TAT 2011

What Went Wrong with Aurora Kinase Inhibitors

March 9, 2011

Tito Fojo, MD, PhD

Mitotic Inhibitors: The Rationale

- Disrupting mitosis is a well-validated method to treat cancer
- Drugs that disrupt mitosis (such as the taxanes and the vinca alkaloids) also target neural cells and cause peripheral neurotoxicity
- Targeting proteins involved exclusively in mitosis will result in an effective chemotherapeutic agent while avoiding neurotoxicity

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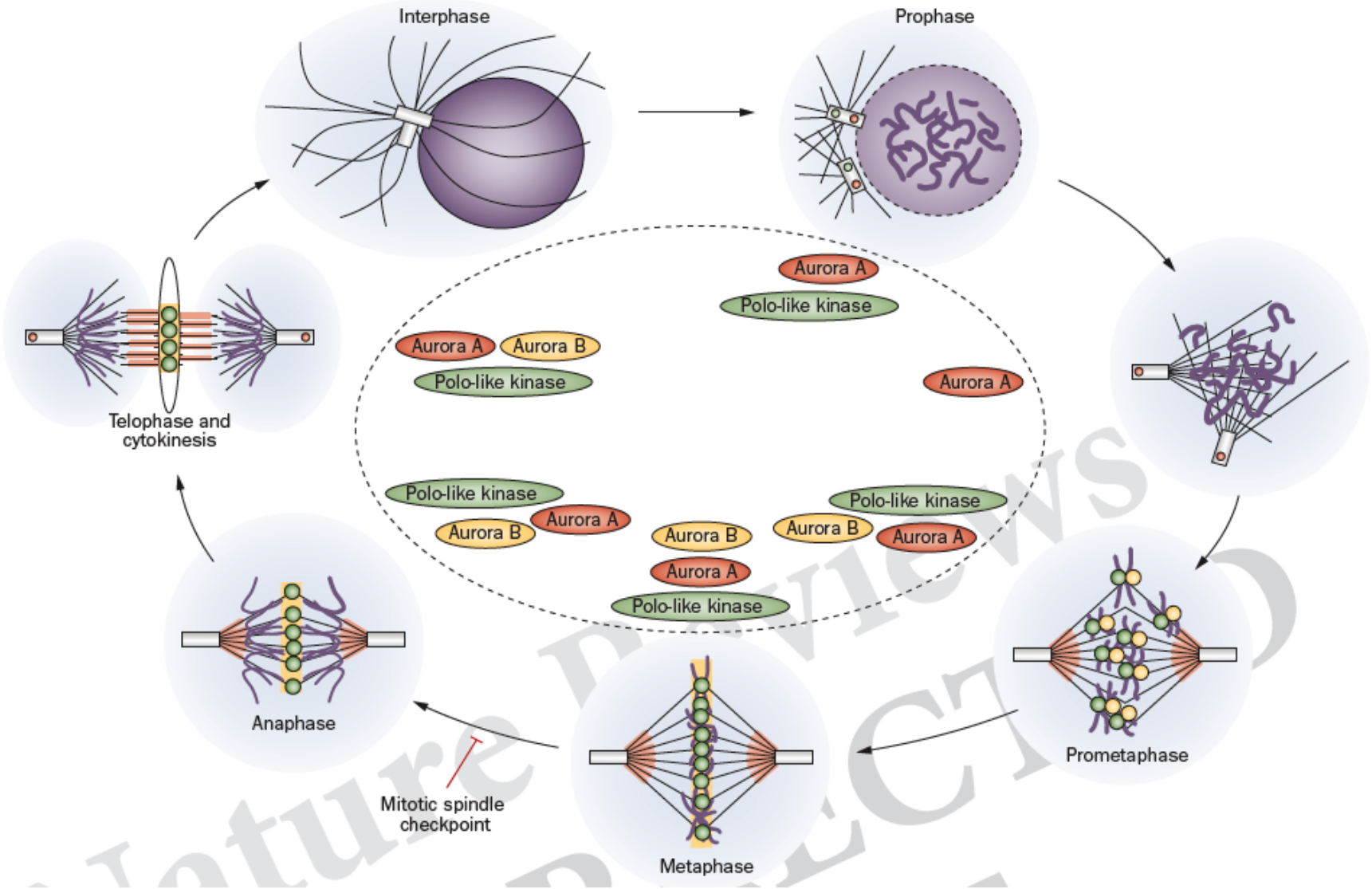
- **Aurora Kinase (AK) Inhibitors**
- **Polo-like Kinase (PLK) Inhibitors**
- **Kinesin Spindle Protein (KSP) Inhibitors**

Aurora A, Aurora B and Polo-like Kinases Proteins with Pivotal Roles in Mitosis



Komlodi-Pasztor et al, Nature Reviews Clinical Oncology 2011

PLK Inhibitors

Agents that disrupt mitosis: Limited activity to date

ON01910	Onconova	SD in 2 (6 wks and 22 wks)/5 - ASCO ‘06 Abstract 13137 0/13 - ASCO ‘06 Abstract 13026 SD in 1/23 - ASCO ‘08 Abstract 2515 OR in 1/20 - JCO “08
BI-2536	Boehringer	**PR in 4/95** - ASCO ‘08 Abstract 8030 **PR in 2/33** - ASCO ‘08 Abstract 8115 SD in 7/23 - ASCO ‘09 Abstract 8108
GSK-461364	GlaxoSmithKline	SD in 2/27 - ASCO ‘09 Abstract 3536
HMN-214	Nippon Shinyaku	No activity - ASCO ‘02 Abstract 419 A minor response and SD - ASCO ‘02 418 1 transient response and 2 SD/33 - ASCO ‘04 Abstract 3034 7/29 SD - CCR ‘06
BI-6727	Boehringer	recruiting

