radical prostatectomy, concurrent intensified-dose docetaxel and long-term androgen deprivation therapy: results of a prospective phase II trial

Andrea Guttilla[1*], Roberto Bortolus[2], Gianluca Giannarini[1,3], Pirus Ghadjar[4], Fabio Zattoni[1], Michele Gnech[1], Vito Palumbo[1], Francesca Valent[5], Antonio Garbeglio[6] and Filiberto Zattoni[1]

35 patients
Radical (80 Gy in 40#) or adjuvant RT (70 Gy in 35#)
Weekly docetaxel 30 or 40 mg)
Acute GI and GU toxicity was grade 2 in 23% and 20% of patients, and grade 3 in 9% and 3% of patients, respectively. Acute blood/bone marrow toxicity was grade 2 in 20% of patients. No acute grade ≥4 toxicity was observed.
Late GI and GU toxicity was grade 2 in 9% of patients each. No late grade ≥3 toxicity was observed.
Actuarial 5-year biochemical and clinical recurrence-free survival rate was 55% (95% confidence interval, 35-75%)
and 70% (95% confidence interval, 52-88%), respectively.

Radiation Oncology 2014, 9:24

Adjuvant radiation, androgen deprivation, and docetaxel for high-risk prostate cancer post-prostatectomy: Results of RTOG 0621.

Subcategory:
Prostate Cancer

Category:
Genitourinary (Prostate) Cancer

Meeting:
2014 ASCO Annual Meeting

Session Type and Session Title:
Poster Highlights Session, Genitourinary (Prostate) Cancer

Abstract Number:
5031

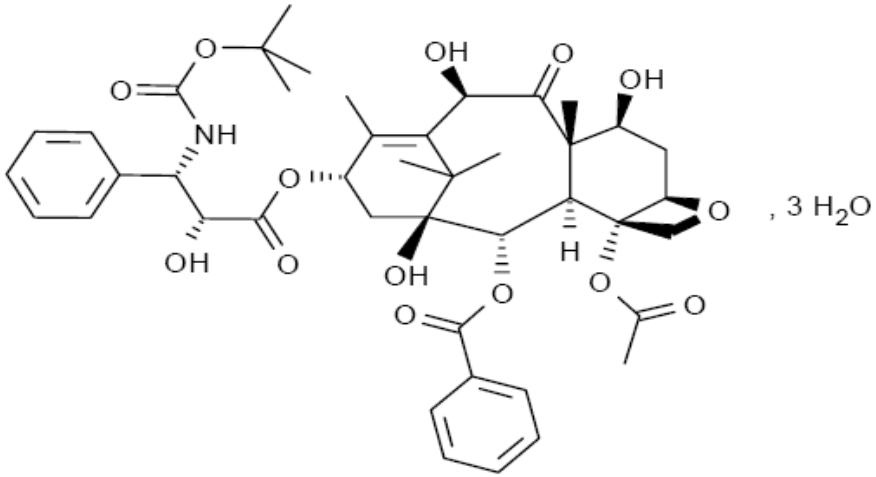
Citation:
J Clin Oncol 32:5s, 2014 (suppl; abstr 5031)

Author(s):
Mark Hurwitz, A. Oliver Sartor, Qiang Zhang, Ying Xiao, Bobby Shayegan, Paul W. Sperduto, Kas Ray Badiozamani, Colleen Anne Lawton, Eric M. Horwitz, Jeff M. Michalski, Kevin S. Roof, David Beyer, Asha George, Howard Mark Sandler; Department of Radiation Oncology, Jefferson Medical College of Thomas Jefferson University, Philadelphia, PA; Tulane University, New Orleans, LA; Statistical Center, Radiation Therapy Oncology Group, Philadelphia, PA; Thomas Jefferson University Hospital, Philadelphia, PA; Division of Urology, McMaster University, Hamilton, ON, Canada; Metro-MN CCOP, Waconia, MN; Virginia Mason Medical Center, Seattle, WA; Medical College of Wisconsin, Milwaukee, WI; Fox Chase Cancer Center, Philadelphia, PA; Washington University in St. Louis, St. Louis, MO; Southeast Radiation Oncology, Charlotte, NC; Arizona Oncology, Scottsdale, AZ; Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA

Background: Phase III trials have shown benefit in progression-free survival and in some cases overall survival with adjuvant radiation therapy (ART) in men with adverse pathologic findings at radical prostatectomy (RP). Despite ART, a high-risk group of patients has been defined with 50% risk of progression at 3 years, a risk factor for prostate cancer specific mortality. RTOG 0621 is a single-arm phase II trial that assessed whether addition of androgen deprivation (ADT) and docetaxel to ART would increase freedom from progression (FFP) at 3 years from 50% to ≥ 70% in these high-risk patients. **Methods:** Eligible subjects had prostatic adenocarcinoma who underwent RP with PSA nadir > 0.2 and Gleason score ≥ 7 or PSA nadir ≤ 0.2 with Gleason score ≥ 8 and ≥ pT3. Subjects received 6 months of ADT + RT to the pelvis with prostatic fossa boost to 66.6 Gy followed in one month with 6 cycles of docetaxel 75 mg/m^2 every 21 days. The primary objective was to assess whether addition of ADT and docetaxel to ART results in FFP of ≥70% as defined as PSA < 0.4 ng/ml, and no clinical failure or death from any cause at 3 years. Multivariate logistic regression was used to model association of factors with the occurrence of FFP. Odds ratios and respective 95% confidence intervals were computed. **Results:** 76 patients with median age 62 meeting eligibility criteria were enrolled on the study. 3 year FFP was 71%, (95% CI:61-81%), p-value<0.001. In univariate and multivariate models, only post-RP PSA was statistically significantly associated with FFP. Two deaths occurred of which only 1 was related to prostate cancer. The most common significant chemotherapy side effects were peripheral neuropathy (12 grade 2 and 1 grade 3) and febrile neutropenia in 3 patients. Six subjects (8%) experienced late grade 3-4 treatment related toxicities. **Conclusions:** Addition of ADT and docetaxel to ART for men as high risk of failure despite ART alone following prostatectomy resulted in a significant improvement in FFP as compared to historical controls. Phase III trials assessing chemotherapy in this high-risk population are warranted. This work was supported by RTOG grant U10 CA21661 and CCOP grant U10 CA37422 from the NCI and Sanofi-Aventis. Clinical trial information: **NCT00528866**.

Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial

Johann Sebastian de Bono, Stephane Oudard, Mustafa Ozguroglu, Steinbjørn Hansen, Jean-Pascal Machiels, Ivo Kocak, Gwenaëlle Gravis, Istvan Bodrogi, Mary J Mackenzie, Liji Shen, Martin Roessner, Sunil Gupta, A Oliver Sartor, for the TROPIC Investigators



Cabazitaxel: a next generation taxane

Prior radiotherapy to ≥ 40% of bone marrow
Surgery, radiation, chemotherapy, or other anti-cancer therapy within 4 weeks prior to enrollment in the study

Lancet 2010; 376: 1147–54

Cabazitaxel-induced stabilization of microtubules enhances radiosensitivity in ovarian cancer cells

Charles A. Kunos[1], Tammy Stefan[2] and James W. Jacobberger[2]*

- SKOV3, OVCAR3, andTOV-112D ovarian cancer cellswere admin-istered cabazitaxel 24 h before (first), 18 h before (second), together (third), or 24 h after (fourth) a single radiation dose, and then, investigated by clonogenic assay and flow cytometric assays.

