Epothilones and the next generation of phase III trials for prostate cancer

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INTRODUCTION

During 2005, an estimated 232 090 men will have prostate cancer diagnosed (one in six men), while 30 350 men will die from the disease in the USA [1]. Because of PSA screening, most patients present with localized prostate cancer and are candidates for definitive local therapy. Despite local therapy for localized disease, the actuarial 10-year likelihood of biochemical disease recurrence is ≈25% [2,3]. For patients who progress to systemic disease, or less commonly for those who initially present with advanced disease, androgen deprivation is regarded as the optimum first-line treatment [4,5]. Unfortunately, androgen-ablative therapy is only palliative, with a median duration of response of 12–24 months [4,5]. Second-line hormonal manipulation in men who progress on androgen deprivation results mostly in a biochemical response [6–8], which is generally transient and has no demonstrable impact on survival. Hormone-refractory prostate cancer (HRPC) is a progressive morbid disease, leading to eventual death over a median of 12–18 months. Chemotherapy in this setting has been actively investigated over the last two to three decades, and until recently was only palliative. The recent studies of docetaxel-based chemotherapy in men with androgen-independent prostate cancer showed a survival benefit for the first time in this disease state [9,10] and lifted the burden of HRPC as a chemoresistant disease [11].

These studies also provided proof-of-principle that targeting the tubulins is a fruitful strategy for effective therapy in HRPC. Based on this optimism, investigations of epothilones are rapidly advancing in HRPC, and this is the only new class of chemotherapeutic agents which have provided phase II activity in HRPC to date.

The broad spectrum of anti-neoplastic activity and the diverse clinical applications of taxanes have engendered significant interest in identifying mechanistically similar but structurally distinct compounds. Epothilones emerged as a new class of putative anti-neoplastic drugs based on *in vitro* assays designed to competitively inhibit the binding of paclitaxel to microtubules [12]. Epothilones are macrolides extracted from a variety of myxobacteria including *Myxococcus xanthus* or *Sorangium cellulosum* [13]. Like paclitaxel and docetaxel, the epothilones function by stabilizing the polymerized microtubule [14]; however, the epothilones are structurally distinct.

While an excellent contemporary review discusses in detail the mechanistic and cell-culture-based observations in the development of epothilones [15], we briefly discuss here their target (tubulins) and biological observations that provide insights to the anti-neoplastic activity of epothilones.

Active anticancer drugs (*Vinca* alkaloids and taxanes) work by perturbing the dynamic equilibrium of microtubule polymerization and depolymerization [16]. The formation of microtubules is essential for normal mitosis and cell division. This involves polymerization of heterodimeric α/β tubulin subunits, with multiple isoforms of both α and β tubulin present in proliferating human cells, and is regulated by several microtubule-associated proteins. Intact microtubule function is required for the formation and functioning of the mitotic spindle, and cells treated with agents that interfere with polymerization or depolymerization show changes in spindle formation, as well as arrest at the G2/M phase of cell cycle, which via poorly understood mechanisms is associated with induction of apoptosis [17–19]. Also, recent data suggest that an important component of the useful anticancer activity of these types of drugs involves anti-angiogenic effects on tumour-associated endothelial cells [20]. Moreover, certain alterations, e.g. loss of p53 function, which is common in many cancer cells, may confer hypersensitivity to taxanes as a result of altered expression of genes that are regulated by p53 [19].

Epothilones also induce microtubule bundling, formation of multipolar spindles and mitotic arrest [12]. Epothilones compete with paclitaxel for binding to microtubules and suppress microtubule dynamics in a manner similar to paclitaxel [21]; cell lines selected for resistance to epothilones contain mutations in β-tubulin that map near the taxane-binding site identified in a crystal structure of a docetaxel-$\alpha\beta$ tubulin complex [22]. However, recent studies in yeast reveal differences in the interactions between taxanes and epothilones with microtubules; epothilones stabilize *Saccharomyces cerevisiae* microtubules whereas paclitaxel does not, presumably as a result of differences of their individual binding interactions on tubulin function [23].