Aurora Kinase Inhibitors
Agents that disrupt mitosis: Limited activity to date

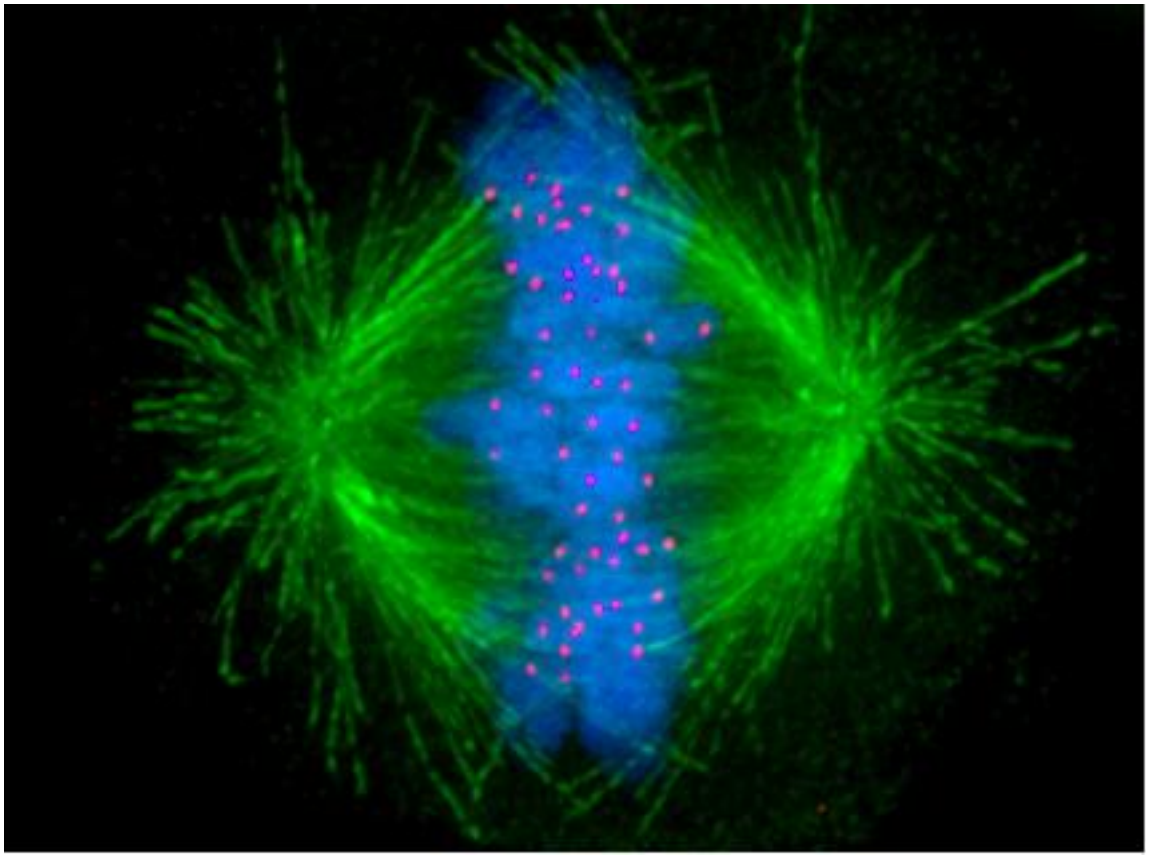
Compound	Company	Comment
MK-0457 (VX-680)	Vertex/Merck	Activity in 3 patients with Imatinib Resistant T315I CML, suspended due to heart safety issue
AZD 1152	Astra Zeneca	No activity reported
PHA 680632	Nerviano	No activity reported
PHA 739358 (Danusertib)	Nerviano	1/56 PR; **SD in 7/42** - CCR '09 + ASCO '08 Abstract 3507
MLN8054	Millenium	**SD in 3/43** - ASCO '09 Abstract 2578
MLN8237	Millenium	**SD in 5/23**
R763	Merck/Serono	Disease progression in 2/15 - ASCO '07 Abstract 14130
AT9283	Astex	PR 1/33 and **SD in 4/33** - ASCO '09 Abstract 2566, Hematological R in 2/29 - ASCO '08 Abstract 2518 **SD in 3/22** - ASCO '08 Abstract 2519
PF-03814735		**SD in 2/25**
SNS-314	Sunesis	**SD in 6/32** - ASCO '09 Abstract 2536.
SU6668	Sugen/Pfizer	**SD in 4/35** - ASCO '02 Abstract 1922 **SD in 3/35** - ASCO '02 Abstract 335
ENMD-2076	EntreMed	2/67 PR; **SD in 4/14** - CCR '11 + ASCO '09 Abstract 3520
CYC116	Cyclacel	one study is ongoing, one study is terminated
ENMD-981693; MKC 1693	Entremed/Miikana	recruiting
BI 811283	Boehringer Ingelheim	recruiting

What about stable disease?

A questionable measure of efficacy with any drug…

SD cannot occur with a mitotic kinase inhibitor

Mitotic Arrest is not Sustainable



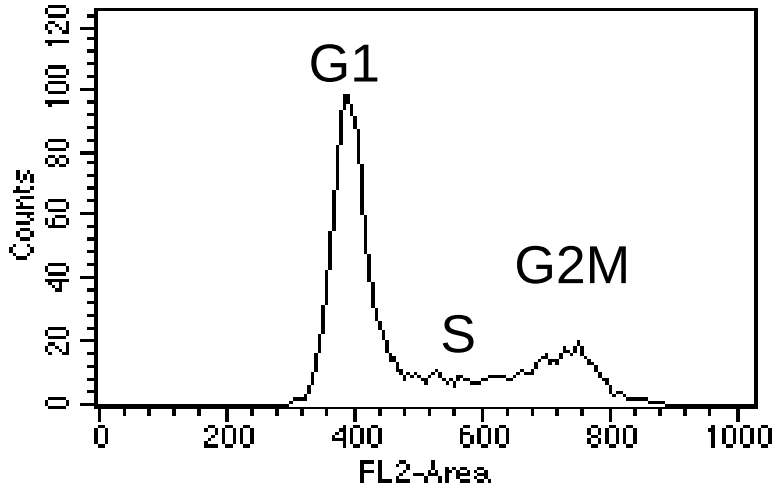
content.answers.com

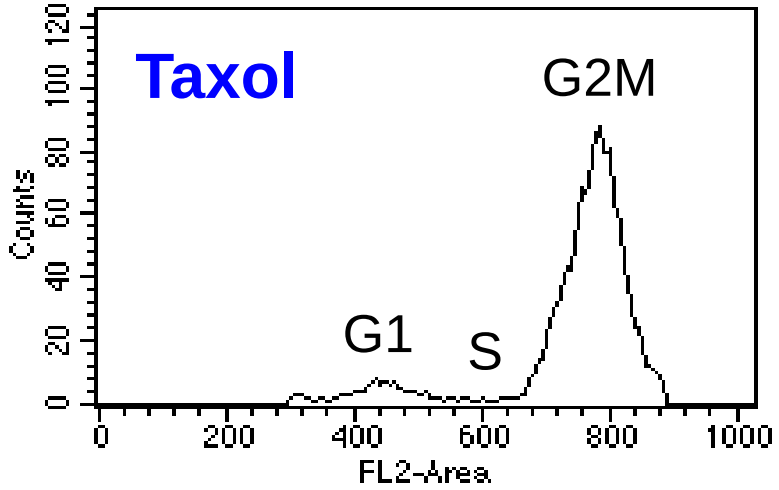
Mitotic Inhibitors: The Rationale
WHAT WAS WRONG?