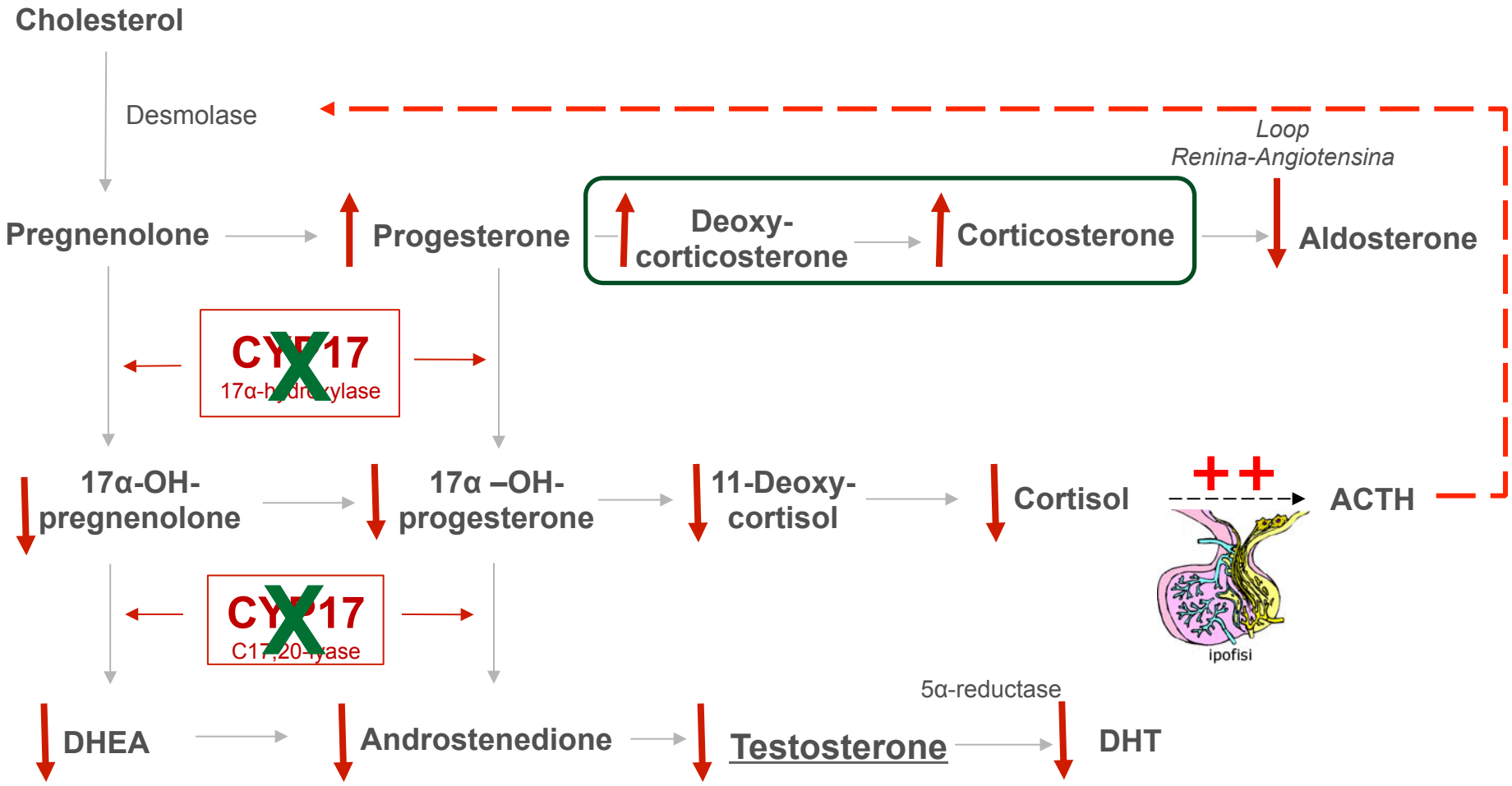
- Cabazitaxel cytotoxicity and radiosensitization were dose dependent. Cabazitaxel added 24 h before radiation was the most lethal schedule.

Front Oncol 013 Sep 18;3:226.

