

La radioterapia nel trattamento multimodale delle metastasi ossee e cerebrali

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Oncologia Medica

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Metastasi Ossee

La chemioterapia

Nicolangelo Calvi



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metàstasi — gr. METÀSTASIS *trasposizione, cambiamento, comp.* di METÀ *al di là, ra* e STÀSIS *stato, posizione, da I-STÈ-MI ui fermo, mi colloco (v. Stare).*

Term. di medic. Il cambiamento di sede di una malattia, ovvero Trasporto di una materia morbosa dalla parte che essa occupava verso di un'altra.

Deriv. Metastatico.

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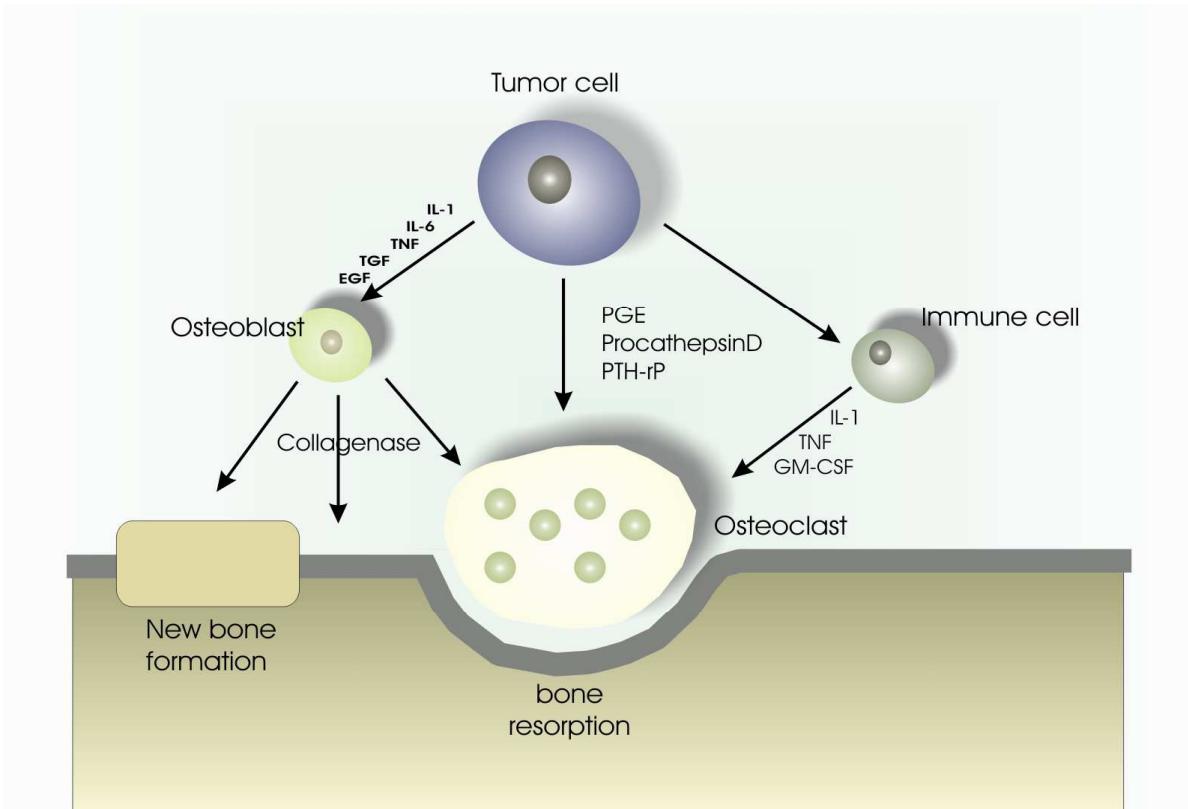
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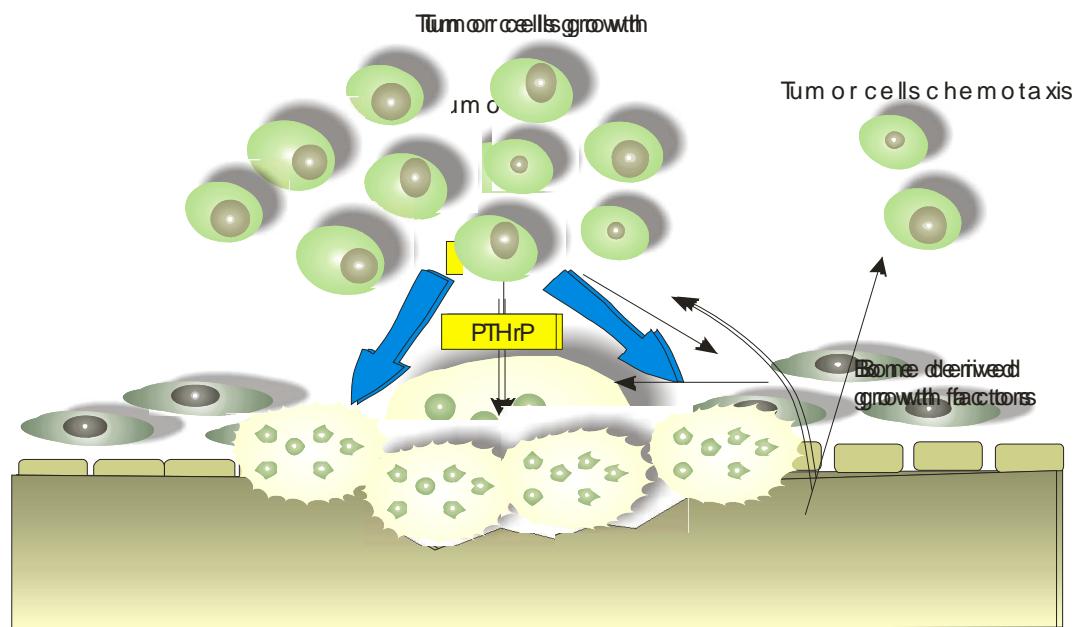
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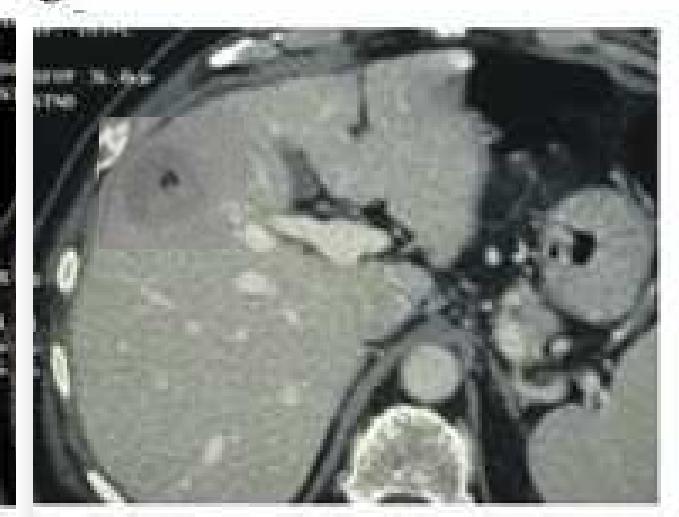
Primary Tumor Site	No. Of Studies	Incidence % of Bone Metastases	
		Median	Range
Breast	5	73	47-85
Prostate	6	68	33-85
Thyroid	4	42	28-60
Kidney	3	35	33-40
Bronchus	4	36	30-55
Esophagus	3	6	5-7
Gastrointestinal	4	5	3-11
Rectum	3	11	8-13

