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Chapter 5

Antimitotic agents for prostate cancer treatment

Chapter 5a

Antimitotic agents for the treatment of patients with metastatic castrate-resistant prostate cancer

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Abstract

Introduction: Metastatic castrate-resistant prostate cancer (mCRPC) is the second deadliest cancer in men. The group of taxanes, which target microtubules of mitotic cells, is currently the only chemotherapy which has proven to increase overall survival in mCRPC patients. Other mitotic inhibitors are being explored for their clinical potential in mCRPC treatment.

Areas covered: In this review, we summarize recent developments in the application of mitotic inhibitors for mCRPC from a clinical perspective. The four main groups of mitotic inhibitors currently being tested in clinical trials are microtubule inhibitors, polo-like kinase 1 inhibitors, aurora kinase inhibitors and kinesin-spindle protein inhibitors. Compounds of these groups of inhibitors that are in clinical development for mCRPC are discussed. For this extensive overview, relevant literature was searched in PubMed and clinicaltrials.gov, and in presentations at ASCO/AACR meetings.

Expert opinion: In general, mitotic inhibitors are clinically well tolerated but exert limited antitumor activity compared to preclinical study results. However, efficacy of mitotic inhibitors is improving, either by personalizing treatment, by introducing more active compounds, by decreasing resistance of cancer cells against mitotic inhibitors, or by using mitotic inhibitors in combination therapies.

Introduction

Metastatic castrate-resistant prostate cancer (mCRPC) is the second deadliest cancer in men, being only surpassed by lung cancer.[1] The five-year survival rate of mCRPC patients is only 30%.[1] Due to this high mortality, a major area of prostate cancer research focuses on the development of new therapies that are effective in mCRPC patients.

Despite clinical testing of a wide variety of compounds, only two groups of compounds have been implemented to treat patients with advanced prostate cancer: hormonal therapy, which targets androgen receptors and/or androgen synthesis, and antimitotic chemotherapeutic agents. This chapter focuses on the latter one.

The development of antimitotic drugs for prostate cancer treatment started in 1974, when patients with advanced prostate cancer were treated with estramustine.[2] In the 1980s, it became known that estramustine interferes with microtubules, thereby targeting cancer cells in mitosis. In 1981, another antimitotic chemotherapeutic agent was tested in mCRPC patients: vincristine.[3] In this study, 15% of patients treated with vincristine monotherapy had an objective response (partial response (PR) or stable disease (SD)), the median response duration being 22 weeks. In the same study, an objective response was established in 26% of estramustine-treated patients for a median duration of 20 weeks. Addition of vincristine to estramustine monotherapy did not improve its efficacy.

Following this study, many other antimitotic agents have been tested in prostate cancer patients, with varying success. In this chapter, we will discuss the recent clinical development of different groups of mitotic inhibitors. We will focus on studies with mCRPC patients, but will also discuss results from clinical studies that tested antimitotic compounds in other advanced solid tumors with a potential impact on the treatment of mCRPC patients. Finally, we will briefly discuss results from recent studies, mostly preclinical, that are paving the way for future directions of clinical trials involving mitotic inhibitors in mCRPC patients.

Taxanes

Four Food and Drug Administration (FDA)-approved drugs have shown to increase progression-free survival (PFS) and overall survival (OS) in mCRPC patients: the hormonal therapies abiraterone acetate (Zytiga) and enzalutamide (Xtandi), and the taxanes docetaxel (Taxotere) and cabazitaxel (Jevtana). Generally, it is considered that taxanes act on cancer cells by targeting and stabilizing microtubules. Taxanes are thought to target cells in mitosis, as the incorrect formation of microtubules leads to mitotic arrest, and ultimately, apoptosis (Fig. 1). Although docetaxel was initially selected as an antitumor agent for its ability to cause mitotic arrest in cancer cells, it is now known that taxanes have other antitumor effects too, such as anti-angiogenic effects and p53 nuclear accumulation, the latter resulting in enhanced p53-induced apoptosis.[4, 5] Furthermore, as reviewed by Thadani-Mulero et al.[6], taxanes inhibit nuclear accumulation of the androgen receptor, as its trafficking is
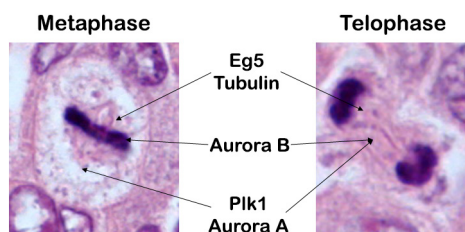
Figure 1. Overview of a cell in metaphase (left) and telophase (right), detailing the main localizations of mitotic targets during mitosis. Eg5 and tubulin are localized at microtubules throughout mitosis. Plk1 and aurora kinases mainly localize to the spindle poles during metaphase and to the midbody at the end of mitosis. While aurora B localizes to the midbody at the end of mitosis as well, during metaphase it mainly localizes to centromeres. It needs to be taken into account that these enzymes localize to a lesser extent to other mitotic structure too.

microtubule-dependent. These intracellular effects may also contribute to mCRPC inhibition.

Docetaxel

In the early 2000s, mCRPC patients were treated with mitoxantrone (Novantrone), an anthracenedione which exerts its antitumor effect by inhibition of type II topoisomerase and by DNA/RNA intercalation.[7] This therapy was approved based on the results of a phase III study in which 160 mCRPC patients were treated with prednisone with or without mitoxantrone.[8] The study concluded that mitoxantrone increased quality of life, but did not increase OS in the (relatively small) group of patients treated with mitoxantrone. The treatment scope for mCRPC patients radically changed with the introduction of docetaxel in 2004. Docetaxel binds to β-tubulin, stabilizing microtubules by polymerization.[9] Therefore, mitosis is disrupted and cells arrest in G2/M phase, resulting in apoptosis, independent from p53. Docetaxel also counters the effect of expression of the anti-apoptotic oncogenes bcl-2 and bcl-xL.[9] In 2004, the TAX-327 phase III study concluded that 335 mCRPC patients treated once every three weeks with docetaxel plus prednisone had an increased median OS compared to 337 mCRPC patients treated with mitoxantrone plus prednisone (18.9 vs. 16.5 months, respectively).[10] Adverse events resulting in discontinuation of treatment were fatigue, musculoskeletal or nail changes, sensory neuropathy, and infections. Similarly, a phase III study from the Southwest Oncology Group found an increased OS of 1.9 months in mCRPC patients treated with docetaxel plus estramustine (median OS 17.5 months) compared to treatment with mitoxantrone plus prednisone (median OS 15.6 months).[11] These studies resulted in FDA approval of docetaxel as first-line therapy in mCRPC patients. About 50% of docetaxel-treated mCRPC patients had a PR. To improve its efficacy, studies combining docetaxel with other antitumor agents have been performed in mCRPC patients. A recent meta-analysis of twelve phase II studies indicated that docetaxel-based combination

therapy may be more effective in mCRPC patients, increasing survival with similar adverse events compared to docetaxel monotherapy.[12] However, treatment efficacy was not improved in any published phase III study in which high-dose calcitriol (vitamin D), bevacizumab (Avastin), risedronate, atrasentan (Xinlay), zibotentan, or GVAX immunotherapy was added to docetaxel treatment (Table 1).[13-20] Furthermore, combining docetaxel with aflibercept (Zaltrap) did not significantly increase median OS in mCRPC patients; the combination of lenalidomide (Revlimid) with docetaxel did not have a statistically significant treatment effect either.[21, 22] Currently, phase III studies are being performed in which docetaxel is combined with dasatinib (Sprycel) or OGX-011 (Custirsen) in mCRPC patients (Table 1).[23-26] Furthermore, multiple combination therapies have been tested with success in phase I/II clinical trials, such as the combination of docetaxel and temozolomide (Temodal) and the combination of docetaxel with zoledronic acid (Zometa).[27, 28] Nevertheless, docetaxel plus prednisone remains standard first-line therapy.

Cabazitaxel

Recently, a second generation taxane, cabazitaxel (Jevtana), has received FDA approval as second-line therapy for mCRPC patients. Cabazitaxel is potentially superior to docetaxel, having low affinity with P-glycoprotein (P-gp), an ATP-dependent drug efflux pump.[29] For registration, a randomised phase III clinical trial was performed in 755 patients with mCRPC who had progression after docetaxel treatment (TROPIC).[30] In this study, patients received either 12 mg/m^2 mitoxantrone or 25 mg/m^2 cabazitaxel in combination with daily oral prednisone. Men treated with cabazitaxel had both increased OS and PFS, the median of the parameters being increased by 2.4 months (15.1 vs. 12.7 months) and 1.4 months (2.8 vs. 1.4 months), respectively. Time to tumor progression (TTP) and time to prostate-specific antigen (PSA) progression were increased after cabazitaxel treatment as well, and 39.2% of cabazitaxel-treated patients had a reduction in serum PSA concentration of ≥50%. Grade ≥3 neutropenia (82% vs. 58%), leukopenia (68% vs. 42%), anemia (11% vs. 5%) and diarrhea (6% vs. <1%) were increased in cabazitaxel-treated patients. Results of compassionate use programs have been published by Heck et al. and others.[31-33] These post-marketing studies report similar responses, but less adverse events in mCRPC patients. Other clinical studies, summarized in Table 2, are being conducted to further optimize cabazitaxel use in mCRPC patients.

Other taxanes

Besides aforementioned FDA-approved taxanes, other taxanes have been or are tested in prostate cancer as well, the most noteworthy being (nab-)paclitaxel and tesetaxel.
Paclitaxel (Taxol) is a taxane that has been approved by the FDA for its use in ovarian cancer, breast cancer, non-small-cell lung cancer (NSCLC), and AIDS-related Kaposi sarcoma. A phase II study concluded that paclitaxel only had minor antitumor activity in mCRPC patients, as

Table 1. Phase III studies testing combination therapy with docetaxel in mCRPC patients.

Docetaxel with	Main mode of action	DLT	Median OS	Compared to	Status	References
estramustine (Emcyt)	alkylating agent	GI disorders	17.5 months (vs. 15.6 months)	mitoxantrone	phase III published	11
high-dose calcitriol	vitamin D	hypercalcemia	17.8 months (vs. 20.2 months)	docetaxel	phase III published	13, 204
bevacizumab (Avastin)	angiogenesis inhibitor	hypertension, hemorrhages	22.6 months (vs. 21.5 months)	docetaxel	phase III published	14
risedronate	bisphosphonate	N/A	19.2 months (vs. 18.4 months)	docetaxel	phase III published	15
atrasentan (Xinlay)	endothelin A receptor antagonist	(febrile) neutropenia	18 months (phase III) / 17.6 months (phase II)	docetaxel	phase III published	16, 17
GVAX	immunotherapy	N/A	13 months in both arms (predicted survival)	docetaxel	phase III published	19
GVAX	immunotherapy	N/A	16 months in both arms (predicted survival)	docetaxel	phase III published	18
Zibotentan	endothelin A receptor antagonist	peripheral edema, headache, cardiac failure	24.5 months (vs. 22.5 months)	docetaxel	phase III published	20
Aflibercept (Zaltrap)	VEGF-inhibitor	neutropenia, dysphonia, hypertension	not significantly improved	docetaxel	phase III halted	21, 205, 206
lenalidomide	Antiangiogenesis, antineoplastic, immune modulation	N/A	N/A	docetaxel	phase III halted	22
dasatinib (Sprycel)	tyrosine kinase inhibitor	rash, lethargy	N/A	docetaxel	phase III ongoing	23, 25, 207
OGX-011 (Custirsen)	antisense clusterin inhibitor	N/A	23.8 months (vs. 16.9 months) (phase II)	docetaxel	phase III ongoing	24, 26

Patients in all treatment groups were treated with prednisone. mCRPC, metastatic castrate-resistant prostate cancer; OS, overall survival; VEGF, vascular endothelial growth factor.

Table 2. Ongoing clinical trials that aim to improve the efficacy of cabazitaxel in mCRPC patients.

Study name	Phase	Aim	Reference
PROSELICA	III	to compare cabazitaxel administered at 20 mg/m² to standard cabazitaxel treatment	208
-	II	to evaluate the use of cabazitaxel administered weekly at 10 mg/m²	209
ConCab	II	to compare cabazitaxel administered on day 1, 8, 15 and 22 at 10 mg/m² in a 5-week cycle to standard cabazitaxel treatment	210
ProstyII	II	to evaluate the use of cabazitaxel administered biweekly at 16 mg/m²	211
-	II	to evaluate the reduction in diarrhea after addition of octreotide to standard cabazitaxel treatment	212
CABARESC	II	to evaluate the reduction in diarrhea after addition of budosenide to standard cabazitaxel treatment	213
FIRSTANA	III	to compare cabazitaxel to docetaxel as first-line therapy	214
AFFINITY	III	to compare standard cabazitaxel treatment with or without the addition of custirsen (OGX-011)	215
CATCH	I	to determine the recommended treatment dose of tasquinimod when added to standard cabazitaxel treatment	216
-	I	to evaluate the use of combination therapy with cabazitaxel and abiraterone acetate	217
-	I/II	to evaluate the use of combination therapy with cabazitaxel and bavituximab	218
-	I/II	to compare standard cabazitaxel treatment with or without the addition of carboplatin	219

a PR was established in only 4.3% of patients, while grade 4 toxicities such as leukopenia occurred in 61% of patients.[34] Since then, multiple phase II studies have been conducted in mCRPC patients combining paclitaxel with radiotherapy or other chemotherapeutic agents.[35-47] Most phase II studies concluded that the results did not warrant a phase III study, as either toxicity was too high, or efficacy was insufficient.[36, 39, 42-46] No phase III study has been initiated in mCRPC patients.