New hormonal drugs

Agent	MOA	Studies	Trial Results
Abiraterone Acetate	Potent and selective inhibitor of CYP17-alpha-hydroxylase and C17,20-lyase	Phase III studies post- and pre-docetaxel with prednisone	COU-AA-301 [7,20]
			Met endpoint of OS
			OS: HR 0.74; 95% CI 0.638-0.859; p < 0.0001
			26% reduction in risk for death
			COU-AA-302[8] met endpoint of rPFS and trend in OS
			OS: HR 0.79; 95% CI 0.66-0.95; p = 0.0151
			21% reduction in risk of death
			rPFS: HR 0.43 ; 95% CI 035-0.52 ; p < 0.0001
			57% reduction in rPFS
			Other combination trials ongoing
Enzalutamide	AR antagonist, inhibits nuclear translocation and blocks DNA binding of the receptor and activation	Phase III studies post- and pre-docetaxel	AFFIRM[9] met endpoint of OS
			OS: HR 0.631; 95% CI 0.529-0.752; p < 0.0001
			37% reduction in risk of death
			PREVAIL[11] met endpoints of OS and rPFS
			OS: HR 0.706; 95% CI 0.60-0.84;
			p <0.0001
			rPFS: HR 0.186; 95% CI 0.15-0.23; p < 0.0001
			MO CRPC PROSPER trial recruiting and other trials ongoing[41]
Orteronel (TAK-700)	Selective, non-steroidal, small-molecule inhibitor of 17,20-lyase	Phase III studies post- and pre-docetaxel with prednisone	ELM-PC5 did not meet primary endpoint of OS[25]
			OS: HR 0.886; 95% CI 0.739-1.062; p = 0.1898
			Substantial regional differences in OS were seen
			rPFS: HR 0.76; 95% CI 0.653-0.885; p = 0.00038
			ELM-PC4
			Fully recruited-ongoing[23]
			Others: orteronel vs. bicalutamide in mCRPC patients failing first-line LHRH agonists or surgical castration[28]
			Orteronel vs. bicalutamide in hormone-naive prostate cancer patients failing on LHRH agonists[29]
Galeterone (TOK-001)	AR antagonist and AR degrader and a CYP17 lyase inhibitor	Phase I/II ARMOR 1 and ARMOR 2	ARMOR 2[32]
			Reformulated galeterone
			Significant improvements in PSA response at 12 weeks in CRPC as compared with ARMOR1
			M1 treatment naive 2,550 mg QD PSA response: 90% ≥ 30% and 81% ≥ 50%
ARN-509	AR antagonist, inhibits nuclear translocation and DNA binding of the receptor	Phase I/II	N = 30 with doses 30 mg to 480 mg
			PSA declines at 12 weeks ≥50% in 46.7%[43]
			Phase II trial recruited[44]
			MO CRPC Spartan trial recruiting[45]
ODM-201 ORM-15341 (main metabolite)	No CYP inhibition or induction with therapeutic doses	Phase I/II	ARCADES Trial[46]
			Chemotherapy.
			CYP17i-naive ≥50% PSA: 65%
			Post-chemotherapy/CYP17i-naive ≥50% PSA 32%
			Post-CYP17i ≥50% PSA: 9%
			MO CRPC trial planned