CYTOTOXIC DRUGS as first treatment in bone metastases

Not hormonoresponsive tumors
Lymphangitic pulmonary metastases
Liver metastases compromised hepatic function
Need of a rapid response

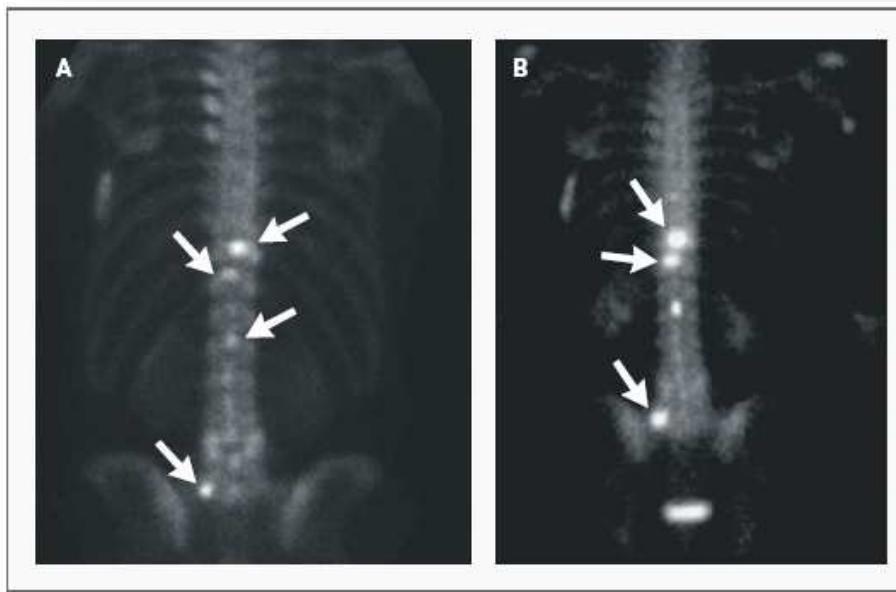
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**Reduction of bone metastases
related pain as a new marker
of tumor response**

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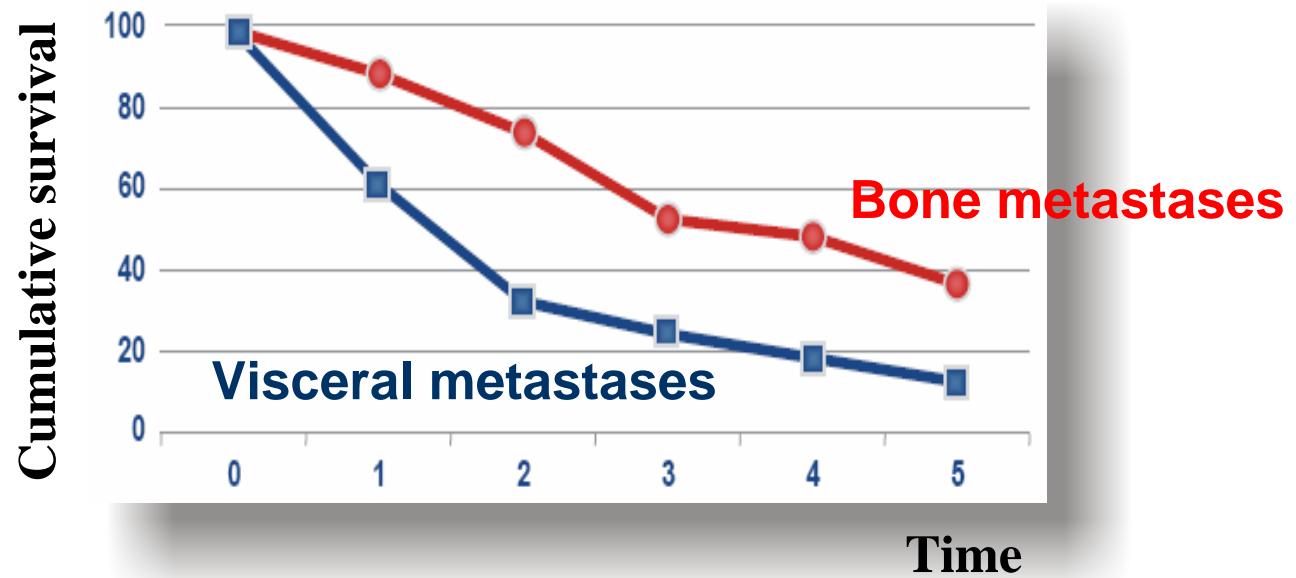
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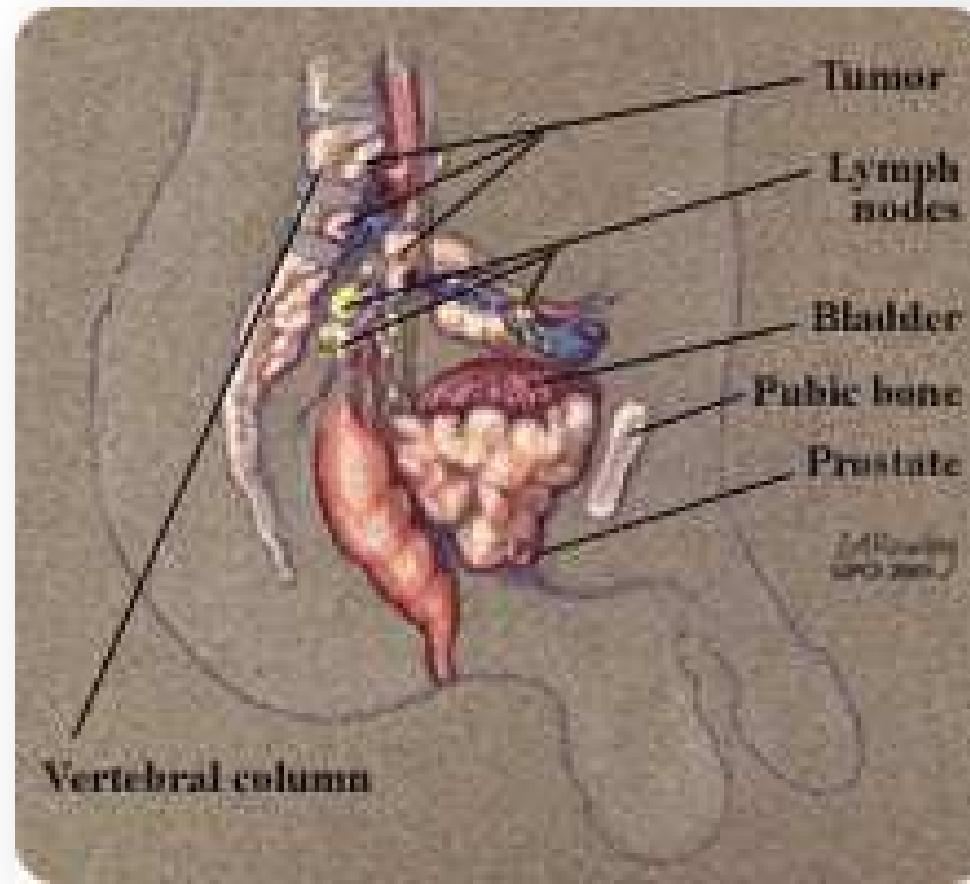
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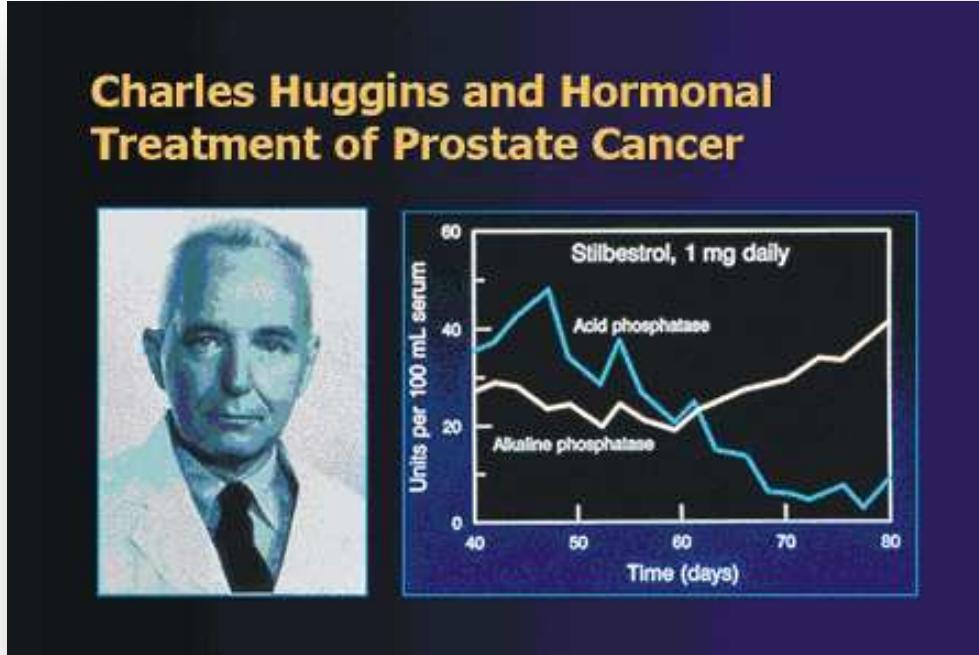
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From the Archives of Urology, Yale University School of Medicine, New Haven, Connecticut
See Weller, J. (1990). The history of urology, history of medicine, and science
© 1990 American Urological Association, Inc.
0882-5963/90/1000-1000\$04.00
Historical Article