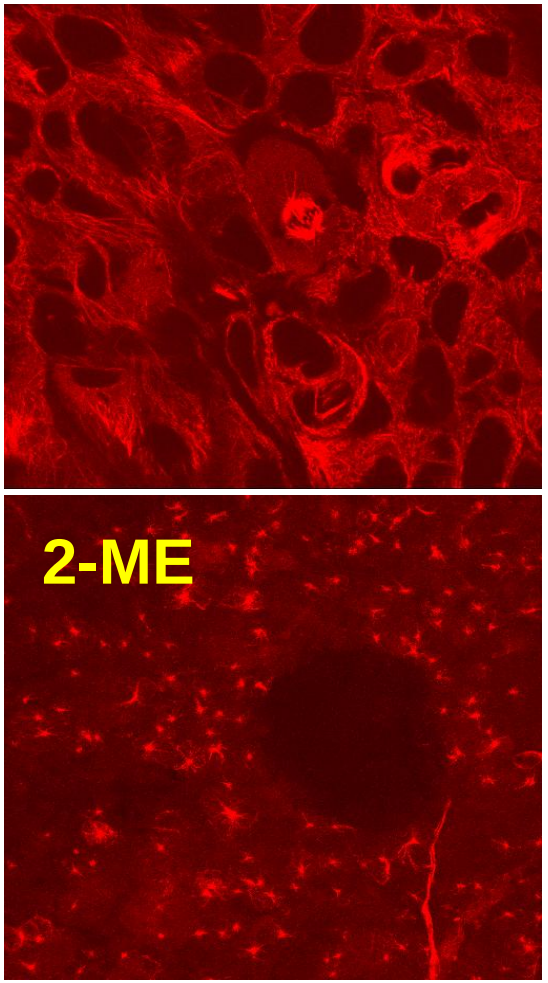
- **Disrupting mitosis is a well-validated method to treat cancer**
- Drugs that disrupt mitosis (such as the taxanes and the vinca alkaloids) also target neural cells and cause peripheral neurotoxicity
- Targeting proteins involved exclusively in mitosis will result in an effective chemotherapeutic agent while avoiding neurotoxicity

- **Disrupting mitosis is NOT a well-validated method to treat cancer**

Mitosis is a well-validated method to treat cancer *in vitro* and in xenografts, where tumor doubling times approach 24 hours





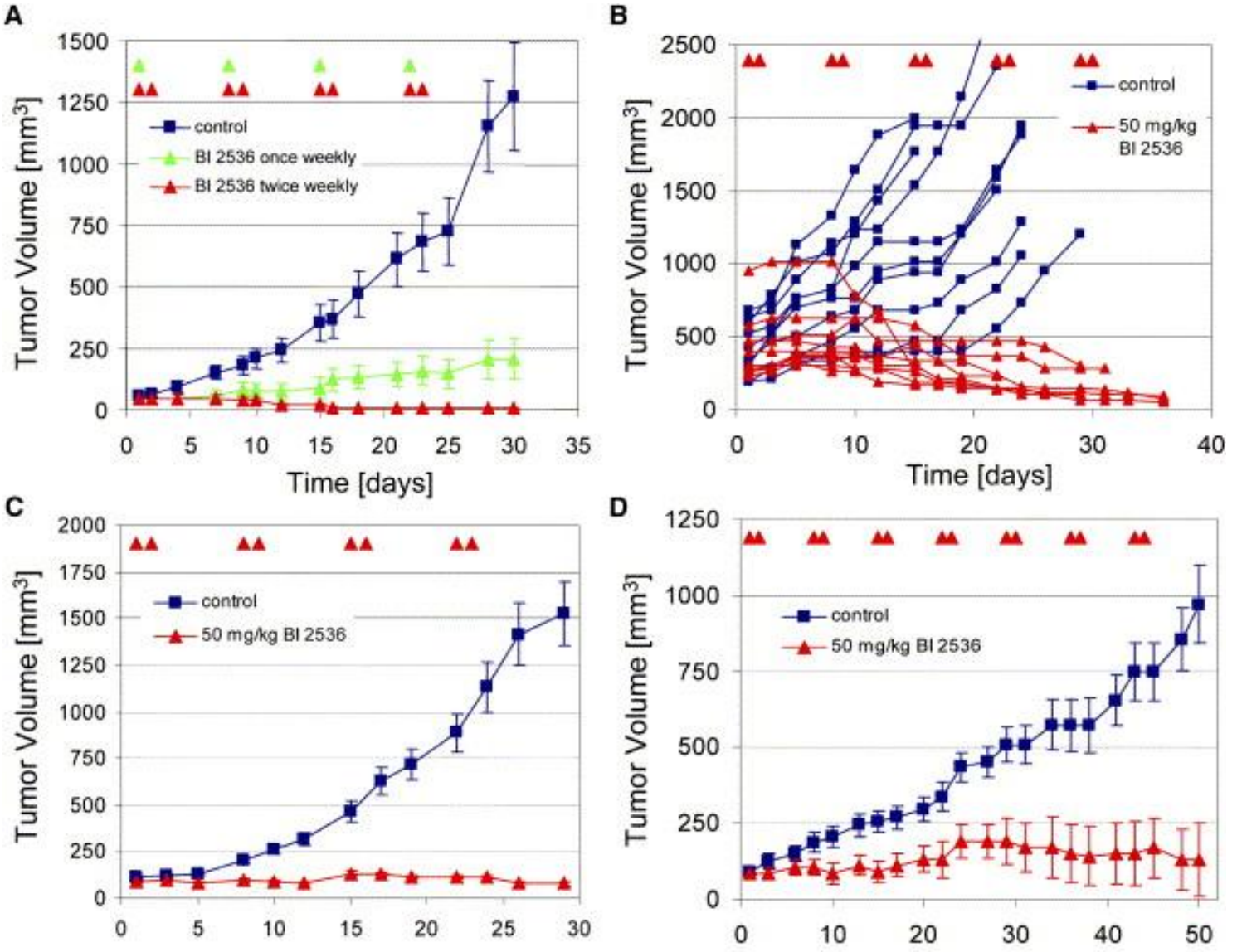


…but mitosis is NOT a well-validated method to treat cancer *in humans*, where tumor doubling times are much, much longer 24 hours

Tumor type	Assessment	# studies	Doubling times
Lung	Imaging	9	29 - 255 days
Colon	CEA values	5	18 - 153 days
Colon	Imaging	5	86 - 942 days
Hepatocellular	Imaging	14	63 - 203 days
Breast	Imaging	12	45 - 325 days
Prostate	PSA values	15	284 - 1694 days
Prostate	Imaging	1	33 - 577 days
Melanoma	Imaging	6	33 - 511 days

Preclinical models: Limited utility / No predictive value

BI 2536, an inhibitor of polo-like kinase 1, inhibits tumor growth *in vivo*



Steegmaier et al Curr Biol 17:316 (2007)