Abiraterone



Yang, Drugs. 2011; Attard, JCO 2008

Use of Abiraterone Acetate in combination with Radiotherapy

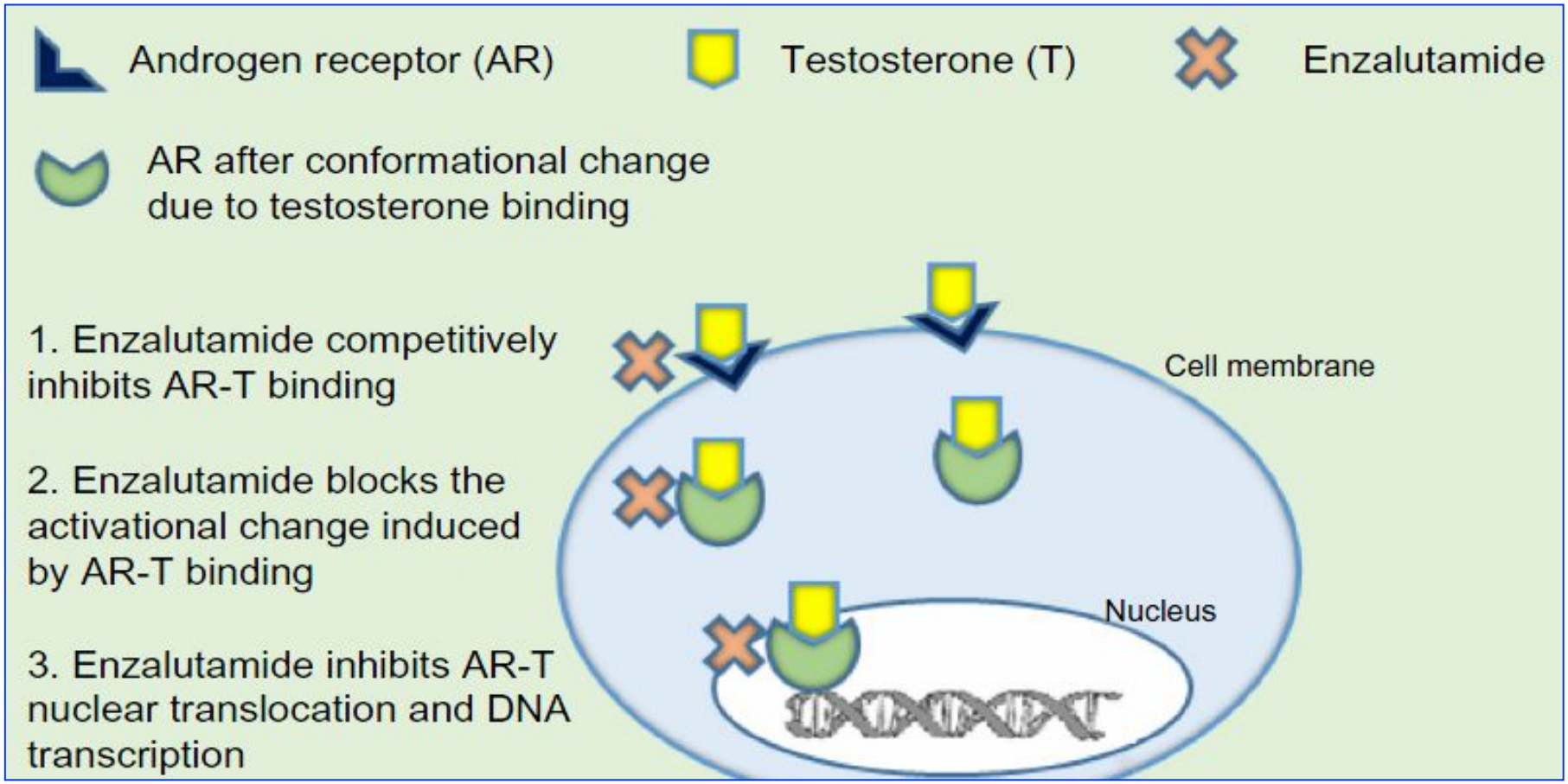
- Within the COU-AA-301 study, the use of palliative radiation was permitted. The study allowed for one course of radiation (single or multi-fraction) to a single site.

- In the COU-AA-301 study, 11.1% of patients in the abiraterone arm and 12.2% in the placebo arm had localized progression at a single site and received concurrent palliative radiotherapy;

- No new safety signals were seen in patients receiving abiraterone plus prednisone and palliative radiation.