Preclinical studies also show important differences between epothilones and taxanes in drug-resistance mechanisms, both at the target site and in the drug-efflux pump, P-glycoprotein. Epothilone cytotoxicity is unaffected by an alanine-to-threonine substitution at reside 364 in β tubulin that confers resistance to paclitaxel [21]. This has led to a hypothesis that clinically, tumour cells resistant to taxanes will retain sensitivity to epothilones and hence provide a role for these class of compounds in the setting of clinical progression after taxane therapy. However, resistance to epothilones may also result from β tubulin mutations [24,25] and these cell lines were also found to be cross-resistant to paclitaxel. Another well established mechanism of taxane resistance to values in the sub- to nanomolar concentration range, and comparison of the inhibitory concentrations, involves over-expression of the multidrug efflux pump, the

TABLE 1 Ixabepilone in front-line HRPC. From [26].

Efficacy	Value
PSA response (41)	
Confirmed, n (%)	14 (34)
Unconfirmed, n (%)	2 (5)
Objective response (19), n (%)	3 (16)
Time to treatment failure, months	3
PFS, months	6
Toxicity (grade 3 or 4), n (%)	
Neutropenia	7 (17)
Neuropathy (grade 3)	
Sensory	5 (12)
Motor	1 (2)
Unspecified	1 (2)
Infection	5 (12)

Variable	Ixabepilone/estramustine	Ixabepilone
N	45	47
Efficacy		
N (%)		
Objective response	11/23 (48)	8/25 (32)
Bone scan stable	28/36 (78)	24/40 (60)
≥50% PSA decline	31/45 (69)	21/44 (48)
Days to PSA progression	141	145
Adverse events		
Grade 3/4, %		
Neutropenia	18/12	13/9
Febrile neutropenia	6/2	0/4
Thrombosis	7/2	0/0
Neuropathy	7/0	13/0

TABLE 2
The efficacy of ixabepilone/estramustine vs ixabepilone, and the prominent adverse events. From [27]

P-glycoprotein. Epothilones are more cytotoxic than paclitaxel in cell culture, with the concentration for 50% inhibition by various epothilones being slightly higher than those of paclitaxel in P-glycoprotein-expressing cell lines [15,26]. These results have led to hypothesis that epothilones may be more active than taxanes in patients with malignancies characterized by high levels of P-glycoprotein expression.

Epothilones exist in at least four forms (A-D) [15]. Four epothilone analogues are currently in human clinical trials in various phases of development, including aza-epothilone B (BMS-247550), a water-soluble semisynthetic analogue of epothilone B (BMS-310705), epothilone B (EPO906), and epothilone D (KOS-862). In the following sections we discuss the early clinical results and observations on the future development of these agents.

CLINICAL DEVELOPMENT OF EPOTHILONE

AZA–EPOTHILONE B (BMS–247550; IXABEPILONE)

This agent has shown potent cytotoxic effects on paclitaxel-sensitive and -insensitive cells, and in taxane-resistant tumour cell lines over-expressing the P-glycoprotein [14]. Phase I trials of BMS-247550 have been conducted for a cremophor-based formulation in a variety of schedules, including a single 60-min infusion every 21 days, a weekly schedule, five-times daily

every 21 days and three times daily every 21 days. There were anti-tumour responses in patients with melanoma, ovarian, nonsmall cell lung cancer and breast cancer, many previously treated with paclitaxel- or docetaxel-containing regimens [15]. Phase I evaluations of this agent in cytotoxic combinations (e.g. with carboplatin) are also ongoing. A dosing schedule of 40 mg/m^2 once every 3 weeks as a single agent was most prominently recommended and subsequently adopted for phase II testing.