PROSTATE CANCER: A BRIEF HISTORY AND THE DISCOVERY OF HORMONAL ABLATION TREATMENT

SETH RABIN LYTTORF

The story of prostate cancer spans nearly 200 years. But treatment of this disease and the evolution of its 4 primary types of treatments—surgery, radiation, and hormonal manipulations—provides a unique opportunity to highlight medical insight and strategy during the last century. This article reviews the history of prostate cancer from its earliest stages as early as 1811, when Langenbeck described benign prostatic nodules as a tumor used at the time for postoperative hemostasis, to the present era of molecular biology. It also highlights the role of the French surgeon, Charles Huggins, in the development of the first effective treatment for prostate cancer. In addition, it reviews the history of the discovery of the first effective treatment for metastatic prostate cancer, namely androgen ablation, and the subsequent evolution of this procedure. The French surgeon, Testoux, observed a dramatic response in a patient with metastatic prostate cancer to androgen ablation in 1890, and he performed a radical prostatectomy on the same patient 1 year later. In 1909, Huggins published a book in which he reported a case of a 60-year-old man with metastatic prostate cancer who responded to androgen ablation. In 1926, Huggins, described a patient who unfortunately had prostate cancer, but was presented with metastases and died of other problems before his prostate could be removed. He noted that the prostate gland that was once hard on palpation was now soft and watery. This case of prostate cancer established the international interest that originated in 1909 by Astley Cooper's report of the London case, and the first report of the New York Society of Urology.¹ A 60-year-old man with a soft fibrotic prostate and a history of pain in the sacrum and rectum was found to have lymph nodes had died 9 years after the initial onset of symptoms. It was suggested that cancer could be a "very rare disease" in the sacral spine.² During the next 20 years, conventional forms of prostate cancer were reported. In 1888, Whitney from Massachusetts reported a case of a 60-year-old man with a palpable prostate and a few years later, Wolff described 35 prostate cancer cases in a 10-year period.³ British and French literature,⁴ to avoid the term "cancer," and the English and French literature,⁵ to avoid the term "carcinoma," were associated with the term "adenoma" and the resulting diagnosis was associated with the term "adenocarcinoma." As a result, treatment was mainly due to surgery, castration, or radiation intervention. However, probably owing to induction in the prostate, the first report of a successful treatment for prostate cancer dates to 1888. Allchurch and Hallie performed a histological study of 2000 malignant prostates and classified it as a "tumor of the prostate." The progression of prostate disease goes back to the early studies of that contemporary surgical technique, John Hunter,