Preclinical models: Limited utility / No predictive value

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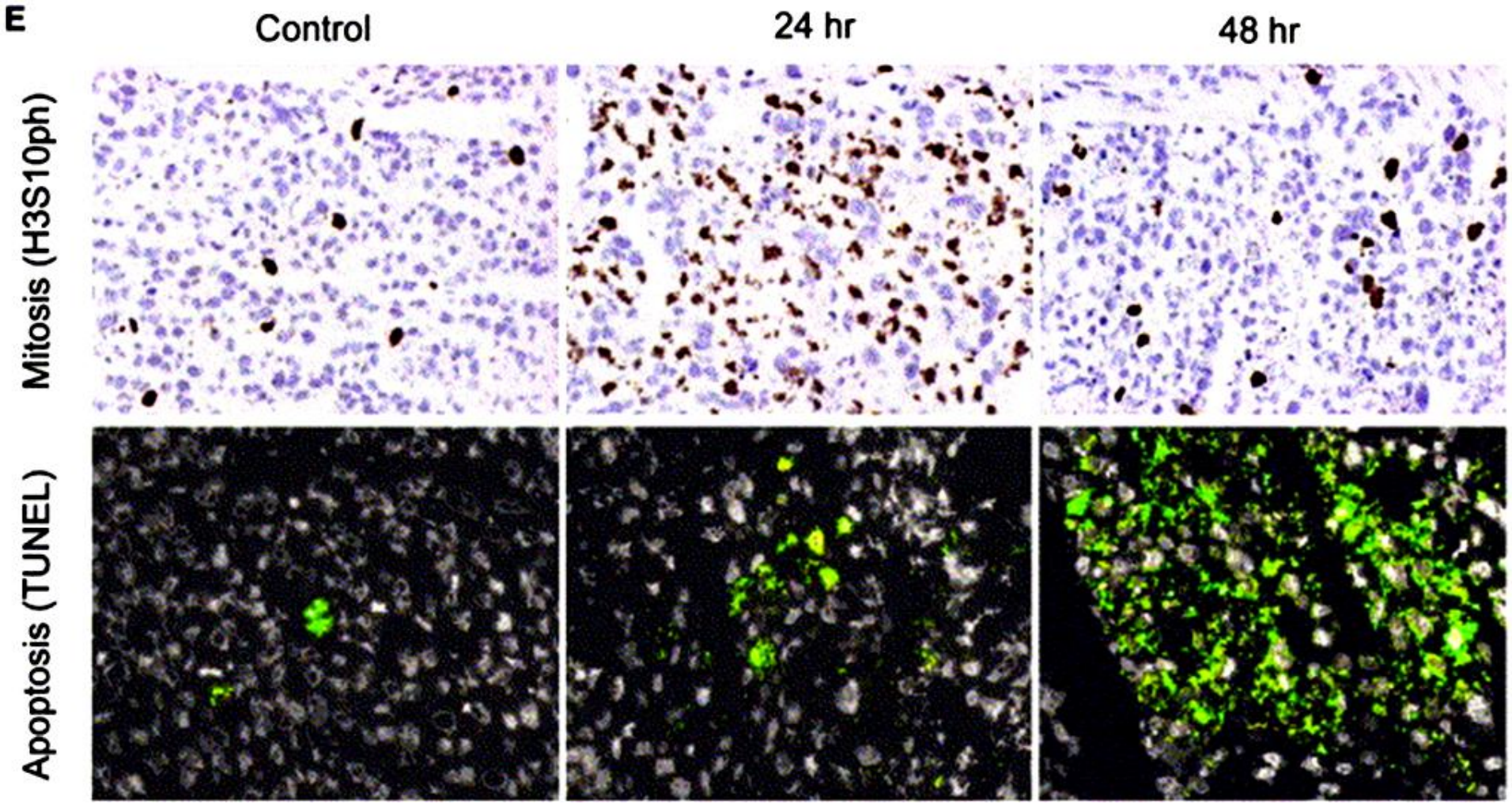
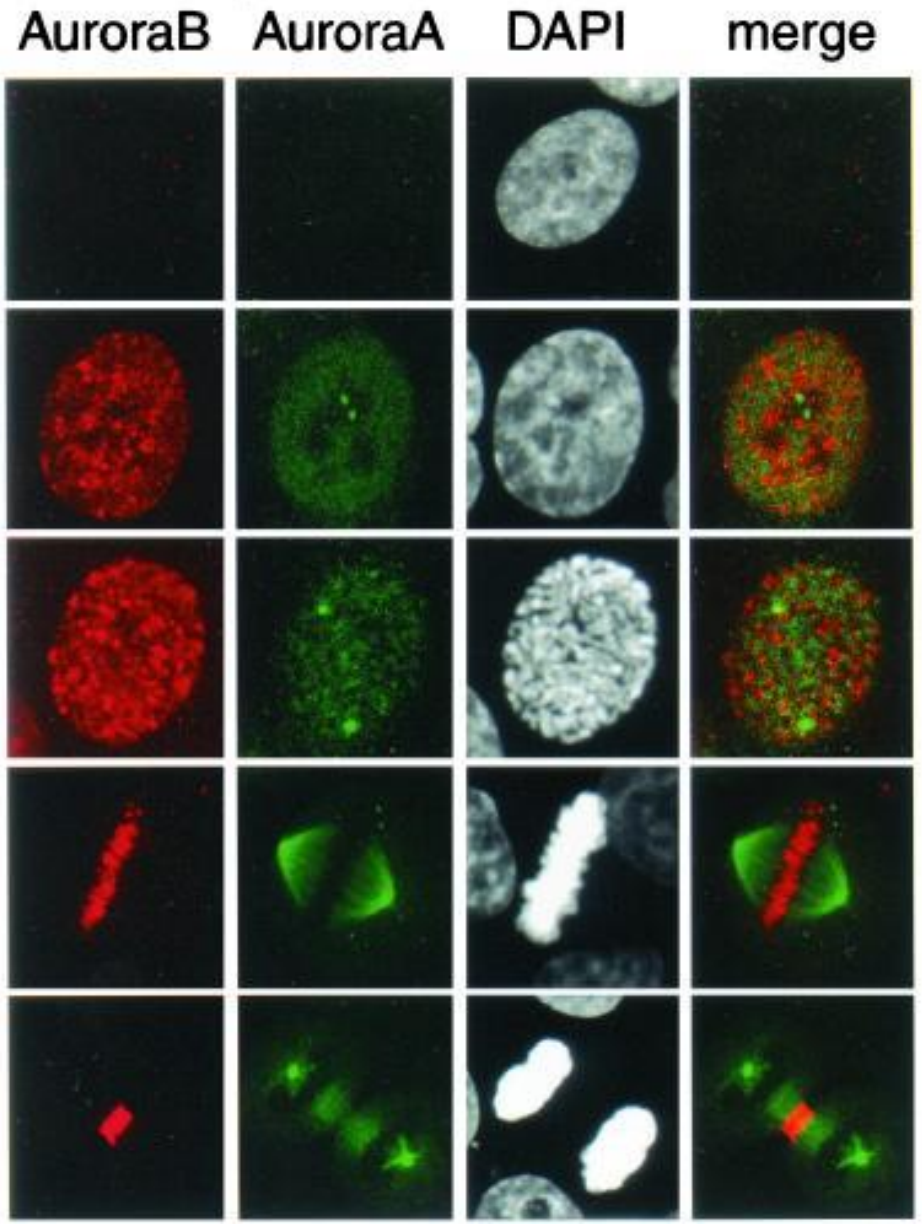


Steegmaier et al Curr Biol 17:316 (2007)

Aurora A and B are expressed in G2 and mitosis



Crosio et al
Mol Cell Biol
22:874 (2002)

mitosis is NOT a well-validated method...