SINGLE–AGENT PHASE II TRIAL IN HRPC

The most mature study reported for front-line activity in phase II settings for any epitholone was for BMS-247550 via two presentations at the annual American Society of Clinical Oncology (ASCO) meeting, 2004. A phase II single-agent trial (South-West Oncology Group, SWOG, 0111) was reported by Hussain et al. [27]. The primary objective of this study was to assess the PSA response. Eligible patients were those who had metastatic prostate cancer and in whom androgen-deprivation therapy and antiandrogen withdrawal had failed; previous chemotherapy was an exclusion criterion. Patients were treatment at 40 mg/m^2 i.v. over 3 h every 3 weeks. Premedication with 50 mg of diphenydramine and 150 mg ranitidine was administered 1 h before treatment. Forty-one patients (median age 73.1 years; median PSA 126.5 ng/mL) were enrolled. There was anti-tumour activity in 16 patients (39%) with a ≥50% PSA decline, and 14 of the responding patients (34%) had a confirmed PSA decrease (Table 1). Of these 14 patients, 10 had a decrease in PSA of >80%. Two

patients had a PSA level after therapy in the undetectable range (<0.2 ng/mL). There were partial responses in three of 19 patients with measurable disease. The median progression-free survival (PFS) was 6 months. Overall survival data were not mature at the time of reporting. The primary side-effects of ixabepilone were haematological and neurological (Table 1). Seven patients (17%) had grade 3 or 4 neutropenia, while grade 3 sensory neuropathy was reported in five (12%). Grade 3 motor neuropathy and neuropathy of unspecified pathology occurred in one patient each (2%).

RANDOMIZED PHASE II TRIAL OF IXABEPILONE ALONE OR COMBINED WITH ESTRAMUSTINE

After earlier data showing that adding oral estramustine to microtubule stabilizers is associated with apparently greater activity in prostate cancer, the combination of ixabepilone and estramustine in HRPC was investigated in another phase II multicentre trial by Kelly et al. [28]. Eligible patients were chemotherapy-naïve with progressive disease. Treatment was with ixabepilone at 35 mg/m^2 i.v. on day 2 with or without estramustine 280 mg orally three times daily on days 1 to 5 every 3 weeks. Low-dose prophylactic warfarin (2 mg/day) was given orally to patients receiving estramustine. There were 45 patients treated in the combination arm and 47 in the ixabepilone arm (92 in all). There was an objective response in eight of 25 patients (32%) treated with ixabepilone alone and in 11 of 23 (48%) in the combined arm (Table 2). PSA response

occurred in 48% of patients treated with ixabepilone alone and in 69% in the combination arm. The time to PSA progression was similar in both arms (141 days in the combined arm and 145 days in the ixabepilone-only arm). Neutropenia and neuropathy were also the main adverse events in this study (Table 2). Neuropathy occurred in 84% of patients but was tolerable (grade 1 or 2); grade 3 neuropathy occurred in 7–13% of patients. The severity of neuropathy improved over time and after a median follow-up of 413 days, grade 2 or 3 neuropathy had improved to grade 0 or 1 in 18 of 19 patients; 9% of patients in the estramustine arm had a grade 3 or 4 thrombotic event.

RESPONSE TO TAXANES AFTER IXABEPILONE THERAPY IN HRPC

Because preclinical data showed no cross-resistance between epothilones and taxanes, patients in the phase II study by Kelly et al. [28] who went on to receive second-line taxane therapy were analysed retrospectively [29]. Of the 49 patients evaluated, those who had been treated with either ixabepilone alone (23 men) or combined with estramustine (28 men) benefited from taxane therapy. There were PSA responses from second-line taxane therapy in 51% of patients (95% CI 33–66%), with a median time to PSA progression of 4.6 months. There were PSA responses in 61% of first-line responding patients, but significantly there were PSA responses also in a third of those who did not respond to first-line ixabepilone therapy.

The median survival in this cohort was 10.7 months from the initiation of second-line taxane-based therapy. Hence, this analysis supports the hypothesis that epothilones and taxanes are not cross-resistant, and may be useful in tandem. A multicentre National Cancer Institute-sponsored phase 2 trial currently recruiting is examining the use of second-line ixabepilone vs mitoxantrone and prednisolone in patients with metastatic disease and progressive disease after taxane therapy.

These preliminary phase II results are consistent with preclinical data and suggest that BMS-247550 is a broadly active anticancer drug. A schedule involving daily administration for 5 days every 3 weeks in second-line nonsmall cell lung cancer

Variable	Placebo	Atrasentan*	
Median days to disease progression	86	115	*TABLE 3*
Incidence of bone pain, %	54	45	*Results of the meta-analysis of atrasentan vs placebo in HRPC [49]*
Median days to bone pain	127	224	

All endpoints were significant vs placebo.

reported less neurotoxicity (6% grade III/IV toxicity) than a single dose given every 21 days [30]; however, whether these schedules differ in terms of anticancer efficacy in HRPC remains to be determined.