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Classics in Oncology

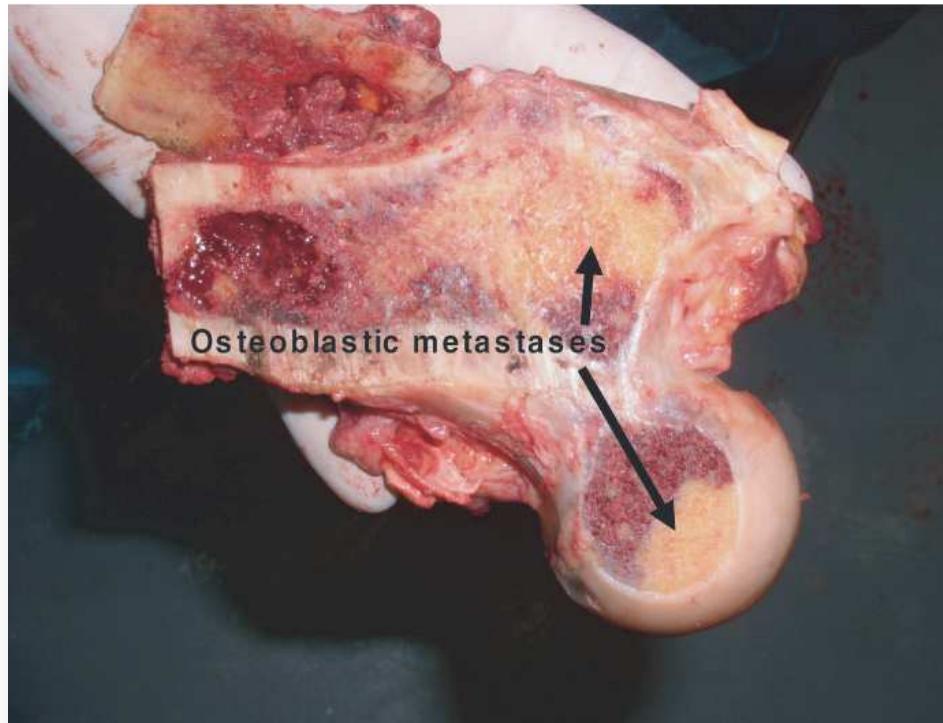
Charles Brenton Huggins
(1901-)

relationship between hormones and cancer of the prostate. Huggins and Hodges showed that prostatic cancer was dramatically affected by castration or administration of estrogens, treatment which reduced the levels of acid phosphatase. Huggins' observation that the synthetic estrogen diethylstilbestrol caused regression in disseminated prostatic cancer initiated the era of cancer chemotherapy.

The following reprinted paper was the

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Cytotoxic chemotherapy for
ADVANCED hormone-resistant
PROSTATE CANCER

Yagoda A, Petryla K D

hormone-refractory prostate cancer unresponsive to cytotoxic agents.

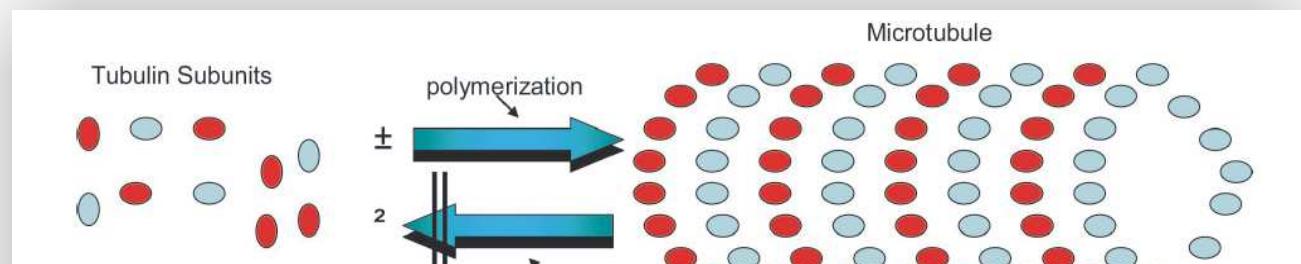
**documentation of response complicated by a lack of established criteria
to judge activity in a disease in which few patients had measurable soft
tissue lesions**

Comparison of Baseline Characteristics of Patients Randomly assigned to the Trials

Study	SWOG 9916	TAX 327
Therapy	Docetaxel + estramustine v M/P	Docetaxel + prednisone v M/P
Author	Petrylak ⁴	Tannock ³
No. of patients	770	1,006
Median age, year	70	68
PSA, median	84	112
Bone metastases, %	88	91
Visceral metastases, %	6	23
Opiate analgesic use, %	36	45
Survival superior arm, months	17.5	18.9
Inferior arm(s), months	15.6	17.4
		16.5

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Trial	Docetaxel	Combination	Patients with $\geq 50\%$ Decline in Prostate-Specific Antigen Level (%)	Patients with a Soft Tissue Response (%)	Overall Survival
Picus and Schultz ³⁶ (1999)	75 mg/m ² every 21 days	Not available	46	24	27 months
Friedland, et al. ³⁷ (1999)	75 mg/m ² every 21 days	Not available	38	29	67% at 15 months
Berry, et al. ³⁸ (2001)	36 mg/m ² weekly for 6 of 8 weeks	Not available	41	33 (complete response: 17)	9.4 months
Beer, et al. ³⁹ (2001)	36 mg/m ² weekly for 6 of 8 weeks	Not available	46	40	39 weeks
Gravis, et al. ⁴⁰ (2003)	35 mg/m ² weekly for 6 of 8 weeks	Not available	48	28 (stable disease)	20 months
Petrylak, et al. ⁴¹ (2000)	70 mg/m ² every 21 days	Estramustine 280 mg three times a day for days 1–5	68	55	77% at 1 year
Sinibaldi, et al. ⁴² (2002)	70 mg/m ² every 21 days	Estramustine 280 mg every 6 hours \times 5 doses; coumadin 2 mg daily	45	20	13.5 months
Savarese, et al. ⁴³ (2001), CALGB 9780	70 mg/m ² every 21 days	Estramustine 10 mg/kg/day in three daily doses for days 1–5; hydrocortisone 30 mg every morning and 10 mg every afternoon daily	68	50 (partial response: 38; complete response: 13)	20 months
Petrylak, et al. ⁴⁴ (2004), SWOG* Intergroup (Phase III)	60 mg/m ² every 21 days	Estramustine 280 mg three times a day for days 1–5	50	17	18 months
Tannock, et al. ⁴⁵ (2004), TAX-327 (Phase III)	75 mg/m ² every 21 days 30 mg/m ² weekly for 5 of 6 weeks	Prednisone 5 mg twice daily	45	12	18.9 months
		Prednisone 5 mg twice daily	48	8	17.3 months

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TAX327 trial

n = 1,006 subjects with androgen-independent HRPC

Stratification

Pain level
PPI ≥ 2 or AS ≥ 10
vs
PPI < 2 or AS < 10

KPS
 ≥ 70 vs ≥ 80

R
A
N
D
O
M
I
Z
A
T
I
O

- Docetaxel 75 mg/m² Q 3 wk + Prednisone 5 mg bid
- Docetaxel 30 mg/m² weekly 5 of 6 wk + Prednisone 5 mg bid
- Mitoxantrone 12 mg/m² Q 3 wk + Prednisone 5 mg bid