Recently, the FDA approved nanoparticle albumin-bound (nab)-paclitaxel (Abraxane) in combination with carboplatin for the initial treatment of advanced NSCLC patients. The *in vivo* antitumor activity of nab-paclitaxel was lower in prostate cancer models than in mice with lung cancer and for this reason less thoroughly explored.[48] However, nab-paclitaxel was evaluated in a phase II study as neoadjuvant therapy in high-risk prostate cancer patients before radical prostatectomy, with disappointing results.[49] In another phase II study, nab-paclitaxel was evaluated as a first-line therapy in 38 mCRPC patients.[50] SD for >8 weeks was established in 43% of evaluable patients, the drug being well tolerated, leading to the conclusion that nab-paclitaxel may be useful in patients who are not suitable for docetaxel-based therapy. No phase III studies have been initiated in mCRPC patients. Currently, a phase I study combining nab-paclitaxel with vandetanib, an inhibitor of tyrosine kinases, vascular endothelial growth factor receptor (VEGFR) and other kinases, is being conducted.[51]

Tesetaxel (DJ-927) is the first identified taxane which is administered orally.[52] This taxane has a half maximal inhibitory concentration (IC_{50}) of 0.395 ng/ml in DU-145 prostate cancer cells, and exerts antitumor effects in P-gp-mediated multidrug resistant cell lines *in vitro* and *in vivo*.[52] Phase I studies with tesetaxel have been conducted; no mCRPC patients were

included in these clinical trials. Patients with advanced solid tumor responded well to tesetaxel treatment (with or without capecitabine), 3.6% of patients having a PR or complete response, and 62.5% having SD.[53, 54] The compound was well absorbed and had acceptable toxicities, the most frequent dose-limiting toxicity (DLT) being (febrile) neutropenia and gastrointestinal disorders. A phase II study with tesetaxel in patients with progressive mCRPC is ongoing.[55]

Other microtubule inhibitors

Besides taxanes, other microtubule inhibitors have been developed for mCRPC patients. The development of most of these inhibitors, such as vincristine, has been discontinued, except for the epothilones.[56]

Epothilones stabilize microtubules by binding to tubulin as well.[57] Despite their similar mechanism of action, the structure of epothilones is quite different from taxanes, and interestingly, epothilones have antitumor effects in taxane-resistant cancer cell lines.[57-59] Furthermore, epothilones are effective in tumors that overexpress multidrug resistance proteins such as multidrug resistance protein 1 (MDR1) and multidrug resistance-associated protein 1 (MRP1).[59, 60]

Ixabepilone (BMS-247550), an epothilone B analogue, is the only epothilone that has received FDA approval, namely for the treatment of advanced breast cancers. Its use is controversial, as OS was only extended in subset analyses of two phase III studies with patients with breast cancer.[61-65] Five phase I/II studies have been conducted with ixabepilone in mCRPC patients (Table 3).[66-70] Because a phase II study comparing mitoxantrone to ixabepilone reported that the two compounds have similar efficacies and toxicities, it is unlikely that ixabepilone will have a future role in mCRPC treatment.[69] However, ixabepilone is currently being tested in a phase II study as neoadjuvant therapy in patients with high risk, clinically localized prostate cancer. Preliminary results indicate that ixabepilone effectively reduced the PSA levels in a majority (87.5%) of patients.[71] However, as the clinical significance of changes in serum PSA levels after therapy is disputed, the prostate cancer working group (PCWG) recommends to focus on PSA progression instead of PSA response.[72] Therefore, long-term follow up of these patients needs to be done to assess the clinical benefit for patients, especially as ixabepilone also had significant toxic effects, with only 31.3% of patients being able to finish treatment. Patupilone (EPO906), epothilone B, has been studied in mCRPC patients in two phase II clinical trials (Table 3).[73, 74] In the phase II study by Hussain et al., patupilone hardly showed

Table 3 (right page). Clinical studies testing epothilones in metastatic castrate-resistant prostate cancer patients. Only studies have been included in which all patients had been diagnosed with mCRPC. # pts, number of patients; SD, stable disease; PR, partial response; PFS, progression-free survival; TTPP, time to PSA progression; TTP, time to progression; OS, overall survival; PSA, prostate-specific antigen; mCRPC, metastatic castrate-resistant prostate cancer; MTD, maximum tolerated dose; RP2D, recommended phase II dose; DLT, dose-limiting toxicity; AE, adverse event; IV, intravenous; Ref, reference.

Compound	Tumors	Dosing schedule	# pts	Most frequent DLT (phase I) or grade 3 or 4 AE (phase II)	Efficacy	Status	Ref.
Ixabepilone (BMS-247550)	mCRPC	3h IV (30-35 mg/m²) on day 2 with oral estramustine (280 mg thrice daily for 5 days) in 3-week cycles	13	neutropenia, peripheral neuropathy	91.7% PSA decrease ≥50%, median TTPP 4.4 months. 14.3% CR, 42.9% PR, 14.3% SD	Pilot study published	66
	mCRPC previously treated with docetaxel	½h IV mitoxantrone 8-12 mg/m² (12 mg/m² RP2D), 3h IV ixabepilone 20-35 mg/m² (35 mg/m² RP2D), pegfilgrastim 0/6 mg subcutaneously day 2, prednisone 5 mg twice daily in 3-week cycles	36	(febrile) neutropenia, diarrhea	30.6% PSA decrease ≥50%. 10.0% PR.	Phase I published	67
	mCRPC	3h IV (35 mg/m²) on day 2 with/without oral estramustine (280 mg thrice daily for 5 days) in 3-week cycles	92	(febrile) neutropenia, neuropathy, fatigue	68.9% PSA decrease ≥50% (vs. 47.7%). TTPP 5.2 months (vs. 4.4 months). 47.8% PR (vs. 32.0%), 34.8% SD (vs. 52.0%)	Phase II published	68
	docetaxel-refractory mCRPC	3h IV (35 mg/m²) or IV mitoxantrone (14 mg/m²) with orally prednisone (5 mg) twice daily in 3-week cycles	82	(febrile) neutropenia, anemia	19.5% PSA decrease ≥50% (vs. 19.5%). 4,2% PR (vs. 9.5%)	Phase II published	69
	mCRPC	1h IV (20 mg/m²) day 1, 8 and 15 in 4-week cycles	109	neutropenia, neuropathy, fatigue	34.1% PSA decrease ≥50%. 9.9% PR. Median OS 12.8 months	Phase II published	70
	high-risk, clinically localized prostate cancer	neoadjuvant IV weekly (20 mg/m²/week) for 12 weeks before prostatectomy	16 (±30)	neuropathy, allergic response	87.5% PSA decrease (mean 46.8%)	Phase II ongoing	71
Patupilone	mCRPC previously treated with docetaxel	5 min. IV (2.5 mg/m²) day 1, 8 and 15 in 4-week cycles	45	diarrhea, fatigue, neuropathy	13.3% PSA decrease ≥50%. 5.3% SD. Median OS 13.4 months	Phase II published	73
	mCRPC previously treated with docetaxel	20 min. IV (8-10 mg/m²) day 1 in 3-week cycles	83	diarrhea, fatigue, anorexia	46.8% PSA decrease ≥50%. 24.3% PR, 56.8% SD. Median TTPP & OS 6.1 & 11.3 months	Phase II published	74
	chemonaive mCRPC patients	IV 10 mg/m² or docetaxel 75 mg/m² every 3 weeks, with twice daily 5 mg prednisone	67	diarrhea, nausea, vomiting, fatigue	55% confirmed ≥50% PSA decline	Phase II ongoing	220
KOS-862	mCRPC previously treated with docetaxel	IV (100 mg/m²) day 1, 8 and 15 in 4-week cycles	38	fatigue, peripheral neuropathy, ataxia	5.3% PSA decrease ≥50%. Median TTP & OS 2.1 & 7.4 months	Phase II published	75
Sagopilone (ZK-Epo)	mCRPC	3h IV (16 mg/m²) day 1 with twice daily 5 mg prednisone in 3-week cycles	53	peripheral neuropathy, fatigue, pain in extremities	37.0% PSA decrease ≥50%. Median PFS 6.4 months	Phase II published	76

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any efficacy, as 15 out of 16 patients with measurable disease had continuous progressive disease (PD), and only 13% of all patients had a decrease in PSA of ≥50%. The second phase II study, performed by the Canadian Urologic Oncology Group, reported that 47% of patients had a PSA decline of ≥50%, and 24% of patients with measurable disease had a measurable PR. This improved response was most likely caused by the different patient population, as patients in the second study had more advanced prostate cancer. Intriguingly, patients in both studies did not have significant hematological toxicities, diarrhea and fatigue being the most frequent grade ≥3 adverse events.

KOS-862, epothilone D, was tested in 38 mCRPC patients who had progressed following docetaxel therapy.[75] This epothilone lacked antitumor activity, while toxicity was severe.

Finally, sagopilone (ZK-EPO), a fully synthetic epothilone, plus prednisone have recently been tested in chemonaive mCRPC patients in a phase II study.[76] Similar to patupilone, very few patients treated with this compound had hematological adverse events. Although 37.0% of patients had a PSA decrease of ≥50%, the measured efficacy did not warrant a comparison between sagopilone and docetaxel in a phase III study.

Kinesin spindle protein inhibitors

While taxanes were the first group of chemotherapeutic agents that successfully extended survival in mCRPC patients, a major disadvantage of these tubulin-targeting agents is that they target microtubules in healthy non-dividing cells too, where microtubules have both mechanical (structural) and transportational functions.[77] Due to this lack of specificity for cancer cells, administration of taxanes may result in serious side effects in patients, such as neurotoxicity.[10] Therefore, mitotic inhibitors with improved specificity for tumor cells would provide benefit for patients. Kinesin spindle protein (KSP) inhibitors specifically target mitotic cells by inhibiting the mitotic kinesin Eg5, an enzyme of the kinesin-5 subfamily.[78, 79] Eg5 is active during mitosis only, separating spindle poles during metaphase, as it crosslinks two antiparallel microtubules and moves to the plus-ends of both microtubules (Fig. 1).[79] Inhibition of Eg5 leads to mitotic arrest, ultimately resulting in apoptosis.[80] The exact mechanism by which apoptosis is induced is still disputed.[80-84] Healthy cells that rapidly divide are inhibited by KSP inhibitors too. Therefore, the major side effects in patients treated with KSP inhibitors are of hematological origin, such as neutropenia and thrombocytopenia. Stimulating the bone marrow by addition of granulocyte colony-stimulating factor (G-CSF) can decrease the severity of some hematological adverse events.

Multiple KSP inhibitors have been identified, but only one KSP inhibitor has been tested specifically in prostate cancer patients, namely ispinesib.

Ispinesib (SB-715992, NSC-727990)

Ispinesib is a highly specific and potent inhibitor of the KSP ATPase.[85] This quinazolinone

Table 4. Clinical studies testing KSP inhibitors in patients with advanced solid tumors

Compound	Tumors	Dosing schedule	# pts	Most frequent DLT	Efficacy	Status	Refs.
Ispinesib (SB-715992)	Advanced solid tumors, majority (58.3%) mCRPC	Docetaxel (50-75 mg/m², MTD 60 mg/m² + ispinesib (6-12 mg/m², MTD 10 mg/m²) IV day 1 of 3-week cycle	24	neutropenia	29.2% SD after 6 cycles	Phase I published	86
	Advanced solid tumors	IV day 1, 8 and 15 of 4-week cycle, 1-8 mg/m²/week (RP2D 7 mg/m²/week)	30	neutropenia	37.5% SD after 6 cycles	Phase I published	87
	Advanced solid tumors	IV day 1 of 3-week cycle, 1-21 mg/m² (RP2D 18 mg/m²)	42	neutropenia	9.5% SD after 4 cycles	Phase I completed	88
	Advanced solid tumors	IV day 1-3 of 3-week cycle, 1-8 mg/m²/day (MTD 6 mg/m²/day)	27	neutropenia / leukopenia	minor response in 3.7%, 7.4% SD after 4 cycles	Phase I completed	89
	mCRPC progressed after docetaxel	IV day 1 of 3-week cycle, 18 mg/m²	21	neutropenia	Median PFS 2.1 months, median OS 14 months	Phase II published	90
SB-743921	Advanced solid tumors or relapsed/ refractory lymphoma	IV day 1 of 3-week cycle, 2-8 mg/m² (MTD 4 mg/m²)	44	neutropenia	2.3% PR (12 months), 13.6% SD after 4 cycles	Phase I published	92
MK-0731	Advanced solid tumors	IV day 1 of 3-week cycle, 6-48 mg/m² (MTD 17 mg/m²)	43	neutropenia	18.2% SD after 8 cycles	Phase I published	93
AZD-4877	Advanced solid tumors	IV day 1, 8 and 15 of 4-week cycle, 10-25 mg/dose	18	neutropenia / febrile neutropenia	32.3% SD after 2 cycles	Phase I published	94
	Advanced solid tumors	IV day 1, 8 and 15 of 4-week cycle, 5-45 mg/dose (MTD 30 mg/dose)	43	neutropenia	17.1% SD after 3 cycles	Phase I published	95
	Advanced tumors	IV day 1, 4, 8 and 11 of 3-week cycle, 2-15 mg/dose (MTD 11 mg/dose)	29	neutropenia	12.5% SD after 12 weeks	Phase I published	221
ARRY-520	Advanced solid tumors	IV day 1 of 3-week cycle or IV day 1 and 2 of 2-week cycle, 2.5-3.3 mg/m² (MTD 2.5 mg/m² per cycle)	>34	neutropenia	8.8% SD after 13 weeks	Phase I completed	97

KSP, kinesin-spindle protein; mCRPC, metastatic castrate-resistant prostate cancer; SD, stable disease; PR, partial response; PFS, progression-free survival; OS, overall survival; MTD, maximum tolerated dose; RP2D, recommended phase II dose; DLT, dose-limiting toxicity; IV, intravenous; # pts, number of patients; Refs, references.