BMS-310705 (WATER-SOLUBLE EPOTHILONE B ANALOGUE)

BMS-310705 is a water soluble, semisynthetic analogue of epothilone B and hence does not require a cremophor-based formulation. It has been evaluated in phase I trials with two different schedules, involving a 15-min infusion given every 3 weeks [31] or weekly for 3 consecutive weeks every 28 days [32]. No premedications were used and there were no hypersensitivity reactions. For the every-3-week schedule, neuropathy was dose-limiting and led to a recommendation of 40 mg/m² as the phase II dose. When administered weekly for 3 consecutive weeks every 28 days, grade 3 diarrhoea was dose-limiting at 30 mg/m². At the 20 mg/m² dose using this schedule, 25% of patients missed the third weekly dose because of diarrhoea.

Also, at this dose sensory neuropathy occurred during the fourth course in two-thirds of the patients. Based on these results, evaluation of a 2-weeks on, 1-week off schedule for BMS-310705 is ongoing. Responses were documented with both schedules, including partial responses in patients with ovarian, bladder, stomach and breast cancer, and a complete response in a patient with nonsmall cell lung cancer. Based on the encouraging activity of BMS-247550, further evaluation of BMS-310705 is also planned in HRPC.

EPOTHILONE B (EPO906; PATUPILONE)

Patupilone (EPO 906; epothilone B) is a more potent microtubule stabilizer than paclitaxel and in preclinical studies was found to accumulate in intracellular concentrations several hundred times greater than in the extracellular medium [33]. It is formulated in

polyethylene glycol-300, minimizing the potential for carrier-associated adverse reactions. Despite being structurally very similar to ixabepilone, patupilone is associated primarily with diarrhoea, whereas ixabepilone is associated with neuropathy as its primary dose-limiting toxicity. This important distinction may favourably affect the further development of this agent, given that its toxicity does not overlap with that of other taxanes.

Hussain et al. [34] reported the results of a multicentre phase II study of weekly patupilone in patients with HRPC. A maximum of one previous chemotherapy regimen was allowed in this trial. Patients were treated with six cycles of patupilone 2.5 mg/m² per week for 3 of 4 weeks. Forty-five patients (median age 69 years) were enrolled and 29 (64%) had received previous chemotherapy. Patupilone was associated with grade 3 diarrhoea in 22% of patients, resulting in grade 3 or 4 dehydration in 11%. No grade 3 or 4 neuropathy was reported. Weekly treatment was associated with a 50% PSA response in seven of 28 patients (25%; Table 3). Importantly, three of the seven responders had received previous taxane-based chemotherapy. The median duration of PSA response was 2.2 months. Also, the preliminary results of several phase II trials of EPO906 in refractory solid tumours were reported at the 20th Chemotherapy Foundation Symposium (http://www.mssm.edu.proxy.lib.umich.edu/tcf/archives/symposiumxx/index.shtml). These early phase II results suggest that EPO906 is a broadly active drug and is able to induce responses in at least some patients with taxane-resistant disease. Further clinical development has not been publicly disclosed, but is anticipated.

EPOTHILONE D (KOS-862)

The phase I evaluation of KOS-862 included several dosing schedules: a single dose every

3 weeks, a daily dose three times every 3 weeks, a fixed-rate dose every 3 weeks, and a weekly dose for 3 weeks with a 1-week rest [15]. There was significant toxicity in patients treated with the single-dose every 3 weeks, which included impaired gait and cognitive/perceptual abnormalities, sensory neuropathies, and fatigue. There were responses observed in heavily pre-treated patients with testicular, ovarian, pancreatic and breast cancers. Dose-limiting toxicities have not been reported yet. Phase II studies in front-line HRPC settings are planned.