Treatment durations in all 3 arms = 30 weeks

Berry, W. et al. Oncologist 2006; 10:30-39



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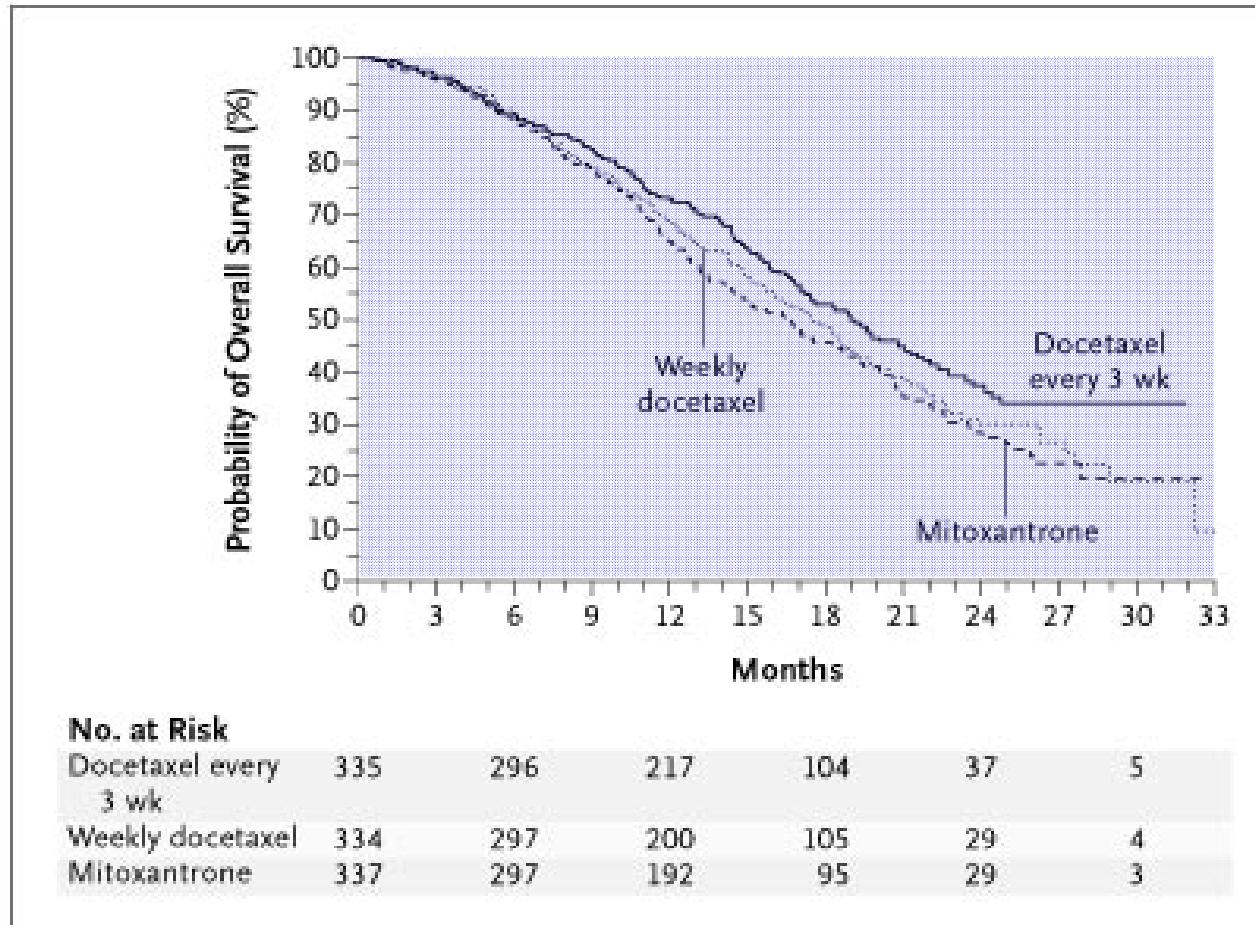
Efficacy outcomes from the **TAX 327 trial**

	Q3W Docetaxel (n = 335)	Weekly docetaxel (n = 334)	Mitoxantrone (n = 337)
Median survival (months)	18.9 <i>p</i> = .009	17.4 <i>p</i> = .36	16.5
<u>Secondary end points</u>			
≥50% decline in serum PSA	45% (131/291) <i>p</i> < .001	48% (135/282) <i>p</i> < .001	32% (96/300)
Pain response rate	35% (54/153) <i>p</i> = .01	31% (48/154) <i>p</i> = .08	22% (35/157)
Tumor response rate	12% (17/141) <i>p</i> = .11	8% (11/134) <i>p</i> = .59	7% (10/137)
Quality of life response rate	22% (61/278) <i>p</i> = .009	23% (62/270) <i>p</i> = .005	13% (35/267)

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Kaplan-Meier Estimates of the Probability of Overall Survival in the Three Groups



Tannock I et al. N Engl J Med 2004;351:1502-1512



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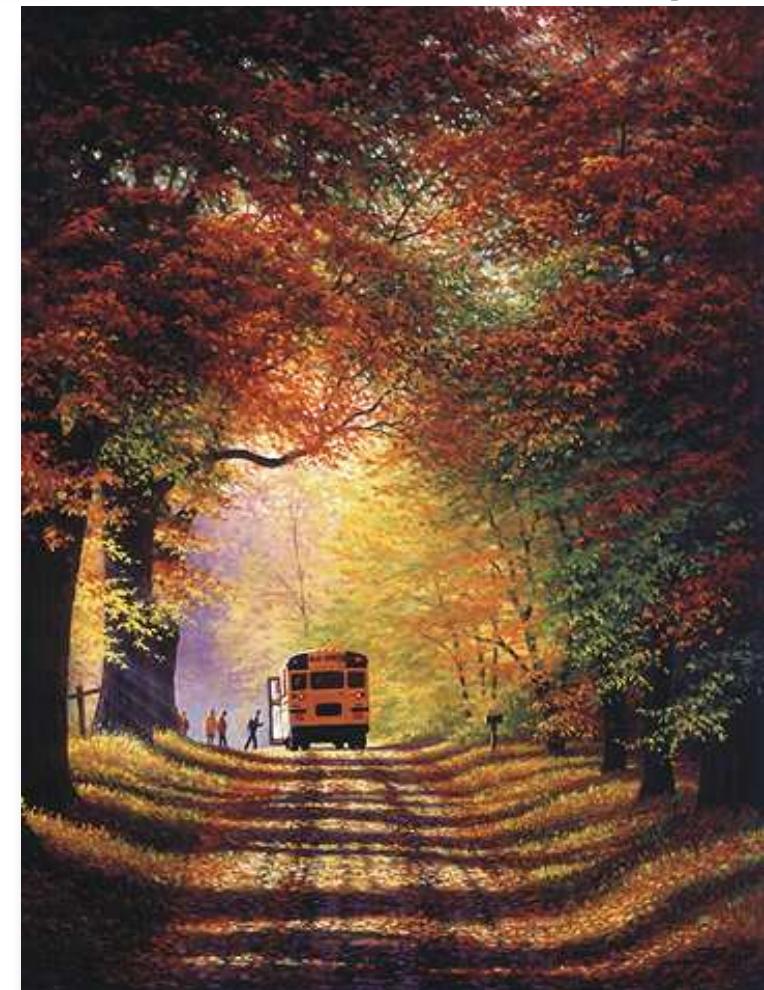
Future for the Treatment of Prostate Cancer with **BONE METASTASES**