The clinical exception and validation:
normal bone marrow
Mitotic kinase inhibitors and neutropenia
…. the principal and recurrent DLT

Aurora Kinase Inhibitors
Human Clinical Trials
DLT: Febrile Neutropenia

MK-0457 (VX-680)	Vertex/Merck	Response in 3 patients with imatinib-resistant T315I CML, suspended due to cardiac safety; SD in 3/16 patients
AZD 1152	Astra Zeneca	No activity reported
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AT9283	Astex	HR in 2/29 patients; SD in 3/22 patients; 1 case of PR and 4/33 patients with SD
SNS-314	Sunesis	SD in 6/32 patients
SU 6668	Sugen/Pfizer	SD in 4/35 patients; SD in 3/19 patients
ENMD-2076	EntreMed	SD in 4/14 patients
BI 811283	Boehringer Ingelheim	SD in 33.3% of 57 patients; SD in 29% of 52 patients
CYC116	Cyclacel	One study ongoing, one study terminated
ENMD 981693	Entremed/Miikana	Ongoing
MKC 1693	Entremed/Miikana	Ongoing

Neutrophil cellularity and kinetics in humans

Mean total marrow neutrophils*	**$7.70 \pm 1.20 \times 10^9$ cells/kg**
The mean number of normoblasts*	**$5.07 \pm 0.84 \times 10^9$ cells/kg**
Neutrophil:Erythroid ratio*	**1.52 ± 0.07[1]**
Post-mitotic pool*‡	**$5.59 \pm 0.90 \times 10^9$ cells/kg (73%)**
Mitotic pool* §	**$2.11 \pm 0.36 \times 10^9$ cells/kg (27%)**
Neutrophil postmitotic transit time*	**6.60 ± 0.03 days**
Rate of marrow neutrophil production*	**0.85×10^9 cells/kg per day**
Seven 2 cm tumors	**$5.6 \text{ X } 10^{10}$ cells**
Neutrophil turnover*	**$1.62 \pm 0.46 \times 10^9$ cells/kg per day**

***Data from 13 normal human bone marrows**
‡Metamyelocytes, bands and segmented neutrophils
§ Promyelocytes and myelocytes

Dancey, JT, et al. Neutrophil kinetics in man. J. Clin. Invest (1976)

Mitotic Inhibitors: The Rationale
WHAT ELSE WAS WRONG?

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- **Drugs that disrupt mitosis (such as the taxanes and the vinca alkaloids)** also target neural cells and cause peripheral neurotoxicity
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- Disrupting mitosis is not a well-validated method to treat cancer
- **The taxanes and the vinca alkaloids do not disrupt mitosis … in patients … So what do they do?**

How do microtubule targeting agents (MTAs) work?

We've established that in patients it cannot be by inhibiting mitosis - tumors do not divide fast enough.

So what are possible other mechanisms

What might be mechanisms that affect not mitotic cells but cells in interphase?

A new paradigm:
Interphase MTs as the key target for MTAs

PARTIAL LIST OF ONCOPROTEINS THAT TRAFFIC ON OR ASSOCIATE WITH MICROTUBULES

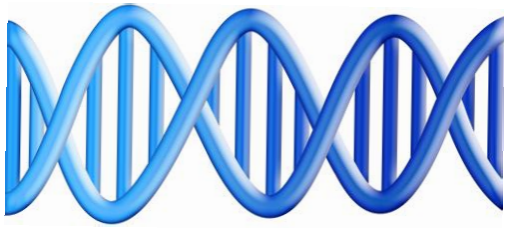
Protein/Gene	Function	Reference
p53	Role in genomic integrity and apoptosis	Giannakakou et al, 02
c-Myc	Roles in proliferation and tumorigenesis	Niklinski et al, 00
APC protein	Degradation of ß-catenin in Wnt signaling pathway	Brocardo and Henderson, 08
BRCA1	Maintain genomic intregrity; controls cell growth	Henderson, 05
RB	Tumor suppressor protein	Roth et al, 07
Smad2, 3 and 4	Signaling effectors of TGF-ß	Dong et al, 00
Glucocorticoid receptor	Binds/transports glucocorticoids	Dvorak et al, 02
ArH receptor	Cytochrome P450 (CYP) induction	Vrzal et al, 08
Androgen receptor	Binds/transports androgens	---
RA receptors	Nuclear receptors with diverse functions	Dvorák et al, 07
GLUT4	Insulin-responsive glucose transporter	Semiz et al, 03
HSP 90	Heat shock protein / important chaperone	Giustiniani et al, 09
PTHrP	Apoptosis, proliferation and hypercalcemia	Lam et al, 02
MIZ-1	myc-interacting zinc finger protein	Ziegelbauer et al, 01
Elk-1	ETS domain transcription factor	Demir et al, 09
Runx2	Regulator of cell growth and differentiation	Pockwinse et al, 06
Alpha 4	Regulatory subunit of PP2-type phosphatases	Liu et al, 01
MID1 (assoc with MID2)	Ubiquitin ligase; Regulates MT function	Aranda-Orgillés et al, 08

Komlodi-Pasztor et al, Nature Reviews Clinical Oncology 2011

Food for thought……..

DNA damaging agents and DNA repair proteins

DNA Damage DSBs



ATM / ATR Activation

p53

Chk1
Chk2

γH2AX

BRCA1

NBS1

Hdm2

NER and
MMR proteins

Rad51

Rad50 / Mrell

p21

14-3-3

Noxa

Puma

[Cdk2
Cyclin E]

[Cdc2
Cyclin B1]

Apoptosis

G1 and G2
Cell Cycle Arrest

DNA Damage
Repair

Microtubules + DNA Damaging Agents (DDAs) Effective Combinations in Clinical Oncology

Non-Hodgkin Lymphoma:
Cytoxan + doxorubicin + vincristine + prednisone [CHOP]
Cytoxan, vincristine, prednisone [CVP]

Hodgkin Lymphoma:
Doxorubicin + bleomycin + vinblastine + dacarbazine [ABVD]

Ovarian Cancer:
Platinum + paclitaxel

Lung Cancer:
Platinum + paclitaxel
Platinum + vinorelbine

Head and Neck Cancer:
Platinum + paclitaxel

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Ruth Plummer:

- **DNA dmage repair inhibitors (DDRi) are chemo- and radio-sensitizers**
- **? danger in combining DDAs with DDRi**
- **Are combinations of DDRi possible**

Prostate cancer and the androgen receptor

Prostate Cancer

An evolution in our understanding….