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derivative has been successfully tested in phase I clinical trials in patients with advanced solid tumors (Table 4).[86-89] In one phase I study combining docetaxel and ispinesib, the majority (58.3%) of patients had been diagnosed with mCRPC.[86] Of the 14 patients with mCRPC included in this trial, six patients had SD for ≥18 weeks, and one patient had a PSA decrease of ≥50%. Toxicity was acceptable. A phase II clinical trial was started by the Southwest Oncology Group in which ispinesib was administered to mCRPC patients who had progressed during/after docetaxel.[90] Patients were i.v. treated once every three weeks with 18 mg/m^2 ispinesib 1h. No response was seen in the first 21 patients included in this trial. Immunohistochemistry analysis on archival tumor tissue from 16 of the 21 patients indicated that 15 out of 16 patients did not have significant expression of KSP inside the tumor. Therefore, it was concluded that ispinesib is most likely not effective in primary prostate tumors due to the low mitotic index of these tumors, resulting in low KSP expression. However, a more recent study found that 50% of prostate tumor samples stained positive for KSP.[91]

Other KSP inhibitors

Four other potent and selective KSP inhibitors have been tested in patients with solid tumors in phase I studies: SB-743921, MK-0731, AZD-4877 and ARRY-520 (Table 4).[92-97] Although none of these phase I studies focused on prostate cancer patients in particular, mCRPC patients were included in studies for MK-0731 and AZD-4877.

MK-0731, a compound that is thought to have an allosteric regulation of KSP, was administered to seven mCRPC patients.[93] Four mCRPC patients received MK-0731 at the maximum tolerated dose (MTD) of 17 mg/m^2. Although PSA reductions of >50% were observed, no mCRPC patient had SD for more than 5 months.

AZD-4877 has been tested in patients with advanced solid malignancies in three phase I studies (Table 4). In the study by Infante et al., two mCRPC patients were included.[95] Individual observations of these patients were not reported. In a Japanese phase I study with AZD-4877, one included patient had prostate cancer and one prostate/renal cancer. Both patients received 15 mg AZD4877 via a 1h i.v. infusion on days 1, 8 and 15 of a 28-day cycle.[94] The patient with prostate/renal cancer had SD for more than two cycles.

ARRY-520 is currently being tested in phase I/II studies in patients with multiple myeloma. The clinical development of ispinesib, SB-743921, MK-0731, or AZD-4877 have all been discontinued, as these KSP inhibitors had limited antitumor effects at the MTD in patients with advanced solid tumors and/or mCRPC in particular. New KSP inhibitors such as K858 and S-trityl-L-cysteine are in preclinical development and could potentially decrease adverse events and/or increase the efficacy of KSP inhibitors.[91, 98, 99]

Aurora kinase inhibitors

Aurora kinases are a group of serine/threonine kinases characterized by an activation loop, a destruction box, and three conserved aurora boxes at the amino terminal domain.[100, 101] The aurora family consists of three enzymes: aurora A, B and C. Aurora A localizes to the spindle poles during mitosis and to the midbody during cytokinesis (Fig. 1).[100] Its activity peaks during pro-metaphase, but it plays a role in regulation of the cell cycle from late S-phase to mitotic exit, including regulation of centrosome maturation, mitotic entry, centrosome separation, bipolar spindle assembly, chromosome alignment and cytokinesis.[101-105] Aurora B has a nuclear localization during mitosis, but during cytokinesis it localizes to the midbody as well (Fig. 1).[100] Aurora B is active during G2/M phase; its activity peaks from the end of metaphase until the end of cytokinesis.[101, 106] It is necessary for mitotic entry, the correct regulation of spindle microtubule-kinetochore attachments, chromosome condensation, the mitotic spindle assembly checkpoint, chromosome segregation, and cytokinesis.[101] Aurora C is hardly expressed in normal cells except germ line cells, and is involved in meiosis. Although it was thought that aurora C does not play a role in tumorigenesis, some recent preclinical studies indicate that aurora C may have oncogenic activity as well.[107, 108]

Aurora A and B are overexpressed in various cancers, including prostate cancer.[109] Overexpression of aurora A is associated with the transformation of prostate adenocarcinoma to treatment-related androgen-independent neuroendocrine prostate cancer.[110-112] Furthermore, preclinical studies have indicated that aurora A may aid in androgen-independent prostate cancer cell growth by phosphorylating and activating the androgen receptor.[113] Inhibition of aurora kinases results in polyploidy and apoptosis.[114, 115] Therefore, multiple aurora kinase inhibitors have been introduced in clinic. In the following sub-sections, aurora kinase inhibitors that have recently been studied in clinical trials with (amongst others) mCRPC patients will be discussed (Table 5).

Danusertib (PHA-739358)

Danusertib is a pan-aurora kinase inhibitor that binds to the ATP pocket. This pyrrolopyrazole targets other tyrosine kinases, most notably Abl, as well.[116, 117] The IC_{50}s were 220 and 120 nM in DU-145 and PC3 prostate cancer cells, respectively, as determined by cell proliferation assays.[117] In the *in vivo* transgenic adenocarcinoma of the mouse prostate model, danusertib inhibited tumor growth in 81.3% of mice.[117] Results from two phase I studies with danusertib in patients with advanced solid tumors, amongst others mCRPC, have been published (Table 5).[118, 119] None of the included mCRPC patients had a PR or prolonged (≥6 months) SD. In the phase II study conducted in mCRPC patients, 2 out of 81 evaluable patients (2.5%) had a PSA reduction of ≥50% after three months.[120] Median PFS was 2.8 months; 13.6% (11/81) of patients had a PFS ≥6 months. The main grade ≥3 adverse event was neutropenia, the most frequent side effect of aurora kinase inhibitors in general. Due to the limited PSA response, danusertib was not further assessed in mCRPC patients.

Table 5. Clinical studies testing aurora kinase inhibitors in patients with advanced solid tumors.

Compound	Tumors	Dosing schedule	# pts	Most frequent DLT (phase I) / grade 3 or 4 AE (phase II)	Efficacy	Status	Refs.
Danusertib (PHA-739358)	Advanced/metastatic solid tumors	3h/6h IV day 1,8 and 15 of 4-week cycles, 45-400 mg/m² (MTD 330 mg/m² 6h IV)	50	(febrile) neutropenia	13.2% SD for ≥6 months.	Phase I published	[118]
	Advanced solid tumors	24h IV biweekly, 45-1000 mg/m², with or without G-CSF (MTD without G-CSF 500 mg/m², recommended dose 750 mg/m² with G-CSF)	56	(febrile) neutropenia	2.4% PR, 9.5% SD for ≥6 months.	Phase I published	[119]
	mCRPC progressed after docetaxel	6h IV day 1, 8 and 15 of 4-week cycles, 330 mg/m²; or 24h IV biweekly, 500 mg/m²	81 (43 + 38)	(febrile) neutropenia	2.5% PSA response. 13.6% SD for ≥6 months. Median PFS 2.8 months	Phase II published	[120]
MLN8054	Advanced solid tumors	orally daily day 1-5&8-12 or 4x daily day 1-14 of 4-week cycles, 25-80 mg/day (MTD 4x daily 70 mg/day for 14 days)	43	somnolence, transaminitis	7.0% SD for ≥4 cycles	Phase I published	[222]
	Advanced solid tumors	orally (1x/4x) daily for 7/14/21 days followed by a 14-day treatment-free period, 5-80 mg/day (MTD4x daily 60 mg for 14 days)	61	reversible grade 3 benzo-diazepine-like effects (somnolence , cognitive AEs, confusion, hallucination)	4.9% SD for >6 cycles	Phase I published	[223]
Alisertib (MLN8237)	Advanced solid tumors	orally 1x/2x daily for 7/14/21 days followed by a 14-day treatment-free period, (MTD 50 mg 2x daily for 7 days of 50 mg daily for 21 days)	59	neutropenia, stomatitis	10.2% SD for >6 months	Phase I published	[224]
	Advanced solid tumors	orally 1x/2x daily for 7/14/21 days followed by a 14-day treatment-free period, 5-150 mg (RP2D 50 mg 2x daily for 7 days)	87	neutropenia, thrombocytopenia, diarrhea	1.1% PR, 23.0% SD for ≥3 months	Phase I published	[124]
	Children with refractory/recurrent solid tumors	orally 1x/2x daily for 7 days of a 3-week cycle, 45-100 mg/m²/day (MTD 80 mg/m²/day 1x daily)	37	neutropenia, thrombocytopenia	3.0% PR, 18.2% SD for ≥6 cycles	Phase I published	[225]
	Platinum-resistant/-refractory epithelial ovarian, fallopian tube or primary peritoneal carcinoma	orally 2x daily (50 mg) for 7 days of a 3-week cycle	31	neutropenia, leukopenia, stomatitis, thrombocytopenia	19.4% SD for ≥3 months. Median PFS 1.9 months	Phase II published	[226]

Drug	Indication	Dosing	# pts	Adverse events	Results	Phase	Ref
	Advanced solid tumors	orally 2x daily (50 mg) for 7 days of a 3-week cycle	100	neutropenia, leukopenia, fatigue, anemia, stomatitis, and thrombocytopenia	11.0% PR, 45.0% SD	Phase I/II ongoing	227
	Platinum and taxane resistant/refractory advanced ovarian or breast cancer	orally 2x daily (10-50 mg) day 1-3,8-108,15-18, with paclitaxel (60-80 mg/m² day 1,88,15) in 4-week cycles (MTD TBD)	28	diarrhea, febrile neutropenia, stomatitis	28.6% PR, 10.7% SD for ≥6 months	Phase I/II ongoing	228
Barasertib (AZD1152)	Advanced solid tumors	2h IV every 7/14 days, 100-650 mg (MTD 200/450 mg, respectively)	59	(febrile) neutropenia	25.4% SD after 6 weeks	Phase I published	129
	Advanced solid tumors	2h IV day 1&2 or 48h IV day 1 every two weeks, 50-300 mg (MTD 110 mg/ day and 150 mg, respectively)	35	(febrile) neutropenia	22.9% SD after 8 weeks	Phase I published	130
ENMD-2076	Advanced solid tumors	orally daily continuously, 60-200 mg/m² (MTD 160 mg/m²)	67	hypertension, neutropenia	3.4% PR, 19.0%% SD for ≥5.7 months (25 weeks)	Phase I published	133
	platinum-resistant recurrent epithelial ovarian cancer	orally daily continuously, 250-325 mg/day	64	hypertension, fatigue, increased liver enzymes	21.9% PFS ≥6 months. 7.8% PR (median duration 7 months). Median OS 12 months	Phase II published	134
tozasertib (MK-0457/ VX-680)	Advanced solid tumors	24h IV every 3 weeks, 4-96 mg/m²/h (MTD 64 mg/m²/h). In 7 pts 100 mg orally 48h before MTD	27	neutropenia, herpes zoster	44.4% SD for ≥2 cycles	Phase I published	138
AT9283	Advanced solid tumors	72h IV in 3-week cycles, 4.5-36mg/m²/72h (MTD 27mg/m²/72h)	40	febrile neutropenia	10.0% SD for ≥6 months	Phase I published	144
PF-03814735	Advanced solid tumors	orally daily day 1-5/1-10 of 3-week cycles, 5-100 mg (MTD 80 mg for 5 days/50 mg for 10 days)	57	(febrile) neutropenia	7.7% SD for ≥6 cycles	Phase I published	147
BI 811283	Advanced solid tumors	24h IV every three weeks, 13.5-300 mg (MTD 230 mg)	57	(febrile) neutropenia	33.3% SD	Phase I completed	145
	Advanced solid tumors	24h IV every two weeks, 5-140 mg (MTD <140 mg)	52	neutropenia	29% SD	Phase I completed	146
AMG-900	Advanced solid tumors	orally daily day 1-4 of 2-week cycles, 1-30 mg (MTD 24mg)	19	(febrile) neutropenia, thrombocytopenia	N/A	Phase I ongoing	153

Studies that included prostate cancer patients are mentioned, as well as studies that included patients with other solid tumors of which (preliminary) results have been published since 2011. mCRPC, metastatic castrate-resistant prostate cancer; SD, stable disease; PR, partial response; PFS, progression-free survival; PSA, prostate-specific antigen; N/A, not available; MTD, maximum tolerated dose; RP2D, recommended phase II dose; DLT, dose-limiting toxicity; AE, adverse event; IV, intravenous; # pts, number of patients; Refs, references.