Classic cytotoxic agents

vaccines

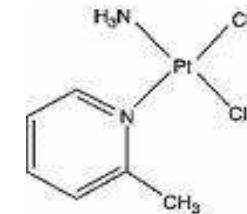
Radiolabeled mAb

targeted agents



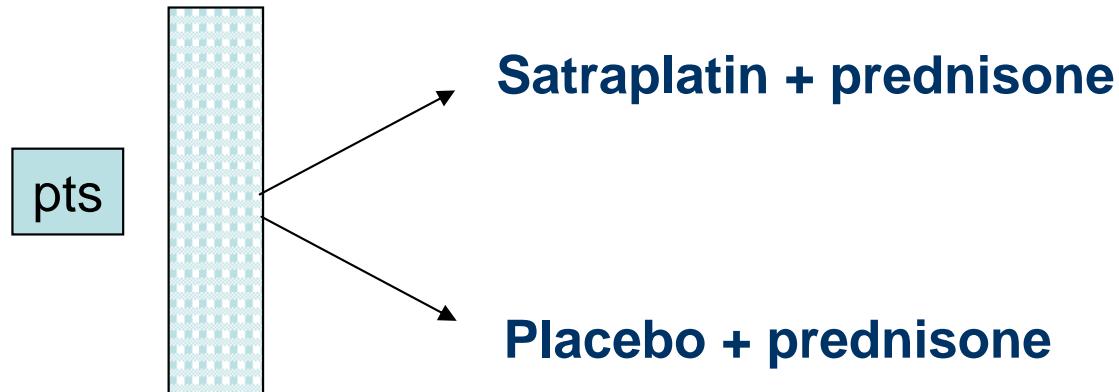
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Satraplatin

SPARC trial



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A trasentan

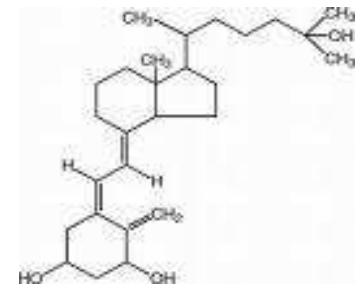
Endothelin-A receptor (ETAR) antagonist

Endothelin-1 (ET-1) is implicated in the development of the osteoblastic bone lesions that characterize metastatic disease.

SWOG S0421 trial, a randomized, placebo-controlled phase III trial designed to compare docetaxel, prednisone, and atrasentan with docetaxel plus prednisone alone in men with advanced HRPC.

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Calcitriol

Antiproliferative and proapoptotic effects in prostate cancer

ASCENT trial

randomized, double-blinded, placebo-controlled trial evaluating
the combination of docetaxel with the proprietary high-dose
calcitriol formulation DN-101

Thalidomide Bevacizumab

Thalidomide is a putative angiogenesis inhibitor. It inhibits angiogenesis and reduces VEGF levels

Bevacizumab, a humanized monoclonal antibody that targets VEGF

The National Cancer Institute is currently conducting a phase II study of a four-drug combination consisting of docetaxel, prednisone, thalidomide, and bevacizumab in men with chemotherapy-naive progressive HRPC, and the CALGB is coordinating a phase III, double-blinded, placebo-controlled trial of docetaxel plus prednisone with or without bevacizumab

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Gleevec

Inhibitor of PDGF-receptor signalling pathway implicated in tumor angiogenesis and bone formation.

Administered with zolendronic acid and paclitaxel in an experimental model of bone metastases of human prostate cancer

Combination with docetaxel

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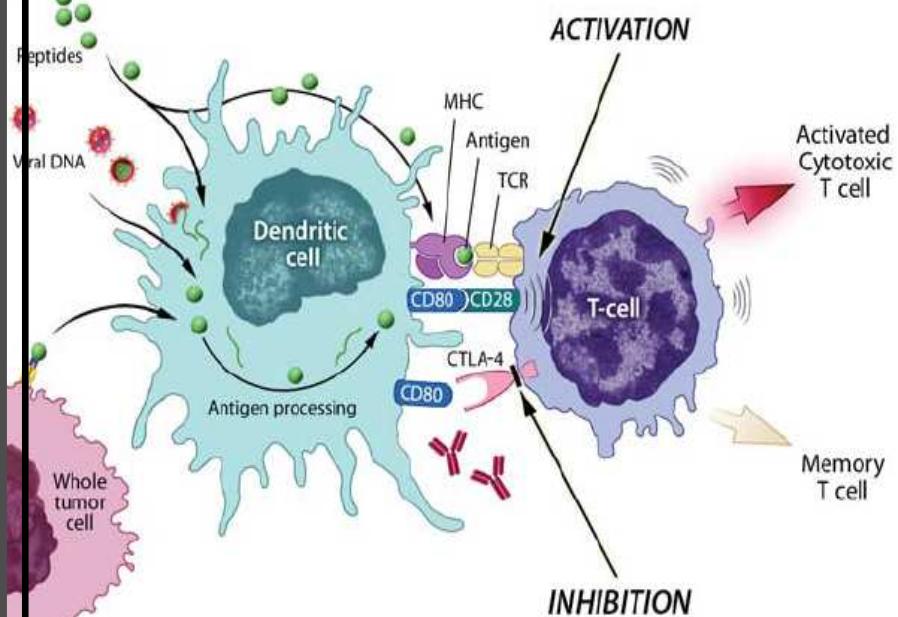
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Therapeutic Vaccines for Prostate Cancer

CHRISTOPHER P. TARASSOFF, PHILIP M. ARLEN, JAMES L. GULLEY

Laboratory of Tumor Immunology and Biology, Center for Cancer Research,
National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA



PSA, prostatic acid phosphatase, and prostate membrane antigens have been used as targets for developing immunotherapy.