An evolution in terminology

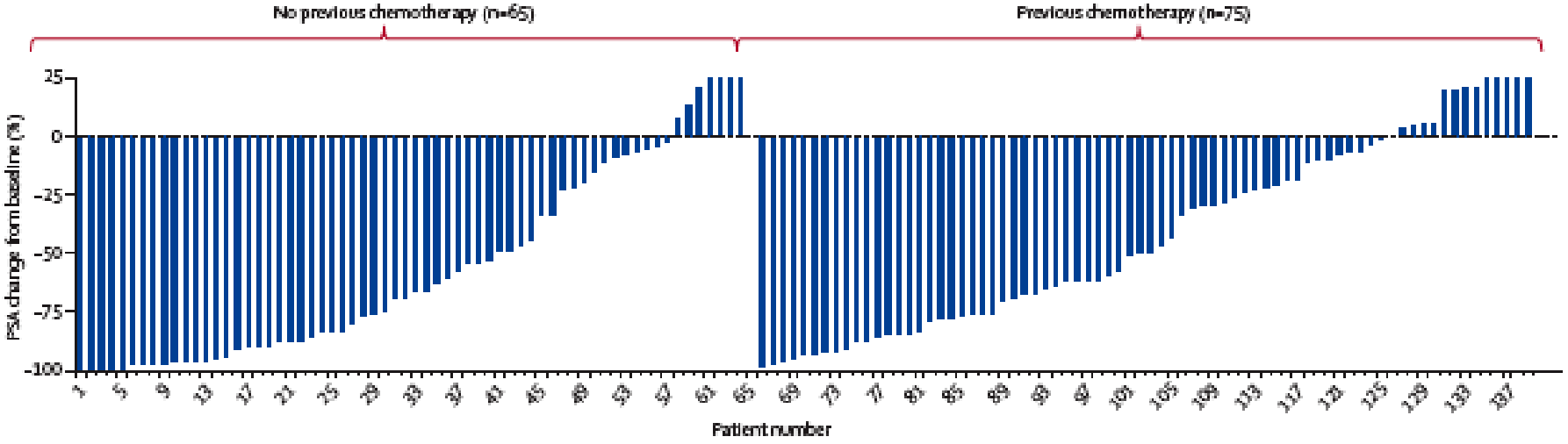
AIPC = Androgen-independent prostate cancer

HRPC = Hormone refractory prostate cancer

CRPC = Castration-resistant prostate cancer

Antitumour activity of MDV3100 in castration-resistant prostate cancer: a phase 1–2 study

Howard I Scher, Tomasz M Beer, Celestia S Higano, Aseem Anand, Mary-Ellen Taplin, Eleni Efstathiou, Dana Rathkopf, Julia Shelkey, Evan Y Yu, Joshi Alumkal, David Hung, Mohammad Hirmand, Lynn Seely, Michael J Morris, Daniel C Danila, John Humm, Steve Larson, Martin Fleisher, Charles L Sawyers, the Prostate Cancer Foundation/Department of Defense Prostate Cancer Clinical Trials Consortium



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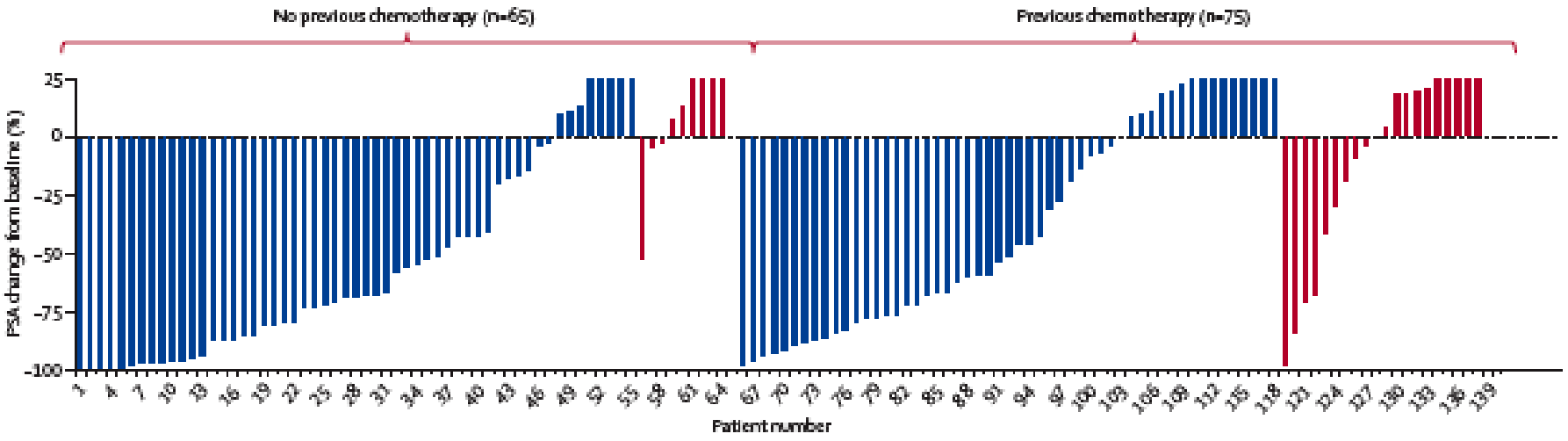

VOLUME 26 · NUMBER 28 · OCTOBER 1 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase I Clinical Trial of a Selective Inhibitor of CYP17, Abiraterone Acetate, Confirms That Castration-Resistant Prostate Cancer Commonly Remains Hormone Driven

Gerhardt Attard, Alison H.M. Reid, Timothy A. Yap, Florence Raynaud, Mitch Dowsett, Sarah Settatree, Mary Barrett, Christopher Parker, Vanessa Martins, Elizabeth Folkerd, Jeremy Clark, Colin S. Cooper, Stan B. Kaye, David Dearnaley, Gloria Lee, and Johann S. de Bono