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Alisertib (MLN8237)

Alisertib is a second-generation aurora kinase A inhibitor. It is thought to be more potent than its predecessor, MLN8054, and has reduced benzodiazepine-like adverse events compared to MLN8054 (Table 5).[121] It effectively inhibits a wide variety of tumor cell lines *in vitro*; in PC3 cells the IC_{50} was 54 nM.[122, 123] *In vivo* administration of alisertib resulted in tumor growth inhibition, amongst others in CWR22 prostate cancer xenografts.[122]

Multiple phase I/II studies have been conducted with alisertib in solid tumors. Only one study by Dees et al. included mCRPC patients; none of the four mCRPC patients had a PR.[124] In addition, one phase I study is currently ongoing to evaluate the safety and tolerability of MLN8237 in combination with docetaxel, which has a focus on mCRPC.[125]

Barasertib (AZD1152)

Barasertib is the first identified highly selective aurora B inhibitor.[126] This 5-acetanilide-substituted 3-aminopyrazole effectively inhibited tumor growth of colorectal, leukemic and lung cancers *in vivo*.[126, 127] A preclinical study in prostate cancer cells concluded that pretreatment of these cells with barasertib, administered at 60 nM for 48 h, increased DNA damage inflicted by radiotherapy, and impaired DNA repair mechanisms.[128]

Two phase I studies with barasertib in patients with advanced solid tumors have been published.[129, 130] In the study by Boss et al., two mCRPC patients were included and received weekly barasertib via a 2h i.v. infusion.[129] Of all patients in this treatment schedule, 36.8% of patients had SD after six weeks of treatment.

ENMD-2076

ENMD-2076, a tartrate salt, is a tyrosine kinase inhibitor with activity not only against aurora A (IC_{50} 14 nM) and B (IC_{50} 350 nM), but also against other enzymes, such as enzymes involved in angiogenesis (VEGFR, fibroblast growth factor receptor (FGFR), etc.) or the FMS-like tyrosine kinase-receptor 3 (Flt3) (IC_{50} 1.86 nM), a potential target for leukemic tumors.[131, 132] The antiproliferative IC_{50} value for PC3 cells was established at 600 nM, for other tumor cell lines IC_{50}s were in the nanomolar range (25-700 nM) as well. Treating mice with doses ranging between 50 and 225 mg/kg resulted in effective tumor growth inhibition of a wide variety of tumors.[132]

In clinical studies, the most frequent DLT/grade ≥3 treatment-emergent adverse event was hypertension instead of neutropenia.[133, 134] No patient included in clinical trials had been diagnosed with mCRPC. Phase II studies with ENMD-2076 are ongoing in patients with metastatic sarcomas and advanced/metastatic triple-negative breast cancer.[135, 136]

Tozasertib (MK-0457, VX-680)

Tozasertib is a pan-aurora kinase inhibitor, targeting the ATP-binding site of aurora kinases, and is most effective in inhibiting aurora A.[137] Its IC_{50} is in the lower nanomolar

range (<100nM) in a variety of cell lines, amongst others PC3 cells. As tozasertib has cross-reactivity with Flt-3, it has most extensively been studied in leukemia, but some phase I/II studies have been conducted with tozasertib in patients with solid tumors as well. In the published phase I study with tozasertib in patients with advanced solid tumors, two mCRPC patients were included, of which one had SD for six cycles.[138] This patient had been treated with a combination of tozasertib orally and i.v. at the MTD.

Other aurora kinase inhibitors

Various other aurora kinase inhibitors have been tested recently in patients with advanced solid tumors: (1) AT9283, an inhibitor of aurora A and B, as well as other serine/threonine kinases, such as Jak2, Jak3 and Abl; (2) PF-03814735, an orally bioavailable inhibitor of aurora A and B; (3) BI 811283, an aurora kinase B inhibitor; (4) MK-5108, an aurora kinase A inhibitor; and (5) SNS-314, a pan-aurora kinase inhibitor.[138-143] SD was reported as the best response in phase I studies with these compounds in patients with advanced solid tumors.[144-149] Due to the limited response, no further studies are conducted with these agents in adults with solid tumors.

New aurora kinase inhibitors are emerging from preclinical research, which potentially optimize the effect of aurora kinase inhibition, while minimizing adverse events. Examples of such inhibitors are HOI-07, AMG-900 and GSK1070916A, of which the latter two are currently studied in clinical trials.[150-152]

AMG-900 is a recently discovered, highly selective and potent orally bioavailable pan-aurora kinase inhibitor. It inhibits cell lines resistant against paclitaxel and the aurora kinase inhibitors AZD1152, MK-0457 and danusertib in low nanomolar ranges (<5 nM).[151] Oral administration of AMG-900 at a concentration of 15 mg/kg (days 1 and 2 weekly) or 3 mg/kg/day *in vivo* inhibited tumor growth by 50-97% in nine different xenograft models, of which three were multidrug-resistant tumor models. A phase I study is ongoing in patients with advanced solid tumors, in which the MTD has been determined at 24 mg without G-CSF support when administered for four consecutive days every two weeks.[153]

GSK1070916A is a selective ATP-competitive inhibitor of aurora B and C, with a high enzyme-inhibitor dissociation half-life of >8h for the aurora B-INCENP (inner centromere protein) enzyme.[152, 154] In PC3, LNCaP and DU-145 prostate cancer cell lines, the IC_{50} was ≤15 nM.[155] In *in vivo* studies, administration of GSK1070916A resulted in delayed tumor growth, and in tumor reductions in lung, colorectal and hematological cancer models.[155] A phase I study has been initiated in patients with advanced solid tumors.[156]

Polo-like kinase 1 inhibitors

Polo-like kinase 1 (Plk1) is a serine/threonine kinase, which is a part of the family of five polo-like kinases.[157] The enzyme plays essential roles during mitosis: major functions include activation of Cdc2, bipolar spindle assembly, centrosome maturation, chromosome condensation and separation, regulation of the anaphase-promoting complex and initiation of cytokinesis (Fig. 1).[158, 159] More recently, extra-mitotic roles of Plk1 have been discovered, such as downregulation of p53.[160, 161] Plk1 is overexpressed in various tumors, amongst others in prostate cancer.[158, 162] Its expression is increased in androgen-insensitive prostate cancer cells, suggesting that it plays a role in androgen-independent growth, similar to aurora kinases.[163] As Plk1 is overexpressed and contains two highly specific polo-box domains (PBDs) in the C terminus, agents that bind to these PBDs can highly selectively target cancer cells.[158] Multiple Plk1 inhibitors have been developed, of which volasertib, TAK-960, TKM-080301, NMS-1286937 and rigosertib are currently being studied in patients with solid tumors. Similar to aurora kinase inhibitors, neutropenia is the most frequent adverse event in patients treated with Plk1 inhibitors.

HMN-214

HMN-214, an oral prodrug of HMN-176, was the first Plk1 inhibitor tested in clinic.[164] HMN-176 is a stilbazole derivative cytotoxic to PC3 and DU-145 cells as well as cisplatin-, adriamycin-, vincristine-, etoposide- and taxol-resistant cancer cell lines.[164] HMN-214 had equal or superior antitumor activity in mice with established PC3 tumors compared to cisplatin, adriamycin, vincristine and tegafur-uracil (UFT).[164] In a phase I study, HMN-214 had limited antitumor effects.[165] No patient had been diagnosed with prostate cancer. From another phase I study, final results have not been reported.[166] No phase II trial has been initiated.

Volasertib (BI 6727)

BI 2536 and its successor volasertib are dihydropteridine derivatives, inhibiting Plk1 by competitively binding to its ATP-binding pocket.[167, 168] The compounds have IC_{50}s in the low nanomolar range in amongst others prostate cancer cells, and exert *in vivo* antitumor activity as well.[167-169] A summary of clinical trials with BI 2536 and volasertib in patients with solid tumors can be found in Table 6.

In one phase II and two phase I studies mCRPC patients were treated with BI 2536. None of the two mCRPC patients included in the phase I study by Mross et al. had SD for >3 months.[170] In the other phase I study, one of three mCRPC patients had SD for >3 months.[171] In the phase II study, twenty mCRPC patients were treated with 200 mg BI 2536 via a 1h i.v. infusion.[172] One-third of evaluable patients had SD after four courses. Grade 3 or 4 neutropenia was observed in 20% (4 out of 20) of patients. Due to the limited antitumor activity, it was decided not to assess BI 2536 any further as a single agent. Although BI

Table 6. Clinical studies testing polo-like kinase 1 (Plk1-)inhibitors in patients with advanced solid tumors.

Compound	Tumors	Dosing schedule	# pts	Most frequent DLT (phase I) / grade 3 or 4 AE (phase II)	Efficacy	Status	Refs
HMN-214	Advanced solid tumors	orally day 1-21 of 4-week cycles, 3-9.9 mg/m²/day (MTD 8 mg/m²/day)	33	myalgia/bone pain syndrome, hyperglycemia	24.1% SD, 3.4% SD >6 months	Phase I published	165
	Advanced tumors	orally day 1-5 of 4-week cycles, 6-48 mg/m² (MTD 18 mg/m²)	32	neutropenia, neutropenic sepsis, myalgia, electrolyte isturbances, neuropathy	3.1% minor response, ≥9.4% SD for >3 months	Phase I completed	166
BI 2536	Advanced solid tumors	1h IV day 1 of 3-week cycles, 25-250 mg (MTD 200 mg)	40	(reversible) neutropenia	3.2% PR, 22.6% SD for >3 months	Phase I published	170
	Advanced solid tumors	1h IV day 1 and 8 (MTD 200 mg/course) or 24h IV day 1 (MTD >225 mg) of 3-week cycles, 25-225 mg	70	neutropenia	11.4% SD for >3 months	Phase I published	171
	Advanced solid tumors-	1h IV day 1-3 of 3-week cycles, 150-210 mg/course (MTD 180 mg/course)	21	neutropenia, anemia, thrombocytopenia, fatigue, hypertension, elevated liver enzymes	28.6% SD for >3 months	Phase I published	229
	recurrent/advanced/ metastatic NSCLC progressed after platinum based therapy	1h IV day 1 of 3-week cycles, 100-325 mg (MTD 300 mg), in combination with pemetrexed (500 mg/m²)	41	neutropenia, pruritis, rash, elevated liver enzymes	5.1% PR, 53.8% SD after 2 cycles	Phase I published	230
	mCRPC	1h IV day 1 of 3-week cycles, 200-250 mg	20	neutropenia	25.0% SD after 4 cycles	Phase II completed	172
	advanced HNC, breast cancer, ovarian cancer, soft tissue sarcoma or melanoma	1h IV day 1 of 3-week cycles, 200-250 mg	71	(febrile) neutropenia, thrombocytopenia, anemia, pain	42.4% SD according to RECIST. Median PFS & OS 1.4 & 9.5 months	Phase II published	231
	stage IIIB/IV NSCLC progressed after chemotherapy	1h IV day 1 (200 mg) or day 1-3 (150/180 mg/course) of 3-week cycles	95	neutropenia, anemia, dyspnea	4.2% PR. Median PFS 1.6-2.5 months, median OS 5.9-8.0 months	Phase II published	232
	unresectable pancreatic adenocarcinoma	1h IV day 1 (200 mg) or day 1-3 (180 mg/course) of 3-week cycles	86	neutropenia, leukopenia, thrombocytopenia	2.3% PR, 24.4% SD after 4 cycles. 27.8% PFS >3 months, median PFS & OS 1.5 & 4.9 months	Phase II published	233