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Phase II Study of APC8015F in Patients With Progressive Metastatic Prostate Cancer and Disease-Related Pain

[Alternate Title](#)

[Basic Trial Information](#)

[Objectives](#)

[Entry Criteria](#)

[Expected Enrollment](#)

[Outcomes](#)

[Outline](#)

[Trial Contact Information](#)

[Registry Information](#)

Alternate Title



APC8015F in Treating Patients With Progressive Metastatic Prostate Cancer and Disease-Related Pain

Basic Trial Information

Phase	Type	Status	Age	Sponsor	Protocol IDs
Phase II	Treatment	Active	18 and over	NCI, Pharmaceutical / Industry	UCLA-0307122-01 DEN-PB01 , NCT00170066

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Synergistic action of CYTOTOXIC DRUGS and BISPHOSPHONATES

Author (year)	Cancer cell line	Type of drug	Type of effect	Synergistic/ additive
Neville-Webbe et al. (2005) ⁴⁸ Woodward et al. (2005) ⁵⁰	Breast and prostate cancer cell lines	Doxorubicin	Induction of apoptosis Inhibition of invasion	Synergistic, timing- dependent and schedule-dependent
Neville-Webbe et al. (2005) ^{48,49}	Breast and prostate cancer cell lines	Paclitaxel	Induction of apoptosis	Synergistic, timing- dependent and schedule-dependent
Neville-Webbe et al. (2005) ^{48,49}	Breast cancer cell line, prostate cancer cell line	Doxorubicin	Induction of apoptosis for increased uptake of bisphosphonates and arrest in G2/M phase	Synergistic, timing- dependent and schedule-dependent
Jagdev et al. (2001) ⁵²	Breast cancer cell lines MCF-7 and MDA-MB-231	Paclitaxel	Induction of apoptosis	Synergistic
Vogt et al. (2004) ⁵¹	Breast cancer cell line	Epirubicin/ cyclophosphamide/ docetaxel/paclitaxel	Growth inhibition	Synergistic

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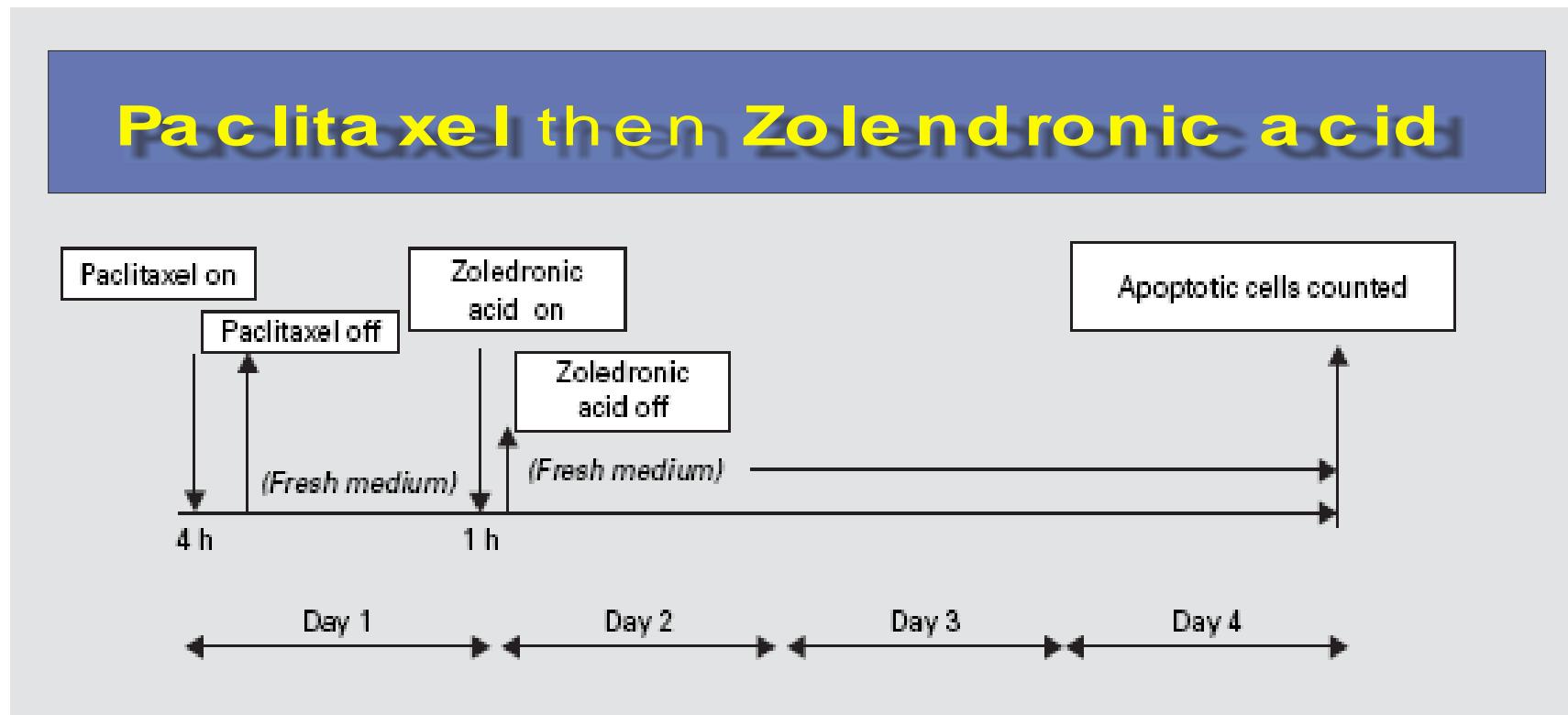
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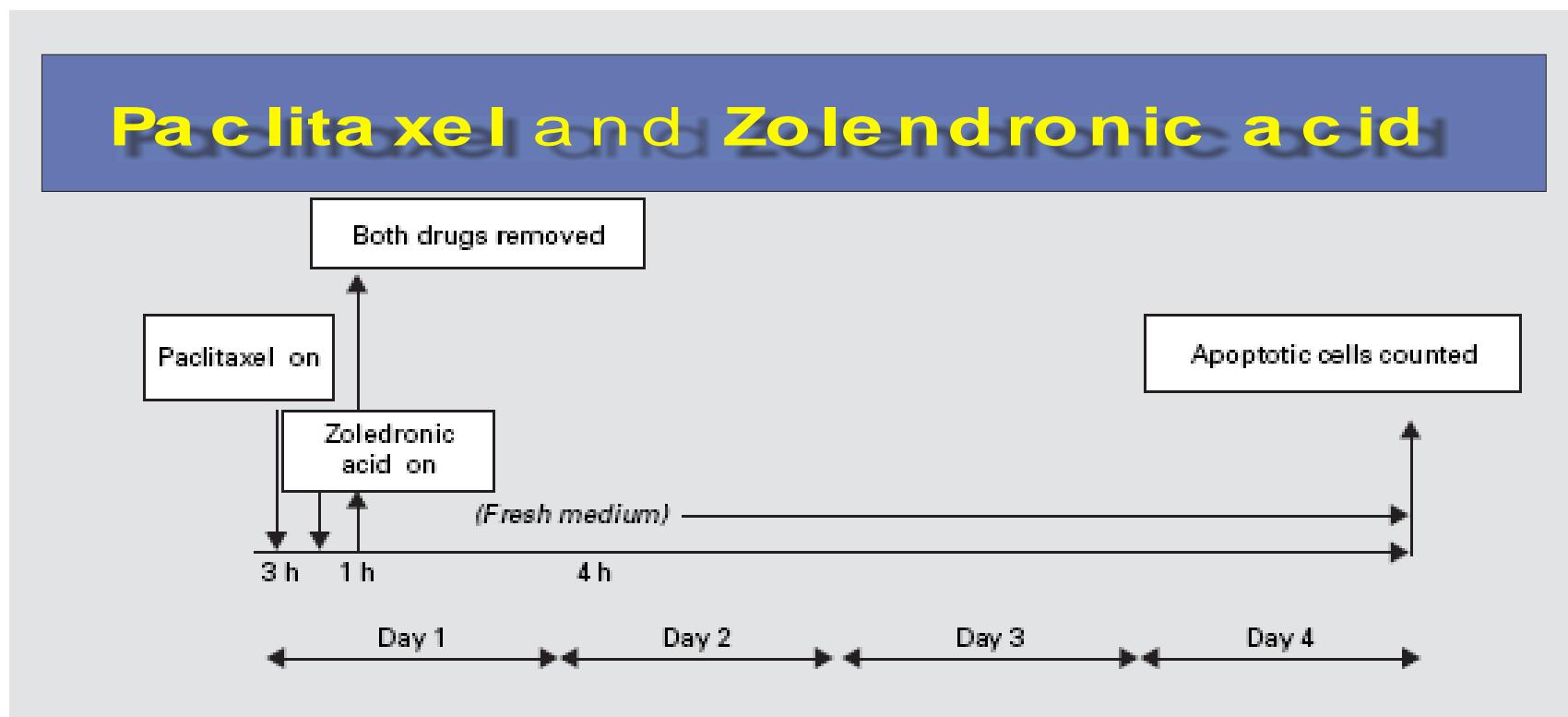