WHERE DO WE GO FROM HERE? NEXT–GENERATION (PHASE III) TRIALS IN HRPC

A new generation of clinical trials will evaluate a variety of newer agents against traditional targets (e.g. epothilones against the mitotic spindle), and against entirely new targets in validated prostate-cancer pathways (angiogenesis and endothelin pathway, among others) based on a deeper understanding of the biology of androgen-independent prostate cancer. This area of 'rational therapy development' based on an understanding of the basic biology of prostate cancer, rather than empirical evaluation of chemotherapeutic agents, is the new frontier which holds the most promise in advancing the systemic treatment of HRPC. This next generation of phase III trials in HRPC are described, along with their rationale and study designs.

TESTING TARGETED THERAPY IN PHASE III SETTINGS: THE SWOG 0421 TRIAL

The endothelin pathway is particularly important in several phases of prostate cancer development and progression, but appears to be especially important in the progression of bone metastases [35–38]. In the normal prostate gland, mature endothelin (endothelin-1) is produced by epithelial cells. The highest concentrations of endothelin-1 in the body are found in seminal fluid. In prostate cancer, key components of endothelin-1 clearance, endothelin-B receptor binding [39] and neutral endopeptidase activity are diminished [40], resulting in an increase in local endothelin-1 concentrations. There is also increased endothelin-A-receptor expression with advancing tumour stage and grade in both primary and metastatic prostate cancer [35,41]. By contrast, endothelin-B tends

not to be expressed, probably due to gene silencing through methylation of the promoter [36,42,43]. Hence, the endothelin axis is hyperactive in prostate cancer, while the pathway has an important and perhaps essential role in the progression of bone metastases from prostate cancer [37,38]. Atrasentan (ABT-627) is an orally bioavailable inhibitor of the endothelin-A receptor [44]. Atrasentan inhibits prostate cancer cell-related paracrine mitogenic stimulation of co-cultured osteoblasts mediated in part through the insulin growth factor pathway and is thought to be important in the initiation of bone metastases [45,46]. Atrasentan also inhibits cascading self-stimulatory autocrine effects of endothelin-1 during the metastatic process seen in model systems [45].

Atrasentan has completed randomized, placebo-controlled phase 2 and 3 studies in men with HRPC, with time to progression as the clinical endpoint. The phase 2 randomized, controlled trial evaluated the activity of 2.5 mg or 10 mg of atrasentan in patients with metastatic HRPC. In that study of 288 patients, there was a significantly longer median time to disease progression (196 days vs 129 days, $P = 0.021$) and to PSA progression (155 days vs 71 days; $P = 0.002$) in the 84 evaluable patients enrolled in the 10-mg arm and the placebo arm (104 men), respectively [47]. Both measures were also longer in the 10-mg group, although the median time to PSA progression was not statistically significant in this arm. Atrasentan was well tolerated, with the most common and significant treatment-related adverse events being headache, rhinitis and peripheral oedema.

Results from the recently reported phase III trial evaluating the 10-mg dose of atrasentan (408 men) vs placebo (401) in patients with metastatic HRPC continued to show beneficial results in favour of atrasentan, although the primary endpoint of disease progression (i.e. new lesions, clinical symptoms, skeletal complications, or pain) were not statistically significant in the intent-to-treat analysis [48]. Nevertheless, increases in bone alkaline phosphatase, total alkaline phosphatase and PSA were significantly reduced in patients treated with atrasentan, suggesting that this agent delays disease progression.

Quality-of-life variables, as measured by the Functional Assessment of Cancer Therapy –

Prostate, were also significantly improved with atrasentan, most notably in the pain component of the prostate cancer subscore. As with the earlier trial, the most common adverse events were rhinitis, headache and peripheral oedema. A pooled intent-to-treat meta-analysis of all 1097 patients randomized to receive either atrasentan or placebo in the two trials [47,48] was conducted to more precisely estimate the treatment effect of the agent and to increase the power to detect a modest but clinically meaningful effect [49].

Results of the meta-analysis showed a significant increase in the time to disease progression with atrasentan ($P = 0.013$), which translated into a 19% reduction (hazard ratio 1.19) in the risk of disease progression. Of note, the improvement was detected by 3 months and was sustained throughout the study period.