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Drug	Indication	Dosing	N	Toxicity	Response	Phase	Ref
volasertib (BI 6727)	Advanced solid tumors	1h IV day 1 of 3-week cycles, 12-450 mg (MTD 400 mg, RP2D 300 mg)	65	(Febrile) neutropenia, thrombocytopenia	4.6% PR, 26.2% SD after 3 months	Phase I published	173
	Advanced solid tumors	2h IV day 1 of 3-week cycles in combination with cisplatin (100 mg/m²) / carboplatin (AUC 6) (MTD 300 mg)	61	neutropenia, thrombocytopenia, fatigue	8.2% PR, 18.0% PR/SD after 6 cycles	Phase I ongoing	174
	Advanced solid tumors	IV day 1 of 3-week cycles	±15	TBD	TBD	Phase I ongoing	179
	Advanced solid tumors	IV day 1 of 3-week cycles in combination with BIBW 2992 orally daily	±60	TBD	TBD	Phase I ongoing	178
	Advanced solid tumors	IV day 1 of 3-week cycles in combination with BIBF 1120 orally daily (200 mg)	±30	TBD	TBD	Phase I ongoing	176
	Advanced solid tumors	IV in 3-week cycles	±7	TBD	TBD	Phase I completed	234
	Advanced solid tumors	IV in 3-week cycles	±59	TBD	TBD	Phase I completed	235
	Locally advanced or metastatic urothelial cancers	2h IV day 1 of 3-week cycles, 300-350 mg	50	neutropenia, thrombocytopenia, anemia, hyponatremia	19.4% PR, 22.6% SD after 4 cycles	Phase II ongoing	175
	Recurrent platinum resistant/refractory ovarian cancer	IV day 1 of 3-week cycles	±110	TBD	TBD	Phase II ongoing	177
	advanced/metastatic NSCLC after platinum based therapy	IV day 1 of 3-week cycles in combination with pemetrexed (500 mg/m²)	±143	TBD	TBD	Phase II completed	236
GSK-461364	Advanced solid tumors	4h IV Day 1, 8 and 15 (MTD 225 mg), or day 1, 2, 8, 9, 15 and 16 (MTD 75 mg) of 4-week cycles, 25-300 mg	40	neutropenia, thrombocytopenia, pulmonary embolism	15% SD after 4 cycles	Phase I published	182
NMS-1286937	Advanced solid tumors	orally, dose escalation study	±21	TBD	TBD	Phase I completed	183
TKM-080301	Advanced solid tumors	IV, dose escalation study	±42	TBD	TBD	Phase I ongoing	184
TAK-960	Advanced solid tumors	orally, dose escalation study	±84	TBD	TBD	Phase I ongoing	185

Drug	Tumor type	Dosing	# pts	AE/DLT	Response	Phase/Status	Refs
rigosertib (ON 01910. Na)	Advanced solid tumors	2h IV biweekly for 3 weeks of 4-week cycles, 80-3120 mg (MTD 3120 mg)	20	Abdominal pain/death	6.3% PR, 6.3% SD	Phase I published	237
	Advanced solid tumors	24h IV weekly (250-1350 mg/m²) in combination with oxaliplatin 2h IV biweekly (85 mg/m²)	13	none	6.7% PR, 13.3% SD for ≥12 weeks	Phase I published	238
	Advanced solid tumors	2h IV biweekly (600-1800 mg/m², MTD 1800 mg/m²) in combination with gemcitabine weekly (750-1000 mg/m², MTD 1000 mg/m²) for 3 weeks of 4-week cycles	40	Death	5.3% PR, 57.9% SD (of the pancreatic cancer patients)	Phase I published	193
	Advanced solid tumors	orally twice daily, 70-700 mg (MTD 560 mg)	25	dysuria	4.0% PR, 24.0% SD for ≥24 weeks	Phase I completed	239
	Advanced tumors	24h IV weekly (250-2750 mg/m²)	23	not reported	No PR, % SD not reported	Phase I completed	240
	Advanced tumors	72h IV in 2-week cycles, 50-250 mg/m²/day	5 (±29)	TBD	40.0% SD for >6 weeks	Phase I completed	241
	Advanced solid tumors	orally twice/thrice daily in 3-week cycles, 140-700 mg/day	2 to 72	TBD	TBD	Phase I ongoing	242
	ovarian cancer resistant to platinum based therapy	2h IV biweekly for 3 weeks of 4-week cycles, 3200 mg	N/A	TBD	TBD	Phase II completed	243
	previously untreated metastatic pancreatic cancer	2h IV biweekly (1800 mg/m²) in combination with gemcitabine weekly (1000 mg/m²) for 3 weeks of 4-week cycles, versus gemcitabine only	650	TBD	TBD	Phase II/III ongoing	244

All studies are mentioned, except for studies that were over a year old, had not been published in journals and did not include mCRPC patients. mCRPC, metastatic castrate-resistant prostate cancer; SD, stable disease; PR, partial response; PFS, progression-free survival; OS, overall survival; MTD, maximum tolerated dose; RP2D, recommended phase II dose; DLT, dose-limiting toxicity; AE, adverse event; IV, intravenous; # pts, number of patients; Refs, references; HNC, head and neck cancer; NSCLC, non-small cell lung cancer; TBD, to be determined.

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2536 was well tolerated by patients, combination therapy was not pursued due to the introduction of volasertib.

Volasertib is thought to have superior efficacy and/or to be less toxic compared to BI 2536.[169] One phase I study in which patients with advanced solid tumors were treated with BI 6727 has been published.[173] In this study, four patients had been diagnosed with mCRPC. Three of 65 patients had a PR (4.6%), none of whom were mCRPC patients. SD for more than 3 months was established in 26.2% of patients. As volasertib was well tolerated, (pre) clinical research with this small molecule as a monotherapy and in combination with other therapies is ongoing.[169, 174-179]

GSK-461364

GSK-461364, a thiophene amide, is an ATP-competitive Plk1 inhibitor, which has over a 100-fold greater potency for Plk1 than 50 other kinases, including Plk2 and Plk3.[180] In a panel of >120 cancer cell lines, GSK-461364 had IC_{50}s below 100 nM in 91% of cell lines, the inhibitor thus causing a prometaphase arrest.[181] In a phase I study performed in patients with advanced solid malignancies (Table 6), one mCRPC patient was included.[182] This patient did not respond to GSK-461364 treatment. No phase II studies have been initiated with this compound.

Other Plk1 inhibitors

Apart from aforementioned Plk1 inhibitors, three Plk1 inhibitors with different delivery methods have been developed: TAK-960, NMS-1286937 and TKM-080301. These compounds had promising results in preclinical studies and are currently being studied in patients with advanced solid tumors in phase I clinical trials (Table 6).[183-185]

NMS-1286937 (NMS-P937) is an orally bioavailable 4,5-dihydro-1H-pyrazolo[4,3-h] quinazoline derivative.[186] It targets highly selectively Plk1 (IC_{50} 2 nM), and inhibits cell proliferation in a wide variety of cancer cell lines, both solid and hematological, at low nanomolar concentrations.[187] NMS-1286937 effectively inhibited tumor growth in established human colorectal and leukemic xenografts with minimal and reversible weight loss.[186, 187]

TAK-960 is another orally bioavailable Plk1 inhibitor. It exhibited antitumor activity *in vitro* at low nanomolar concentrations, arresting tumor cells, including cells that express MDR1, in G2/M phase.[188] TAK-960 inhibited tumor growth amongst others in mice with established PC3 human prostate tumors.

TKM-080301 is a lipid nanoparticle (LNP) containing small interfering RNA against human Plk1 mRNA.[189, 190] Due to its selective distribution, myelosuppression and other common side effects of Plk1 inhibitors may be reduced. Indeed, *in vivo* studies reported that tumor growth was inhibited and toxicity largely restricted to the liver and spleen.[190]

Rigosertib (ON 01910.Na)

Rigosertib (Estybon) is a benzyl styryl sulfone analog, which inhibits both Plk1, by competitively binding to the substrate binding site, and the PI3K pathway.[191, 192] IC$_{50}$ values of rigosertib in DU-145 and PC3 cells were 200 and 150 nM, respectively.[191] The *in vivo* antitumor activity of rigosertib was increased when combined with other chemotherapeutic agents (oxaliplatin, doxorubicin or gemcitabine).[191] Therefore, clinical studies have not been initiated in mCRPC patients, but mostly focus on tumors in which these chemotherapies are used, such as pancreatic cancer (Table 6).[193]

Conclusions

Docetaxel and cabazitaxel are mitotic inhibitors and are currently used in clinic as first- and second-line therapies for mCRPC patients. Due to this success, and with new mitotic targets for cancer therapy being discovered, multiple mitotic inhibitors are being studied for their use in mCRPC treatment. These inhibitors can be divided into four groups: microtubule inhibitors, KSP inhibitors, Plk1 inhibitors and aurora kinase inhibitors. Of these last three groups, Plk1 inhibitors and aurora kinase inhibitors are currently most extensively studied in mCRPC patients. Currently, these inhibitors seem to have most clinical potential in hematological tumors. However, combination therapies and new compounds with increased potency and selectivity are being studied in patients with prostate cancer and other solid tumors as well.

Expert opinion

Recently, the treatment scope for mCRPC patients has expanded. Besides docetaxel, other life-extending therapies, such as the second-generation taxane cabazitaxel, have entered the market. Therefore, the need for a good biomarker to assess the response to therapy has become stringent. Although changes in serum PSA levels are now mostly used as an indicator for the response to mCRPC treatment, its clinical significance remains controversial. Increasing serum PSA levels during the first 12 weeks of treatment are considered unreliable; therefore, physicians are encouraged to continue treatment beyond 12 weeks despite rising PSA levels, unless PD is determined via other objective assessments.[72] This recommendation would cause overtreatment and a treatment delay in patients who do have continuous PD. Overtreatment and treatment delays could be further reduced by introducing markers that predict the response to therapy. Such markers form the basis for targeted therapy in other cancers: e.g., breast cancer patients whose tumors express estrogen receptor or human epidermal growth factor receptor 2 will be treated with tamoxifen or trastuzumab, respectively.[194, 195] Although mitotic inhibitors are targeted therapies against a single or group of enzyme(s), such as Plk1, it is intriguing that none of aforementioned clinical trials

determined *a priori* the expression of the targeted enzyme(s) in the tumor, while tissue is available from all mCRPC patients as biopsies have been taken. Not all tumors overexpress these enzymes: e.g., only about 50% of prostate tumors overexpress KSP or Plk1.[91, 162] Future clinical studies need to determine whether the *a priori* expression of the targeted mitotic enzyme inside mCRPC cells is of influence of the antitumor efficacy of the mitotic inhibitor in humans. KSP inhibitors or Plk1 inhibitors may have no effect in 50% of mCRPC patients whose tumors do not overexpress the targeted enzyme. Aurora kinase inhibitors may exert most antitumor effect in aggressive tumors with a treatment-related neuroendocrine phenotype, as aurora A is more regularly overexpressed in these tumors.[111] If this is confirmed, treatment of mCRPC patients may be personalized based on this expression profile. Alternatively, if these inhibitors do exert an antitumor effect in tumors that do not express the targeted enzyme, off-target antitumor effects of these inhibitors need to be assessed.

With an increasing number of therapies to which only part of mCRPC patients respond, it is expected that personalized medicine, in which treatment is based on the expression profiles of tumors, will play an increasingly important role in mCRPC treatment.

The antitumor effect of mitotic inhibitors could be further improved by improving the specificity of the compound for cancer cells. This can be achieved by optimizing the compound itself and/or by improving its method of delivery, e.g. by delivery in LNPs which specifically bind to tumor cells. Furthermore, compounds could potentially be used in combination therapy to accomplish synergistic antitumor effects.

Preclinical studies suggest that mitotic inhibitors may be combined with docetaxel.[112, 196, 197] In a recently performed phase I study in patients with advanced solid tumors, combination of MK-5108 with docetaxel resulted in a PR in 2 out of 17 patients (no patient with MK-5108 mono-therapy had a PR), but also in more serious adverse events.[148] Other clinical trials combining aurora kinase inhibitors with docetaxel are being performed, such as a phase I study with MLN8237.[125] An important limitation of these clinical studies is that aurora kinase inhibitors are administered after docetaxel treatment, while a preclinical report suggests that this combination therapy is most effective when aurora kinase inhibitors are administered before docetaxel.[143]

Recently, Feng et al. discovered that miR-100 (microRNA) resensitized docetaxel-resistant lung adenocarcinoma SPC-A1 cells to docetaxel.[198] Plk1 was identified as a direct target of miR-100, and knock-down of Plk1 or (over)expression of miR-100 resulted in increased sensitivity to docetaxel *in vitro* and *in vivo*, respectively.

These data indicate that the combination of mitotic inhibitors with docetaxel could potentially result in an enhanced antitumor effect in mCRPC patients.

Other combinations involving mitotic inhibitors should be tested as well. Multiple clinical trials are currently being performed in which mitotic inhibitors are combined with other compounds, such as the combination of volasertib with the triple angiokinase inhibitor

BIBF1120 (an inhibitor of the VEGF receptor, and PDGFR (platelet-derived growth factor receptor) and FGFR kinase activity in cancer cells).[176] With the increasing interest in combination therapies for cancer treatment, it is important to select combination therapies based on a rationale. Recently, a preclinical study from our group indicated that the combination of mitotic inhibitors with histone deacetylase (HDAC-)inhibitors may have clinical benefit in prostate cancer patients.[169, 199, 200] This combination therapy targets the mitotic pathway from both a genetic and epigenetic perspective, while other cancer-related pathways are targeted as well. More (pre)clinical studies need to be performed to create and test such rational combination therapies.