De Bono J et al.NEJM 2011; Saad F et. 2012

Enzalutamide



Enzalutamide is an androgen-receptor–signaling inhibitor.
Enzalutamide has 5-8 fold higher binding affinity to AR than the first generation anti-androgen bicalutamide.

Patel, Therapeutics and Clinical Risk Management. 2014

Use of Enzalutamide in combination with Radiotherapy

- Both in PREVAIL and AFFIRM trial the use of palliative radiation therapy within 3 weeks (if single fraction of radiotherapy within 2 weeks) and radionuclide therapy within 8 weeks of enrollment (Day 1 visit) were exclusion criteria.

Beer et al.NEJM 2014 Jul 31;371(5):424-33; Scher HI et al NEJM. 012 Sep 27;367 (13):1187-97

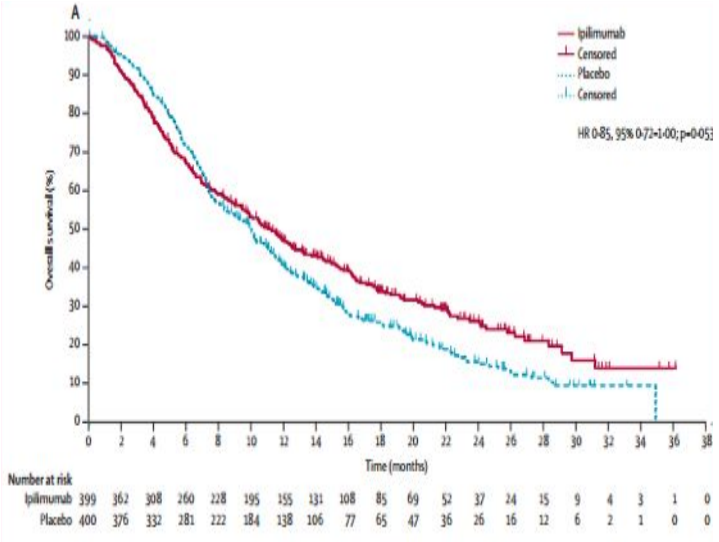
Immunotherapy

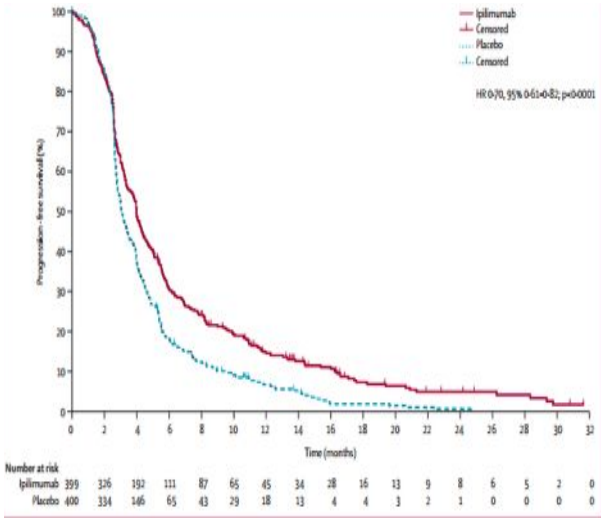
ClinicalTrials.gov Identifier	Treatment Arms	Phase	Patient Population	Primary End Point
NCT01057810	Ipilimumab versus placebo	Phase III (completed accrual)	Chemotherapy-naive mCRPC	Overall Survival
NCT01322490	Prostvac + GM-CSF versus Prostvac alone versus placebo	Phase III	Chemotherapy-naive mCRPC	Overall Survival
NCT01867333	Prostvac + enzalutamide versus enzalutamide	Phase II	Chemotherapy-naive mCRPC	Time To Progression
NCT01981122	sipuleucel-T with enzalutamide versus sipuleucel-T followed by enzalutamide	Phase II	mCRPC	Immune Response at 1 year

Abbreviations: mCRPC, metastatic castration-resistant prostate cancer; GM-CSF, granulocyte macrophage colony-stimulating factor.

Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial

Eugene D Kwon, Charles G Drake, Howard I Scher, Karim Fizazi, Alberto Bossi, Alfons J M van den Eertwegh, Michael Krainer, Nadine Houede, Ricardo Santos, Hakim Mahammedi, Siobhan Ng, Michele Maio, Fabio A Franke, Santhanam Sundar, Neeraj Agarwal, Andries M Bergman, Tudor E Ciuleanu, Ernesto Korbenfeld, Lisa Sengeløv, Steinbjorn Hansen, Christopher Logothetis, Tomasz M Beer, M Brent McHenry, Paul Gagnier, David Liu, Winald R Gerritsen, for the CA184-043 Investigators*





Although there was no significant difference between the ipilimumab group and the placebo group in terms of overall survival in the primary analysis, there were signs of activity with the drug that warrant further investigation.

Lancet Oncol 2014; 15: 700–12

Beyond Sipuleucel-T: Immune Approaches to Treating Prostate Cancer

Michael L. Cheng, MD
Lawrence Fong, MD

is being evaluated. Whereas this treatment failed to show significant improvement in overall survival in CRPC patients treated with docetaxel, results from a phase III trial in the predocetaxel setting are pending. Conventional therapies for prostate cancer, such as radiation and hormonal therapy, may have immunomodulatory effects. Future areas for research include the sequencing and combination of immunotherapies as well as other conventional therapies.

Current Treatment Options in Oncology (2014) 15:115–126

Review

Molecularly Targeted Agents as Radiosensitizers in Cancer Therapy—Focus on Prostate Cancer

Sara Alcorn [1,†], Amanda J. Walker [1,†], Nishant Gandhi [1], Amol Narang [1], Aaron T. Wild [1], Russell K. Hales [1], Joseph M. Herman [1,2], Danny Y. Song [1,2,3], Theodore L. DeWeese [1,2,3], Emmanuel S. Antonarakis [2] and Phuoc T. Tran [1,2,3,*]

Table 1. Recent trials investigating targeted agents used neoadjuvantly, concurrently or adjuvantly with radiotherapy for prostate cancer *.

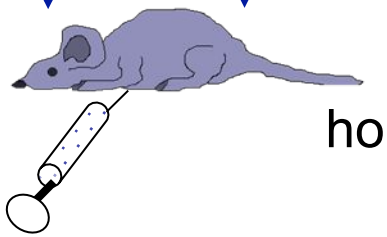
Radiosensitizer	Risk group	Target	Trial number **	Trial phase	Trial status	Outcomes
Semaxanib + ADT	Intermediate-to high-risk	VEGF receptor	NCT00026377	I	Completed	See note †
Sunitinib + ADT	High-risk	Multi-targeted RTK	NCT00631527	I	Completed	Feasibility achieved with recommended phase 2 dose of sunitnib (25 mg daily) [112]
Panobinostat	High-risk	HDAC	NCT00670553	I	Completed	-
Everolimus + ADT	High-risk	mTOR	NCT00943956	I	Unknown ‡	-
Everolimus	Biochemical recurrence (salvage)	mTOR	NCT01548807	I	Recruiting	-
Everolimus + ADT	High-risk	mTOR	NCT01642732	I	Recruiting	-
Dasatinib + ADT	Intermediate-to high-risk	SRC	NCT01826838	I	Recruiting	-
Ganetespib + ADT	High-risk	HSP90	Pending	I	Pending	-
Sorafenib + ADT	Intermediate-to high-risk	Multi-targeted RTK	NCT00924807	I/II	Terminated	-
Bevacizumab + ADT	High-risk	VEGF receptor	NCT00349557	II	Completed	Bevacizumab + ADT does not exacerbate acute side effects but may worsen late effects following IMRT [113]
Sunitinib + docetaxel	Biochemical recurrence (salvage)	Multi-targeted RTK	NCT00734851	II	Active but not recruiting	-
TAK-700 + ADT	High-risk	CYP17A1	NCT01546987 (RTOG 1115)	III	Recruiting	-