Table 1. Patient Characteristics

Patient No.	Dose (mg)	Age (years)	Gleason Score at Diagnosis	Previous Systemic Treatments*	Baseline PSA (ng/mL)	PSA Doubling Time Prior to Study Entry		Presence of Measurable Disease on Baseline CT Scan	Presence of Bone Metastasis on Baseline Bone Scan	*ERG* Gene Class	Baseline DHEA (ng/dL)	Baseline Androstenedione (ng/dL)	Confirmed PSA Decline (%)†	Duration of PSA Decline (days)
						Months	Days							
01	250	52	4 + 5	Dex, DES	34.2	0.5	16	No	Yes	2N	67	< 2	No	—
02	250	66	4 + 5	HDACi‡	75	1.7	53	No	Yes	Edel	172	13	≥ 90	206
03	250	68	3 + 4	—	8.8	3.7	112	Yes	No	Esplit	407	77	≥ 90	578§
04	500	72	3 + 3	Dex, DES, antiangiogenic, and pan-CDKi‡	354	2.2	66	Yes	No	Edel	221	32	≥ 75	421
05	500	77	N/A	Dex	79	1.6	49	Yes	Yes	N/A	285	46	≥ 90	427
06	500	58	4 + 4	Dex, DES	290	2.2	67	Yes	No	Edel¶	466	23	No	—
07	750	74	4 + 5	—	28.1	2.5	75	None	Yes	2N¶	437	52	No	—
08	750	69	N/A	—	36.8	2.6	78	None	Yes	Edel¶	70	16	≥ 90	451§
09	750	85	4 + 4	Dex, DES	46	2.4	73	Yes	Yes	2N	192	46	≥ 90	465§
10	1,000	62	4 + 4	Dex, DES, HDACi‡	110	12.3	375	No	Yes	N/A	524	70	≥ 50	69
11	1,000	69	3 + 3	—	34.3	11.6	354	Yes	Yes	2N	320	27	≥ 90	406§
12	1,000	75	3 + 4	Dex, DES, pamidronate	58	5.5	166	No	Yes	2N	320	43	No	—
13	2,000	60	3 + 4	Dex	39.3	2	61	No	Yes	2N¶	122	15	≥ 75	351§
14	2,000	82	3 + 3	Dex	56	5.5	166	Yes	Yes	N/A	227	34	No‖	—
15	2,000	62	4 + 5	—	35.5	22.7	81	Yes	Yes	3N¶	102	9	No	—
16	1,000	62	3 + 4	DES	75	1.1	34	No	Yes	2N	87	8	No (≥ 30)	—
17	1,000	78	5 + 3	Dex, DES	279	0.6	19	No	Yes	2N	93	19	No	—
18	1,000	72	5 + 4	panERBi‡	34.6	3	91	No	Yes	2N¶	285	51	≥ 50	70
19	1,000	72	5 + 3	—	30.2	3.5	108	No	No	2N	902	125	≥ 75	145
20	1,000	62	3 + 5	—	28.4	0.7	20	No	Yes	2N	1310	107	≥ 50‖	84
21	1,000	67	3 + 3	DES	205	1.3	41	No	Yes	2 + Esplit¶	320	50	No (≥ 30)‖	—

Revisiting the ultimate target of treatment for prostate cancer

Published Online
April 15, 2010
DOI:10.1016/S0140-6736(10)60400-X

See Articles page 1437

Targeted treatment has become the mantra of medical oncologists. With some exceptions (MS4A1 [CD20] in non-Hodgkin lymphoma, ERBB2 [HER2] in breast cancer, and the fusion protein BCR-ABL in chronic myeloid leukaemia), a drug's mechanism of action or its appropriate target in a tumour can be uncertain. One of the original targeted treatments was for prostate cancer. For almost 70 years, men with this metastatic disease have been treated with medical or surgical procedures targeted against testosterone. Initially, patients who progressed after testosterone-lowering treatment were believed to be hormone-refractory and, therefore, unlikely to respond to additional hormonal strategies. However, chemotherapy is clinically meaningful, particularly for a class of agents believed, until recently, to have no rationale whatsoever in this population.

In terms of safety, MDV3100 was generally well tolerated. However, three seizures were reported in today's study; because seizures were also noted in a trial of a different androgen-receptor antagonist, these adverse effects warrant scrutiny as clinical development continues.

Now is an exciting time to revisit targeted treatments in castration-resistant prostate cancer. Abiraterone, a modern inhibitor of androgen synthesis via the CYP17A approach. When initial results were promising, each of the last six dose levels was expanded to include 24 patients, resulting in total accrual of 140 men.

Declines in prostate-specific antigen (PSA) were similar in both groups (62% chemotherapy-naive *vs* 51% chemotherapy-treated). Some separation was recorded between the two populations in both time to progression (41 *vs* 21 weeks) and radiographic response rate (not reached *vs* 29 weeks). Since the androgen receptor is important for production of PSA, some discordance between clinical activity and decrease in PSA is possible. However, tumour regression—notoriously difficult to achieve in prostate cancer—was tumour and develop potent drugs effective against this target. Although this approach has been successful in infectious diseases for nearly a century, treatment for metastatic prostate cancer has remained empirical. Scher and colleagues have shown the importance of targeted therapy, and their work is an important step in advancing the treatment science of prostate cancer.

William L Dahut, Ravi A Madan
Division of Clinical Sciences, National Cancer Institute, Bethesda, MD 20892, USA
dahutw@mail.nih.gov

OK so prostate cancer remains dependent on androgens….

What does that tell us about interphase microtubules as drug targets?

Prostate Cancer and Taxotere

FDA NEWS RELEASE

FOR IMMEDIATE RELEASE
P04-55
May 19, 2004

Media Inquiries: 301-827-6242
Consumer Inquiries: 888-INFO-FDA

FDA Approves New Indication for Taxotere -- Prostate Cancer

Today the Food and Drug Administration (FDA) approved Taxotere (docetaxel), injection in combination with prednisone (a steroid), for the treatment of patients with advanced metastatic prostate cancer. This is the first drug approved for hormone refractory prostate cancer that has shown a survival benefit.

"We consider this approval an important advance in the treatment of prostate cancer because it can help some patients live longer. Patients need as many effective treatment options as possible and Taxotere, in combination with prednisone, offers hope to certain patients who have not responded to other treatments," said Dr. Lester M. Crawford, Acting FDA Commissioner.

Prostate cancer is the second leading cause of cancer death in men and for those patients who have not responded to hormone therapy, Taxotere, in combination with prednisone, is a new treatment option that has now shown a survival advantage.

Taxotere works by inhibiting tubulin, a protein essential to cell division, thus preventing cancer cells from dividing and growing in number.

The safety and effectivness of Taxotere was established in a randomized, multi-center global clinical trial with over 1,000 patients comparing chemotherapy with taxotere and prednisone to mitoxantrone and prednisone in men with metastatic, hormone–refractory prostate cancer. Taxotere, in combination with prednisone, given every three weeks showed a survival advantage of approximately 2.5 months over the control group in the trial.

The most common adverse events reported were nausea, alopecia (hair loss), and bone marrow suppression. In addition, fluid retention and peripheral neuropathy (tingling sensations in the extremities), known effects of taxotere, were also observed.