Resistance of tumor cells to taxanes and other chemotherapies limits their use. Only 50% of mCRPC patients respond to docetaxel therapy, and eventually all tumors become docetaxel refractory.[10] The response rate is similar or even lower after treatment with other mitotic inhibitors. A wide variety of intracellular alterations have occurred in docetaxel-resistant mCRPC cells, such as increased expression of the Notch and Hedgehog signaling pathways and increased expression of TGF-β, MDR1 and MRP1.[201, 202] As summarized by Madan et al., these alterations result in increased drug efflux by transmembranic pumps such as P-gp, changes in the site to which taxanes bind to microtubules, increased dynamic activity of microtubules, and changed expression of subunits of microtubules such as βIII.[203] Research is ongoing in which intracellular changes leading to chemotherapy resistance are being utilized as markers for therapy response. Furthermore, other studies are assessing how these intracellular changes can be prevented, reverted or targeted, which would have significant clinical consequences.

As aforementioned therapy improvements – overcoming therapy resistance, and introducing personalized medicine, compounds with improved specificity, improved methods of delivery and combination therapy – are currently extensively studied, it is expected that in the next decade more mitotic inhibitors will find their way into the clinic for (prostate) cancer treatment.

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References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin 2012;62(1):10-29.
2. Muntzing J, Shukla SK, Chu TM, Mittelman A, Murphy GP. Pharmacoclinical study of oral estramustine phosphate (Estracyt) in advanced carcinoma of the prostate. Invest Urol 1974;12(1):65-68.
3. Soloway MS, de Kernion JB, Gibbons RP et al. Comparison of estramustine phosphate and vincristine alone or in combination for patients with advanced, hormone refractory, previously irradiated carcinoma of the prostate. J Urol 1981;125(5):664-667.
4. Belotti D, Vergani V, Drudis T et al. The microtubule-affecting drug paclitaxel has antiangiogenic activity. Clin Cancer Res 1996;2(11):1843-1849.
5. Giannakakou P, Nakano M, Nicolaou KC et al. Enhanced microtubule-dependent trafficking and p53 nuclear accumulation by suppression of microtubule dynamics. Proc Natl Acad Sci U S A 2002;99(16):10855-10860.
6. Thadani-Mulero M, Nanus DM, Giannakakou P. Androgen receptor on the move: boarding the microtubule expressway to the nucleus. Cancer Res 2012;72(18):4611-4615.
7. Poirier TI. Mitoxantrone. Drug Intell Clin Pharm 1986;20(2):97-105.
8. Tannock IF, Osoba D, Stockler MR et al. Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative end points. J Clin Oncol 1996;14(6):1756-1764.
9. Khan MA, Carducci MA, Partin AW. The evolving role of docetaxel in the management of androgen independent prostate cancer. J Urol 2003;170(5):1709-1716.
10. Tannock IF, de Wit R, Berry WR et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004;351(15):1502-1512.
11. Petrylak DP, Tangen CM, Hussain MH et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. N Engl J Med 2004;351(15):1513-1520.
12. Serpa NA, Tobias-Machado M, Kaliks R, Wroclawski ML, Pompeo AC, Del GA. Ten years of docetaxel-based therapies in prostate adenocarcinoma: a systematic review and meta-analysis of 2244 patients in 12 randomized clinical trials. Clin Genitourin Cancer 2011;9(2):115-123.
13. Scher HI, Jia X, Chi K et al. Randomized, open-label phase III trial of docetaxel plus high-dose calcitriol versus docetaxel plus prednisone for patients with castration-resistant prostate cancer. J Clin Oncol 2011;29(16):2191-2198.
14. Kelly WK, Halabi S, Carducci M et al. Randomized, double-blind, placebo-controlled phase III trial comparing docetaxel and prednisone with or without bevacizumab in men with metastatic castration-resistant prostate cancer: CALGB 90401. J Clin Oncol 2012;30(13):1534-1540.
15. Meulenbeld HJ, van Werkhoven ED, Coenen JL et al. Randomised phase II/III study of docetaxel with or without risedronate in patients with metastatic Castration Resistant Prostate Cancer (CRPC), the Netherlands Prostate Study (NePro). Eur J Cancer 2012;48(16):2993-3000.
16. Armstrong AJ, Creel P, Turnbull J et al. A phase I-II study of docetaxel and atrasentan in men with castration-resistant metastatic prostate cancer. Clin Cancer Res 2008;14(19):6270-6276.
17. Quinn DI, Tangen CM, Hussain M et al. SWOG S0421: Phase III study of docetaxel (D) and

atrasentan (A) versus docetaxel and placebo (P) for men with advanced castrate resistant prostate cancer (CRPC). [abstract]. J Clin Oncol 30, 2012 (suppl; abstr 4511).

18. Higano C, Saad F, Somer B et al. A phase III trial of GVAX immunotherapy for prostate cancer versus docetaxel plus prednisone in asymptomatic, castration-resistant prostate cancer (CRPC). [abstract]. In: Genitourinary Cancers Symposium, 2009 Feb 26-28, Orlando, FL (Abstr LBA150).

19. Small E, Demkow T, Gerritsen R et al. A phase III trial of GVAX immunotherapy for prostate cancer in combination with docetaxel versus docetaxel plus prednisone in symptomatic, castration-resistant prostate cancer (CRPC). [abstract]. In: Genitourinary Cancers Symposium, 2009 Feb 26-28, Orlando, FL (Abstr 7).

20. Nelson JB, Fizazi K, Miller K et al. Phase 3, randomized, placebo-controlled study of zibotentan (ZD4054) in patients with castration-resistant prostate cancer metastatic to bone. Cancer 2012;118(22):5709-5718.

21. Sanofi and Regeneron Announce Regulatory and Clinical Update for Zaltrap® (aflibercept). Tarrytown, NY; Sanofi, 2012. Available at: http://en.sanofi.com/Images/30138_20120405_ZALTRAP_BLA_VENICE_en.pdf [Last accessed 11 December 2012].

22. Lenalidomide Plus Docetaxel: Phase III Results Fall Short. Plainsboro, NJ: OncLive, 2012. Available at: http://www.onclive.com/publications/oncology-live/2012/january-2012/Lenalidomide-Plus-Docetaxel-Phase-III-Results-Fall-Short [Last accessed 11 December 2012].

23. Randomized Study Comparing Docetaxel Plus Dasatinib to Docetaxel Plus Placebo in Castration-Resistant Prostate Cancer (READY). Bethesda, MD: US National Institute of Health, 2012. Available at: http://clinicaltrial.gov/ct2/show/NCT00744497 [Last accessed 12 December 2012].

24. Comparison of Docetaxel/Prednisone to Docetaxel/Prednisone in Combination With OGX-011 in Men With Prostate Cancer (SYNERGY). Bethesda, MD: US National Institute of Health, 2012. Available at: http://clinicaltrial.gov/ct2/show/NCT01188187 [Last accessed 12 December 2012].

25. Araujo JC, Mathew P, Armstrong AJ et al. Dasatinib combined with docetaxel for castration-resistant prostate cancer: results from a phase 1-2 study. Cancer 2012;118(1):63-71.

26. Chi KN, Hotte SJ, Yu EY et al. Randomized phase II study of docetaxel and prednisone with or without OGX-011 in patients with metastatic castration-resistant prostate cancer. J Clin Oncol 2010;28(27):4247-4254.

27. Tamaskar I, Mekhail T, Dreicer R et al. Phase I trial of weekly docetaxel and daily temozolomide in patients with metastatic disease. Invest New Drugs 2008;26(6):553-559.

28. Facchini G, Caraglia M, Morabito A et al. Metronomic administration of zoledronic acid and taxotere combination in castration resistant prostate cancer patients: phase I ZANTE trial. Cancer Biol Ther 2010;10(6):543-548.

29. Bradshaw DM, Arceci RJ. Clinical relevance of transmembrane drug efflux as a mechanism of multidrug resistance. J Clin Oncol 1998;16(11):3674-3690.

30. de Bono JS, Oudard S, Ozguroglu M et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet 2010;376(9747):1147-1154.

31. Heck MM, Hoppner M, Horn T, Thalgott M, Gschwend JE, Retz M. Compassionate use of abiraterone and cabazitaxel: First experiences in docetaxel-pretreated castration-resistant prostate cancer patients. Urologe A 2012.

5

32. De Velasco G, Aparicio LA, Esteban E et al. Cabazitaxel in patients with advanced CRPC after docetaxel failure: Results of expanded access program (EAP) in Spain: Safety and efficacy. [abstract]. J Clin Oncol 30, 2012 (suppl; abstr e15149).

33. Bracarda S, Di Lorenzo G, Gasparro D et al. Updated safety result of a large Italian early access program (EAP) with cabazitaxel plus prednisone (CbzP) in metastatic castration-resistant prostate cancer (mCRPC) patients who progressed during or after docetaxel (D) therapy. [abstract]. J Clin Oncol 30, 2012 (suppl; abstr e15185).

34. Roth BJ, Yeap BY, Wilding G, Kasimis B, McLeod D, Loehrer PJ. Taxol in advanced, hormone-refractory carcinoma of the prostate. A phase II trial of the Eastern Cooperative Oncology Group. Cancer 1993;72(8):2457-2460.

35. Hudes GR, Nathan F, Khater C et al. Phase II trial of 96-hour paclitaxel plus oral estramustine phosphate in metastatic hormone-refractory prostate cancer. J Clin Oncol 1997;15(9):3156-3163.

36. Smith DC, Esper P, Strawderman M, Redman B, Pienta KJ. Phase II trial of oral estramustine, oral etoposide, and intravenous paclitaxel in hormone-refractory prostate cancer. J Clin Oncol 1999;17(6):1664-1671.

37. Smith DC, Chay CH, Dunn RL et al. Phase II trial of paclitaxel, estramustine, etoposide, and carboplatin in the treatment of patients with hormone-refractory prostate carcinoma. Cancer 2003;98(2):269-276.

38. Berry W, Friedland D, Fleagle J et al. A phase II study of weekly paclitaxel/estramustine/carboplatin in hormone-refractory prostate cancer. Clin Genitourin Cancer 2006;5(2):131-137.

39. Mackler NJ, Pienta KJ, Dunn RL et al. Phase II evaluation of oral estramustine, oral etoposide, and intravenous paclitaxel in patients with hormone-sensitive prostate adenocarcinoma. Clin Genitourin Cancer 2007;5(5):318-322.

40. Kelly WK, Halabi S, Elfiky A et al. Multicenter phase 2 study of neoadjuvant paclitaxel, estramustine phosphate, and carboplatin plus androgen deprivation before radiation therapy in patients with unfavorable-risk localized prostate cancer: results of Cancer and Leukemia Group B 99811. Cancer 2008;113(11):3137-3145.

41. Sanfilippo NJ, Taneja SS, Chachoua A, Lepor H, Formenti SC. Phase I/II study of biweekly paclitaxel and radiation in androgen-ablated locally advanced prostate cancer. J Clin Oncol 2008;26(18):2973-2978.

42. Sella A, Yarom N, Zisman A, Kovel S. Paclitaxel, estramustine and carboplatin combination chemotherapy after initial docetaxel-based chemotherapy in castration-resistant prostate cancer. Oncology 2009;76(6):442-446.

43. Sewak S, Kosmider S, Ganju V et al. Phase II study of paclitaxel and vinorelbine (Pacl-Vin) in hormone-refractory metastatic prostate cancer: double tubulin targeting. Intern Med J 2010;40(3):201-208.

44. DiPaola RS, Chen YH, Stein M et al. A randomized phase II trial of mitoxantrone, estramustine and vinorelbine or bcl-2 modulation with 13-cis retinoic acid, interferon and paclitaxel in patients with metastatic castrate-resistant prostate cancer: ECOG 3899. J Transl Med 2010;8:20.

45. Beer TM, Ryan C, Alumkal J, Ryan CW, Sun J, Eilers KM. A phase II study of paclitaxel poliglumex in combination with transdermal estradiol for the treatment of metastatic castration-resistant prostate cancer after docetaxel chemotherapy. Anticancer Drugs 2010;21(4):433-438.

46. Smith DC, Tangen CM, van Veldhuizen PJJ et al. Phase II evaluation of early oral estramustine, oral etoposide, and intravenous paclitaxel combined with hormonal therapy in patients with high-risk metastatic prostate adenocarcinoma: Southwest Oncology Group S0032. Urology 2011;77(5):1172-1176.

47. Jeske S, Tagawa ST, Olowokure O, Selzer J, Giannakakou P, Nanus DM. Carboplatin plus paclitaxel therapy after docetaxel in men with metastatic castrate resistant prostate cancer. Urol Oncol 2011;29(6):676-681.

48. Desai N, Trieu V, Yao Z et al. Increased antitumor activity, intratumor paclitaxel concentrations, and endothelial cell transport of cremophor-free, albumin-bound paclitaxel, ABI-007, compared with cremophor-based paclitaxel. Clin Cancer Res 2006;12(4):1317-1324.