There were also significant decreases in the incidence of and the onset to pain in the atrasentan vs placebo groups ($P = 0.003$). The median pain-free duration in the atrasentan arm was 7 months, which was 97 days longer than in the placebo arm. Patients receiving atrasentan had a lower incidence of pain and remained pain-free longer, for a median of 224 vs 127 days in the placebo arm (Table 3).

There is good preclinical evidence for an additive effect of atrasentan and taxanes. In ovarian cell-line models pretreatment with atrasentan sensitizes the cells to paclitaxel-induced apoptosis [50]. In xenograft models, the combination has additive effects on tumour detumescence, apoptotic indices and angiogenesis [51]. Based on this, and the independent activity of both agents in HRPC, the SWOG designed a protocol (SWOG 0421) to evaluate, in a randomized, placebo-controlled and direct comparison, treatment with docetaxel with or without atrasentan (Fig. 1). With the PFS as the primary outcome and median survival as the main secondary outcome, this trial with 706 patients is powered at 96% to detect a 33% increase in PFS (from 6 to 8 months) and powered at 85% to detect a 30% increase in median survival with the addition of atrasentan to docetaxel-based chemotherapy. Additional outcomes, such as improvement in pain, quality of life, PSA response and its surrogates for survival, objective tumour response and bone turn-over markers, will also be ascertained.

TESTING BIO–CHEMOTHERAPY IN PHASE III SETTINGS: THE CANCER AND LEUKAEMIA GROUP B (CALGB) 9040 TRIAL

An essential step in the metastasis of solid tumours is the growth of new blood vessels, which must be generated for metastases to grow. Vascular growth factors, including vascular endothelial growth factor (VEGF), matrix metalloproteins and integrins, regulate the process of angiogenesis. Inhibiting these targets can arrest tumour growth and inhibit metastatic spread. These vascular growth factors are expressed in both the tissue and serum of patients with prostate cancer [52]. Elevated VEGF levels portend a poor prognosis in HRPC. Bevacizumab, a humanized monoclonal antibody directed against VEGF, is active in combination with chemotherapeutic agents in advanced colorectal carcinoma. A similar therapeutic approach has been undertaken with bevacizumab in prostate cancer. A trial by the CALGB found promising activity in HRPC with the combination of docetaxel 70 mg/m^2 every 3 weeks, estramustine 280 mg oral three times daily on days 1–5 and bevacizumab 16 mg/kg every 3 weeks [53]; 79 patients were enrolled and nine of 17 evaluable patients had a partial radiographic response. Of 20 patients evaluable for PSA decline, 13 (65%) had a confirmed PSA decline by half. At the time that this trial was reported, the trial had yet to mature and the median survival was not reported. Encouraged by this early indication of significant activity, the CALGB initiated the CALGB 9040 phase III trial (Fig. 2) to evaluate the first bio-chemotherapy combination in phase III settings in HRPC. In cooperation with the Easter Oncology Cooperative Group and the National Cancer Institute of Canada, the trial is designed to enrol 1020 patients, stratified by the Halabi nomogram [54]. The primary outcome is overall survival with a 95% power to detect a 25% increase in median survival (from 19 to 24 months). Secondary outcomes include PSA response, PFS and response rate. This trial is designed to recruit over 36 months and have data on follow-up for at least 24 months.

SUMMARY

While the phase II trials of epothilones are currently ongoing, ixabepilone (BMS-247550) and patupilone (EPO906) have provided the most convincing phase II data for activity in
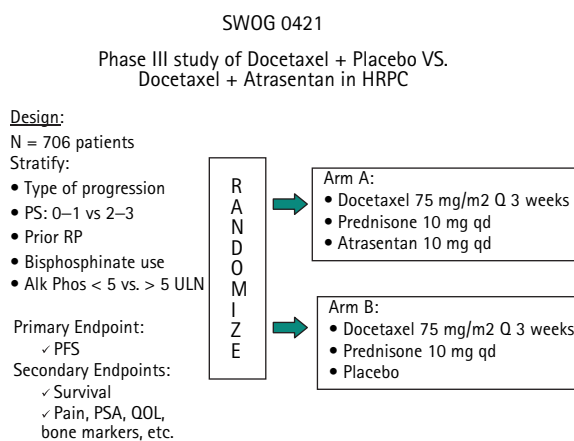