Neville-Webbe HL et al. (2006) Tumor Biol 27:92–103

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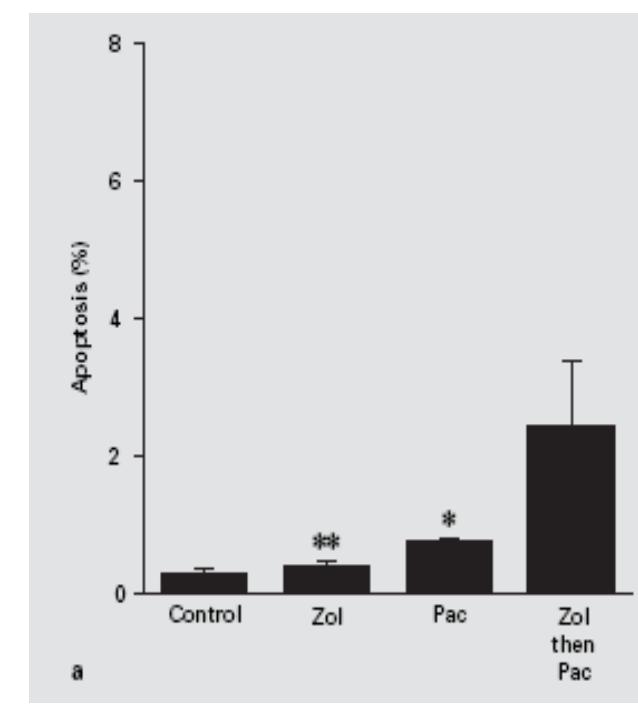
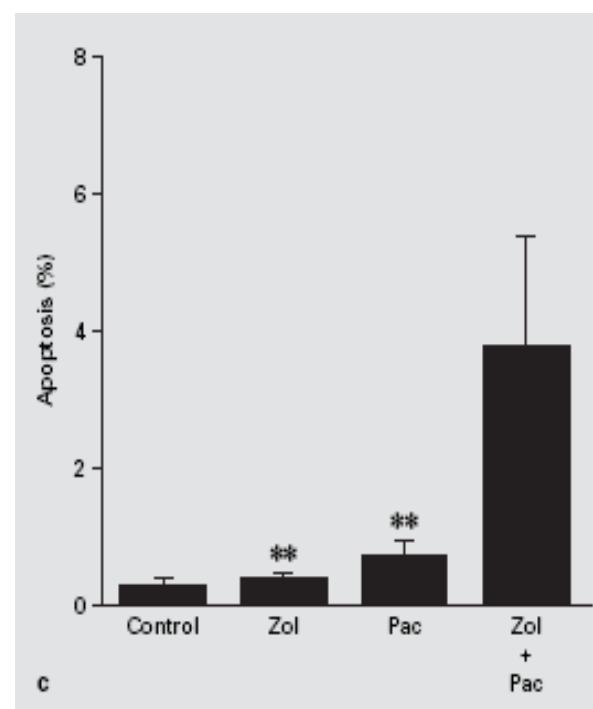
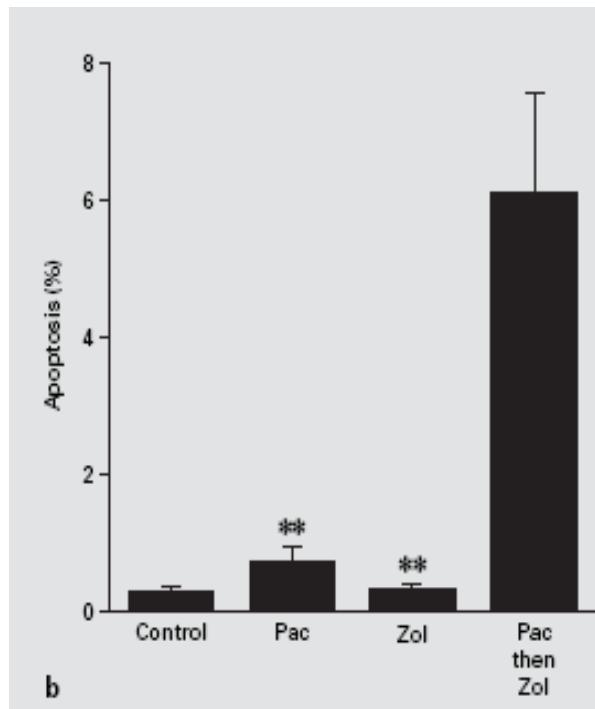


Neville-Webbe HL et al. (2006) *Tumor Biol* 27:92–103

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Matsumoto et al. (2005) ⁵⁶	SCLC cell line	Paclitaxel/etoposide/ cisplatin/irinotecan	Induction of apoptosis	Synergistic
Trojan et al. (2005) ⁵⁸	Gastric cancer cell line	Gemcitabine, oxaliplatin	Induction of apoptosis	Synergistic
Ullen et al. (2003) ⁶¹	Hormone-refractory prostate cancer cell lines	Gemcitabine	Induction of cytotoxicity	Additive/synergistic

Synergistic action of CYTOTOXIC DRUGS and BISPHOSPHONATES

conclusions

In the clinic, chemotherapy and bisphosphonates are not given in any particular sequence, and treatment intervals vary; preclinical data indicate that to achieve maximum effects from the combination of treatments, the sequence and the timing of drug administration have an important role and could determine the efficacy of the therapy, both in advanced disease and in the adjuvant setting.