49. Shepard DR, Dreicer R, Garcia J et al. Phase II trial of neoadjuvant nab-paclitaxel in high risk patients with prostate cancer undergoing radical prostatectomy. J Urol 2009;181(4):1672-1677.

50. Kolevska T, Ryan CJ, Huey V et al. Phase II trial of nab-paclitaxel as first-line therapy of hormone refractory metastatic prostate cancer (HRPC). [abstract]. J Clin Oncol 27:15s, 2009 (suppl; abstr 5152).

51. Phase I Abraxane Weekly and Three Weekly Schedule With Vandetanib. Bethesda, MD: US National Institute of Health, 2013. Available at: http://clinicaltrial.gov/ct2/show/NCT00667147 [Last accessed 21 January 2013].

52. Shionoya M, Jimbo T, Kitagawa M, Soga T, Tohgo A. DJ-927, a novel oral taxane, overcomes P-glycoprotein-mediated multidrug resistance in vitro and in vivo. Cancer Sci 2003;94(5):459-466.

53. Baas P, Szczesna A, Albert I et al. Phase I/II study of a 3 weekly oral taxane (DJ-927) in patients with recurrent, advanced non-small cell lung cancer. J Thorac Oncol 2008;3(7):745-750.

54. Saif MW, Sarantopoulos J, Patnaik A, Tolcher AW, Takimoto C, Beeram M. Tesetaxel, a new oral taxane, in combination with capecitabine: a phase I, dose-escalation study in patients with advanced solid tumors. Cancer Chemother Pharmacol 2011;68(6):1565-1573.

55. Tesetaxel in Chemotherapy-naive Patients With Progressive, Castration-resistant Prostate Cancer. Bethesda, MD: US National Institute of Health, 2012. Available at: http://clinicaltrial.gov/ct2/show/NCT01296243 [Last accessed 12 December 2012].

56. Daliani DD, Assikis V, Tu SM et al. Phase II trial of cyclophosphamide, vincristine, and dexamethasone in the treatment of androgen-independent prostate carcinoma. Cancer 2003;97(3):561-567.

57. Sepp-Lorenzino L, Balog A, Su DS et al. The microtubule-stabilizing agents epothilones A and B and their desoxy-derivatives induce mitotic arrest and apoptosis in human prostate cancer cells. Prostate Cancer Prostatic Dis 1999;2(1):41-52.

58. Lee FY, Borzilleri R, Fairchild CR et al. BMS-247550: a novel epothilone analog with a mode of action similar to paclitaxel but possessing superior antitumor efficacy. Clin Cancer Res 2001;7(5):1429-1437.

59. Chou TC, O'Connor OA, Tong WP et al. The synthesis, discovery, and development of a highly promising class of microtubule stabilization agents: curative effects of desoxyepothilones B and F against human tumor xenografts in nude mice. Proc Natl Acad Sci U S A 2001;98(14):8113-8118.

60. Dorff TB, Gross ME. The epothilones: new therapeutic agents for castration-resistant prostate cancer. Oncologist 2011;16(10):1349-1358.

61. Hortobagyi GN, Gomez HL, Li RK et al. Analysis of overall survival from a phase III study

5

of ixabepilone plus capecitabine versus capecitabine in patients with MBC resistant to anthracyclines and taxanes. Breast Cancer Res Treat 2010;122(2):409-418.

62. Sparano JA, Vrdoljak E, Rixe O et al. Randomized phase III trial of ixabepilone plus capecitabine versus capecitabine in patients with metastatic breast cancer previously treated with an anthracycline and a taxane. J Clin Oncol 2010;28(20):3256-3263.

63. Roche H, Conte P, Perez EA et al. Ixabepilone plus capecitabine in metastatic breast cancer patients with reduced performance status previously treated with anthracyclines and taxanes: a pooled analysis by performance status of efficacy and safety data from 2 phase III studies. Breast Cancer Res Treat 2011;125(3):755-765.

64. Jassem J, Fein L, Karwal M et al. Ixabepilone plus capecitabine in advanced breast cancer patients with early relapse after adjuvant anthracyclines and taxanes: a pooled subset analysis of two phase III studies. Breast 2012;21(1):89-94.

65. Withdrawal of IXEMPRA, (ixabepilone) EMEA/H/C/000930. London, UK: European Medicines Agency, 2009. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/01/WC500062430.pdf [Last accessed 12 December 2012].

66. Smaletz O, Galsky M, Scher HI et al. Pilot study of epothilone B analog (BMS-247550) and estramustine phosphate in patients with progressive metastatic prostate cancer following castration. Ann Oncol 2003;14(10):1518-1524.

67. Rosenberg JE, Ryan CJ, Weinberg VK et al. Phase I study of ixabepilone, mitoxantrone, and prednisone in patients with metastatic castration-resistant prostate cancer previously treated with docetaxel-based therapy: a study of the department of defense prostate cancer clinical trials consortium. J Clin Oncol 2009;27(17):2772-2778.

68. Galsky MD, Small EJ, Oh WK et al. Multi-institutional randomized phase II trial of the epothilone B analog ixabepilone (BMS-247550) with or without estramustine phosphate in patients with progressive castrate metastatic prostate cancer. J Clin Oncol 2005;23(7):1439-1446.

69. Rosenberg JE, Weinberg VK, Kelly WK et al. Activity of second-line chemotherapy in docetaxel-refractory hormone-refractory prostate cancer patients : randomized phase 2 study of ixabepilone or mitoxantrone and prednisone. Cancer 2007;110(3):556-563.

70. Liu G, Chen YH, Dipaola R, Carducci M, Wilding G. Phase II trial of weekly ixabepilone in men with metastatic castrate-resistant prostate cancer (E3803): a trial of the Eastern Cooperative Oncology Group. Clin Genitourin Cancer 2012;10(2):99-105.

71. Layton JL, Plette AM, Renzulli JF et al. The impact of neoadjuvant weekly ixabepilone for high-risk prostate cancer: A phase I/II clinical trial. [abstract]. J Clin Oncol 30, 2012 (suppl 5; abstr 158).

72. Scher HI, Halabi S, Tannock I et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol 2008;26(7):1148-1159.

73. Hussain A, DiPaola RS, Baron AD, Higano CS, Tchekmedyian NS, Johri AR. Phase II trial of weekly patupilone in patients with castration-resistant prostate cancer. Ann Oncol 2009;20(3):492-497.

74. Chi KN, Beardsley E, Eigl BJ et al. A phase 2 study of patupilone in patients with metastatic castration-resistant prostate cancer previously treated with docetaxel: Canadian Urologic Oncology Group study P07a. Ann Oncol 2012;23(1):53-58.

75. Beer TM, Higano CS, Saleh M et al. Phase II study of KOS-862 in patients with metastatic androgen independent prostate cancer previously treated with docetaxel. Invest New Drugs

2007;25(6):565-570.

76. Beer TM, Smith DC, Hussain A et al. Phase II study of first-line sagopilone plus prednisone in patients with castration-resistant prostate cancer: a phase II study of the Department of Defense Prostate Cancer Clinical Trials Consortium. Br J Cancer 2012;107(5):808-813.

77. Roberts K. Cytoplasmic microtubules and their functions. Prog Biophys Mol Biol 1974;28:371-420.

78. Mayer TU, Kapoor TM, Haggarty SJ, King RW, Schreiber SL, Mitchison TJ. Small molecule inhibitor of mitotic spindle bipolarity identified in a phenotype-based screen. Science 1999;286(5441):971-974.

79. Kapitein LC, Peterman EJ, Kwok BH, Kim JH, Kapoor TM, Schmidt CF. The bipolar mitotic kinesin Eg5 moves on both microtubules that it crosslinks. Nature 2005;435(7038):114-118.

80. Sarli V, Giannis A. Targeting the kinesin spindle protein: basic principles and clinical implications. Clin Cancer Res 2008;14(23):7583-7587.

81. Vijapurkar U, Wang W, Herbst R. Potentiation of kinesin spindle protein inhibitor-induced cell death by modulation of mitochondrial and death receptor apoptotic pathways. Cancer Res 2007;67(1):237-245.

82. Tao W, South VJ, Diehl RE et al. An inhibitor of the kinesin spindle protein activates the intrinsic apoptotic pathway independently of p53 and de novo protein synthesis. Mol Cell Biol 2007;27(2):689-698.

83. Liu M, Aneja R, Liu C et al. Inhibition of the mitotic kinesin Eg5 up-regulates Hsp70 through the phosphatidylinositol 3-kinase/Akt pathway in multiple myeloma cells. J Biol Chem 2006;281(26):18090-18097.

84. Chin GM, Herbst R. Induction of apoptosis by monastrol, an inhibitor of the mitotic kinesin Eg5, is independent of the spindle checkpoint. Mol Cancer Ther 2006;5(10):2580-2591.

85. Lad L, Luo L, Carson JD et al. Mechanism of inhibition of human KSP by ispinesib. Biochemistry 2008;47(11):3576-3585.

86. Blagden SP, Molife LR, Seebaran A et al. A phase I trial of ispinesib, a kinesin spindle protein inhibitor, with docetaxel in patients with advanced solid tumours. Br J Cancer 2008;98(5):894-899.

87. Burris III HA, Jones SF, Williams DD et al. A phase I study of ispinesib, a kinesin spindle protein inhibitor, administered weekly for three consecutive weeks of a 28-day cycle in patients with solid tumors. Invest New Drugs 2011;29(3):467-472.

88. Chu QS, Holen KD, Rowinsky EK et al. Phase I trial of novel kinesin spindle protein (KSP) inhibitor SB-715992 IV Q 21 days. [abstract]. J Clin Oncol 22:14S, 2004 (July 15 Suppl; abstr 2078).

89. Heath EI, Alousi A, Eder JP et al. A phase I dose escalation trial of ispinesib (SB-715992) administered days 1-3 of a 21-day cycle in patients with advanced solid tumors. [abstract]. J Clin Oncol 24:18S, 2006 (June 20 suppl; abstr 2026).

90. Beer TM, Goldman B, Synold TW et al. Southwest Oncology Group phase II study of ispinesib in androgen-independent prostate cancer previously treated with taxanes. Clin Genitourin Cancer 2008;6(2):103-109.

91. Xing ND, Ding ST, Saito R et al. A potent chemotherapeutic strategy in prostate cancer: S-(methoxytrityl)-L-cysteine, a novel Eg5 inhibitor. Asian J Androl 2011;13(2):236-241.

92. Holen KD, Belani CP, Wilding G et al. A first in human study of SB-743921, a kinesin spindle protein inhibitor, to determine pharmacokinetics, biologic effects and establish a recommended phase II dose. Cancer Chemother Pharmacol 2011;67(2):447-454.

5

93. Holen K, DiPaola R, Liu G et al. A phase I trial of MK-0731, a Kinesin Spindle Protein (KSP) inhibitor, in patients with solid tumors. Invest New Drugs 2011.

94. Esaki T, Seto T, Ariyama H et al. Phase I Study to Assess the Safety, Tolerability and Pharmacokinetics of AZD4877 in Japanese Patients with Solid Tumors. Arch Drug Inf 2011;4(2):23-31.

95. Infante JR, Kurzrock R, Spratlin J et al. A Phase I study to assess the safety, tolerability, and pharmacokinetics of AZD4877, an intravenous Eg5 inhibitor in patients with advanced solid tumors. Cancer Chemother Pharmacol 2012;69(1):165-172.

96. Stephenson JJ, Lewis N, Martin JC et al. Phase I multicenter study to assess the safety, tolerability, and pharmacokinetics of AZD4877 administered twice weekly in adult patients with advanced solid malignancies. [abstract]. J Clin Oncol 26, 2008 (May 20 suppl; abstr 2516).

97. Goncalves PH, Sausville EA, Edelman MJ et al. A phase I study of ARRY-520 in solid tumors. [abstract]. J Clin Oncol 28:15s, 2010 (suppl; abstr 2570).

98. Nakai R, Iida S, Takahashi T et al. K858, a novel inhibitor of mitotic kinesin Eg5 and antitumor agent, induces cell death in cancer cells. Cancer Res 2009;69(9):3901-3909.

99. Wiltshire C, Singh BL, Stockley J et al. Docetaxel-resistant prostate cancer cells remain sensitive to S-trityl-L-cysteine-mediated Eg5 inhibition. Mol Cancer Ther 2010;9(6):1730-1739.

100. Carmena M, Earnshaw WC. The cellular geography of aurora kinases. Nat Rev Mol Cell Biol 2003;4(11):842-854.

101. Dar AA, Goff LW, Majid S, Berlin J, El-Rifai W. Aurora kinase inhibitors--rising stars in cancer therapeutics? Mol Cancer Ther 2010;9(2):268-278.

102. Hirota T, Kunitoku N, Sasayama T et al. Aurora-A and an interacting activator, the LIM protein Ajuba, are required for mitotic commitment in human cells. Cell 2003;114(5):585-598.