Prostate Cancer and Cabazitaxel

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Cabazitaxel

On June 17, 2010, the U.S. Food and Drug Administration (FDA) approved cabazitaxel (Jevtana Injection, sanofi-aventis) for use in combination with prednisone for treatment of patients with metastatic hormone-refractory prostate cancer (mHRPC) previously treated with a docetaxel-containing regimen.

The approval is based primarily on the results of a randomized, open-label, international trial of 755 patients with mHRPC previously treated with docetaxel-containing regimens. Patients were randomized to receive either cabazitaxel 25 mg/m2 intravenously every three weeks in combination with prednisone 10 mg/day or mitoxantrone 12 mg/m2 intravenously every three weeks in combination with prednisone 10 mg/day. Patients were treated until disease progression, death, unacceptable toxicity, or completion of 10 cycles of therapy.

Median survivals were 15.1 and 12.7 months for cabazitaxel-treated and mitoxantrone-treated patients, respectively [HR 0.70 (95% CI 0.59-0.83), $p<0.0001$.] Investigator-assessed response rates using RECIST criteria was 14.4 and 4.4% for cabazitaxel-treated and mitoxantrone-treated patients, respectively, $p=0.0005$. No complete responses were observed on either arm.

The most common (≥10%) grade 1-4 adverse reactions included neutropenia, anemia, leukopenia, thrombocytopenia, diarrhea, fatigue, nausea, vomiting, constipation, asthenia, abdominal pain, hematuria, back pain, anorexia, peripheral neuropathy, pyrexia, dyspnea, dysgeusia, cough, arthralgia and alopecia. The most common (≥5%) grade 3-4 adverse reactions were neutropenia, leukopenia, anemia, febrile neutropenia, diarrhea, fatigue and asthenia.

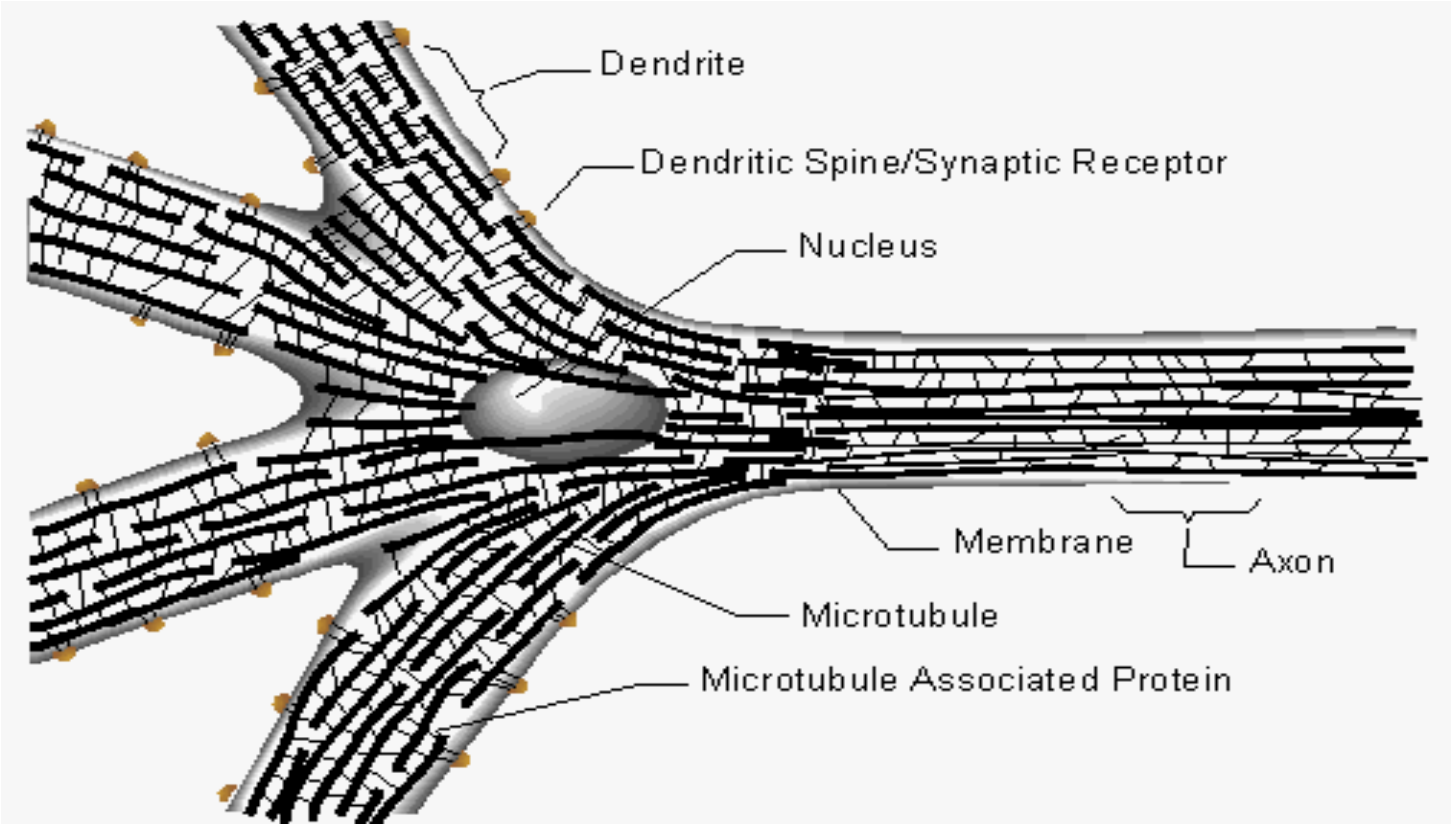
Prostate cancer

Berges RR et al (1995)	
High-grade prostatic intraepitherlial neoplastic cells	154 days
Localized prostatic cancer cells - low Gleason sum	577 days
Localized prostatic cancer cells - high Gleason sum	495 days
Metastatic hormone-naïve tumors – lymph node metastases	33 days
Metastatic hormone-naïve tumors - bone metastases	54 days
Hormone-refractory tumors - within distinct nonbone sites	126 days
Hormone-refractory tumors - within the bone	94 days
Range	33 days - 577 days

Johann de Bono agrees

Neurotoxicity

Neurotoxicity is evidence that disrupting interphase microtubules leads to cell death



“Restricted Expression” of Mitotic Kinases

The root cause of their failure in the clinic

Inhibition of mitotic kinases

Tumor cells	Myeloid cells
< 5%	30%
⇩	⇩
No effect	Severe neutropenia

Inactive against patient tumors

Toxic to normal bone marrow elements

Superb drug design

Conclusion

Microtubule targeting agents

Preclinical models with rapidly dividing cells ☑

Patients with tumor doubling times > 80 days ☑

Mitotic kinase inhibitors

Preclinical models with rapidly dividing cells ☑

Patients with tumor doubling times > 80 days ☒

Evidence that MTAs work not only by targeting mitotic cells but also by inhibiting cells in interphase

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