SWOG 0421

Phase III study of Docetaxel + Placebo VS. Docetaxel + Atrasentan in HRPC

Design:
N = 706 patients
Stratify:
• Type of progression
• PS: 0–1 vs 2–3
• Prior RP
• Bisphosphinate use
• Alk Phos < 5 vs. > 5 ULN

Primary Endpoint:
✓ PFS
Secondary Endpoints:
✓ Survival
✓ Pain, PSA, QOL, bone markers, etc.

RANDOMIZE

Arm A:
• Docetaxel 75 mg/m2 Q 3 weeks
• Prednisone 10 mg qd
• Atrasentan 10 mg qd

Arm B:
• Docetaxel 75 mg/m2 Q 3 weeks
• Prednisone 10 mg qd
• Placebo

FIG. 1.
The details of the SWOG 0421 trial.

CALGB 9040

Phase III study of Docetaxel + Prednisone with or without Bevacizumab (Avastin®) in HRPC

Design:
N = 1020 patients
Stratify:
• Halabi nomogram

Primary Endpoint:
✓ Overall survival
Secondary Endpoints:
✓ PSA response
✓ PFS
✓ Objective response

• Reported participation from ECOG and NCIC

RANDOMIZE

Arm A:
• Dexamethasone 8 mg po × 3 doses
• Docetaxel 75 mg/m2 on D#1 q21d
• Prednisone 10 mg po daily
• Bevacizumab 15 mg/kg on D#1 q21d

Arm B:
• Dexamethasone 8 mg po × 3 doses
• Docetaxel 75 mg/m2 on D#1 q21d
• Prednisone 10 mg po daily
• Placebo IV on D#1 q21d

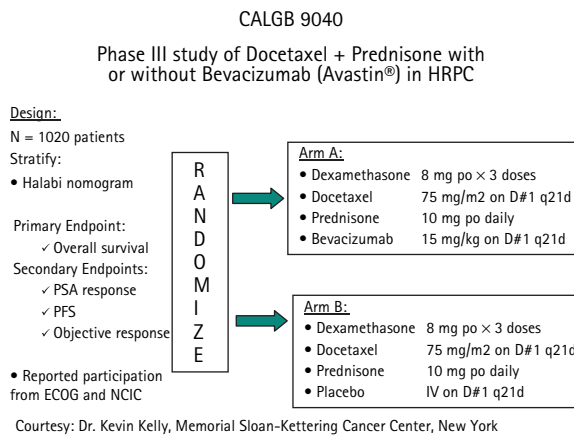Courtesy: Dr. Kevin Kelly, Memorial Sloan-Kettering Cancer Center, New York

FIG. 2.
The details of the CALGB 9040 trial.

HRPC, including no cross-resistance with taxanes. This class of compounds is the only new chemotherapeutic to have provided the most advanced data in phase II settings in HRPC. Therefore, the logical next step will be to pursue definitive phase III trials to confirm the activity of epothilones in tandem with docetaxel, given the experience to date. Such trials will lay the foundation for defining the role of epothilones in the first- and second-line settings in HRPC. The distinct toxicity profiles of each of these drugs will probably influence their future development and combination therapy with existing chemotherapy regimens.

Also, for the first time, phase III trials in rationally designed combinations of targeted therapeutics (SWOG 0421 and CALGB 9040) are being undertaken in the USA for patients with HRPC, under the auspices of the major cooperative groups. However, we will not be able to rapidly develop and provide these agents for patients with cancer unless there is a concerted and serious effort by all involved

in the care of these patients to enrol them into key clinical trials investigating exciting new classes of compounds.

CONFLICT OF INTEREST

Maha Hussein received research support from BMS.

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Abbreviations: **HRPC**, hormone-refractory prostate cancer; **SWOG**, South-West Oncology Group; **CALGB**, Cancer and Leukaemia Group B; **PFS**, progression-free survival; **VEGF**, vascular endothelial growth factor.