* Adapted from Palacios, *et al.* [114]; ** As listed on USA National Institutes of Health's ClinicalTrials.gov registry; ADT—Androgen deprivation therapy; VEGF—Vascular growth factor; RTk—Receptor tyrosine kinase; HDAC—Histone deacetylase; mTOR—Mammalian target of rapamycin; HSP90—Heat shock protein 90; CYP17A1—Cytochrome P450 17A1; † A phase II trial of SU5416 by the same author investigating its use in hormone-refractory prostate cancer states that additional study of SU5416 in prostate cancer patients is not recommended given negative results of the phase II trial [115]; ‡ The recruitment status of this study is unknown because the information has not been verified recently on clinical trials.gov.

Int. J. Mol. Sci. ***2013, 14, 14800-14832***

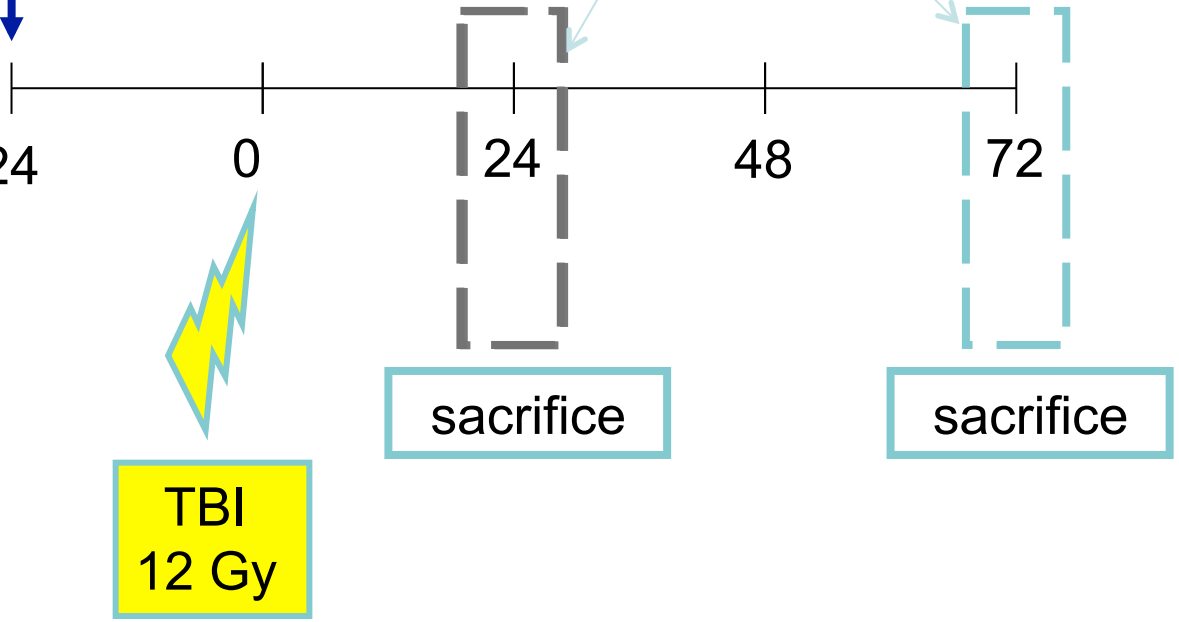
EFFECT OF ENANTONE ON ACUTE INTESTINAL DAMAGE INDUCED BY RADIOTHERAPY

Leuprorelin 0,054 mg/ Kg/month (i.p.) for 3 months before RT



C57black/6J
7 weeks

Group 1 = control
Group 2 = Leu
Group 3 = RT
Group 4= RT+Leu



Collection of jejunum and colon segments

- Histological analysis
- Microcolony assay
- q-RT PCR
- Western blot