103. Marumoto T, Hirota T, Morisaki T et al. Roles of aurora-A kinase in mitotic entry and G2 checkpoint in mammalian cells. Genes Cells 2002;7(11):1173-1182.

104. Marumoto T, Honda S, Hara T et al. Aurora-A kinase maintains the fidelity of early and late mitotic events in HeLa cells. J Biol Chem 2003;278(51):51786-51795.

105. Berdnik D, Knoblich JA. Drosophila Aurora-A is required for centrosome maturation and actin-dependent asymmetric protein localization during mitosis. Curr Biol 2002;12(8):640-647.

106. Terada Y, Tatsuka M, Suzuki F, Yasuda Y, Fujita S, Otsu M. AIM-1: a mammalian midbody-associated protein required for cytokinesis. EMBO J 1998;17(3):667-676.

107. Slattery SD, Mancini MA, Brinkley BR, Hall RM. Aurora-C kinase supports mitotic progression in the absence of Aurora-B. Cell Cycle 2009;8(18):2984-2994.

108. Khan J, Ezan F, Cremet JY et al. Overexpression of active Aurora-C kinase results in cell transformation and tumour formation. PLoS One 2011;6(10):e26512.

109. Chieffi P, Cozzolino L, Kisslinger A et al. Aurora B expression directly correlates with prostate cancer malignancy and influence prostate cell proliferation. Prostate 2006;66(3):326-333.

110. Beltran H, Rickman DS, Park K et al. Molecular characterization of neuroendocrine prostate cancer and identification of new drug targets. Cancer Discov 2011;1(6):487-495.

111. Mosquera JM, Beltran H, Park K et al. Concurrent AURKA and MYCN gene amplifications are harbingers of lethal treatment-related neuroendocrine prostate cancer. Neoplasia 2013;15(1):1-10.

112. Jeet V, Russell PJ, Verma ND, Khatri A. Targeting Aurora Kinases: A Novel Approach to Curb

the Growth & Chemoresistance of Androgen Refractory Prostate Cancer. Curr Cancer Drug Targets 2011.

113. Shu SK, Liu Q, Coppola D, Cheng JQ. Phosphorylation and activation of androgen receptor by Aurora-A. J Biol Chem 2010;285(43):33045-33053.

114. Jeong NY, Yoon YG, Rho JH et al. The novel resveratrol analog HS-1793-induced polyploid LNCaP prostate cancer cells are vulnerable to downregulation of Bcl-xL. Int J Oncol 2011;38(6):1597-1604.

115. Moretti L, Niermann K, Schleicher S et al. MLN8054, a small molecule inhibitor of aurora kinase a, sensitizes androgen-resistant prostate cancer to radiation. Int J Radiat Oncol Biol Phys 2011;80(4):1189-1197.

116. Fancelli D, Moll J, Varasi M et al. 1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazoles: identification of a potent Aurora kinase inhibitor with a favorable antitumor kinase inhibition profile. J Med Chem 2006;49(24):7247-7251.

117. Carpinelli P, Ceruti R, Giorgini ML et al. PHA-739358, a potent inhibitor of Aurora kinases with a selective target inhibition profile relevant to cancer. Mol Cancer Ther 2007;6(12 Pt 1):3158-3168.

118. Steeghs N, Eskens FA, Gelderblom H et al. Phase I pharmacokinetic and pharmacodynamic study of the aurora kinase inhibitor danusertib in patients with advanced or metastatic solid tumors. J Clin Oncol 2009;27(30):5094-5101.

119. Cohen RB, Jones SF, Aggarwal C et al. A phase I dose-escalation study of danusertib (PHA-739358) administered as a 24-hour infusion with and without granulocyte colony-stimulating factor in a 14-day cycle in patients with advanced solid tumors. Clin Cancer Res 2009;15(21):6694-6701.

120. Meulenbeld HJ, Bleuse JP, Vinci EM et al. Randomized phase II study of danusertib in patients with metastatic castration-resistant prostate cancer after docetaxel failure. BJU Int 2012.

121. Sells T, Ecsedy JA, Stroud S et al. MLN8237: an orally active small molecule inhibitor of aurora A kinase in phase I clinical trials. [abstract]. Proc Am Assoc Cancer Res (AACR) 49, 2008 (abstr 2997).

122. Manfredi MG, Ecsedy JA, Chakravarty A et al. Characterization of Alisertib (MLN8237), an investigational small-molecule inhibitor of aurora A kinase using novel in vivo pharmacodynamic assays. Clin Cancer Res 2011;17(24):7614-7624.

123. Maris JM, Morton CL, Gorlick R et al. Initial testing of the aurora kinase A inhibitor MLN8237 by the Pediatric Preclinical Testing Program (PPTP). Pediatr Blood Cancer 2010;55(1):26-34.

124. Dees EC, Cohen RB, von Mehren M et al. Phase I study of aurora A kinase inhibitor MLN8237 in advanced solid tumors: safety, pharmacokinetics, pharmacodynamics, and bioavailability of two oral formulations. Clin Cancer Res 2012;18(17):4775-4784.

125. A Phase 1 Study of MLN8237 in Patients With Advanced Solid Tumors Including Castration-Resistant Prostate Cancer Receiving a Standard Docetaxel Regimen. Bethesda, MD: US National Institute of Health, 2012. Available at: http://clinicaltrial.gov/ct2/show/NCT01094288 [Last accessed 12 December 2012].

126. Mortlock AA, Foote KM, Heron NM et al. Discovery, synthesis, and in vivo activity of a new class of pyrazoloquinazolines as selective inhibitors of aurora B kinase. J Med Chem 2007;50(9):2213-2224.

127. Wilkinson RW, Odedra R, Heaton SP et al. AZD1152, a selective inhibitor of Aurora B kinase, inhibits human tumor xenograft growth by inducing apoptosis. Clin Cancer Res 2007;13(12):3682-3688.

5

128. Niermann KJ, Moretti L, Giacalone NJ et al. Enhanced radiosensitivity of androgen-resistant prostate cancer: AZD1152-mediated Aurora kinase B inhibition. Radiat Res 2011;175(4):444-451.

129. Boss DS, Witteveen PO, van der Sar J et al. Clinical evaluation of AZD1152, an i.v. inhibitor of Aurora B kinase, in patients with solid malignant tumors. Ann Oncol 2011;22(2):431-437.

130. Schwartz GK, Carvajal RD, Midgley R et al. Phase I study of barasertib (AZD1152), a selective inhibitor of Aurora B kinase, in patients with advanced solid tumors. Invest New Drugs 2012.

131. Sawyers CL. Finding the next Gleevec: FLT3 targeted kinase inhibitor therapy for acute myeloid leukemia. Cancer Cell 2002;1(5):413-415.

132. Fletcher GC, Brokx RD, Denny TA et al. ENMD-2076 is an orally active kinase inhibitor with antiangiogenic and antiproliferative mechanisms of action. Mol Cancer Ther 2011;10(1):126-137.

133. Diamond JR, Bastos BR, Hansen RJ et al. Phase I safety, pharmacokinetic, and pharmacodynamic study of ENMD-2076, a novel angiogenic and Aurora kinase inhibitor, in patients with advanced solid tumors. Clin Cancer Res 2011;17(4):849-860.

134. Matulonis UA, Lee J, Lasonde B et al. ENMD-2076, an oral inhibitor of angiogenic and proliferation kinases, has activity in recurrent, platinum resistant ovarian cancer. Eur J Cancer 2012.

135. Study of ENMD-2076 in Patients With Advanced/Metastatic Soft Tissue Sarcoma. Bethesda, MD: US National Institute of Health, 2012. Available at: http://clinicaltrials.gov/ct2/show/NCT01719744 [Last accessed 12 December 2012].

136. A Phase II Study of the Aurora and Angiogenic Kinase Inhibitor ENMD-2076 in Previously Treated Locally Advanced and Metastatic Triple-Negative Breast Cancer. Bethesda, MD: US National Institute of Health, 2012. Available at: http://clinicaltrials.gov/ct2/show/NCT01639248 [Last accessed 12 December 2012].

137. Harrington EA, Bebbington D, Moore J et al. VX-680, a potent and selective small-molecule inhibitor of the Aurora kinases, suppresses tumor growth in vivo. Nat Med 2004;10(3):262-267.

138. Traynor AM, Hewitt M, Liu G et al. Phase I dose escalation study of MK-0457, a novel Aurora kinase inhibitor, in adult patients with advanced solid tumors. Cancer Chemother Pharmacol 2011;67(2):305-314.

139. Howard S, Berdini V, Boulstridge JA et al. Fragment-based discovery of the pyrazol-4-yl urea (AT9283), a multitargeted kinase inhibitor with potent aurora kinase activity. J Med Chem 2009;52(2):379-388.

140. Dawson MA, Curry JE, Barber K et al. AT9283, a potent inhibitor of the Aurora kinases and Jak2, has therapeutic potential in myeloproliferative disorders. Br J Haematol 2010;150(1):46-57.

141. Jani JP, Arcari J, Bernardo V et al. PF-03814735, an orally bioavailable small molecule aurora kinase inhibitor for cancer therapy. Mol Cancer Ther 2010;9(4):883-894.

142. Gürtler U, Tontsch-Grunt U, Jarvis M, et al. Effect of BI 811283, a novel inhibitor of Aurora B kinase, on tumor senescence and apoptosis. [abstract]. J Clin Oncol 28, 2010 (suppl; abstr e13632).

143. van der Porten EC, Taverna P, Hogan JN, Ballinger MD, Flanagan WM, Fucini RV. The Aurora kinase inhibitor SNS-314 shows broad therapeutic potential with chemotherapeutics and synergy with microtubule-targeted agents in a colon carcinoma model. Mol Cancer Ther 2009;8(4):930-939.

144. Arkenau HT, Plummer R, Molife LR et al. A phase I dose escalation study of AT9283, a small

molecule inhibitor of aurora kinases, in patients with advanced solid malignancies. Ann Oncol 2011.

145. Mross KB, Scheulen ME, Frost A et al. A phase I dose-escalation study of BI 811283, an Aurora B inhibitor, administered every three weeks in patients with advanced solid tumors. [abstract]. J Clin Oncol 28:15s, 2010 (suppl; abstr 3011).

146. Scheulen ME, Mross KB, Richly H et al. A phase I dose-escalation study of BI 811283, an Aurora B inhibitor, administered days 1 and 15, every four weeks in patients with advanced solid tumors. [abstract]. J Clin Oncol 28, 2010 (suppl; abstr e13065).

147. Schoffski P, Jones SF, Dumez H et al. Phase I, open-label, multicentre, dose-escalation, pharmacokinetic and pharmacodynamic trial of the oral aurora kinase inhibitor PF-03814735 in advanced solid tumours. Eur J Cancer 2011;47(15):2256-2264.

148. Minton SE, LoRusso P, Lockhart AC, et al. A phase I study of MK-5108, an oral aurora A kinase inhibitor, in both monotherapy and in combination with docetaxel in patients with advanced solid tumors. [abstract]. J Clin Oncol 28, 2010 (suppl; abstr e13026).

149. Robert F, Verschraegen C, Hurwitz H et al. A phase I trial of sns-314, a novel and selective pan-aurora kinase inhibitor, in advanced solid tumor patients. [abstract]. J Clin Oncol 27:15s, 2009 (suppl; abstr 2536).

150. Xie H, Lee MH, Zhu F et al. Identification of an Aurora kinase inhibitor specific for the Aurora B isoform. Cancer Res 2012.

151. Payton M, Bush TL, Chung G et al. Preclinical evaluation of AMG 900, a novel potent and highly selective pan-aurora kinase inhibitor with activity in taxane-resistant tumor cell lines. Cancer Res 2010;70(23):9846-9854.

152. Anderson K, Lai Z, McDonald OB et al. Biochemical characterization of GSK1070916, a potent and selective inhibitor of Aurora B and Aurora C kinases with an extremely long residence time1. Biochem J 2009;420(2):259-265.

153. Carducci MA, Shaheen MF, Paller CJ et al. First-in-human study of AMG 900, an oral pan-Aurora kinase inhibitor, in adult patients (pts) with advanced solid tumors. [abstract]. J Clin Oncol 30, 2012 (suppl; abstr 3009).

154. Adams ND, Adams JL, Burgess JL et al. Discovery of GSK1070916, a potent and selective inhibitor of Aurora B/C kinase. J Med Chem 2010;53(10):3973-4001.

155. Hardwicke MA, Oleykowski CA, Plant R et al. GSK1070916, a potent Aurora B/C kinase inhibitor with broad antitumor activity in tissue culture cells and human tumor xenograft models. Mol Cancer Ther 2009;8(7):1808-1817.

156. Aurora B/C Kinase Inhibitor GSK1070916A in Treating Patients With Advanced Solid Tumors. Bethesda, MD: US National Institute of Health, 2012. Available at: http://clinicaltrials.gov/ct2/show/NCT01118611 [Last accessed 12 December 2012].

157. de Cárcer G, Manning G, Malumbres M. From Plk1 to Plk5: functional evolution of polo-like kinases. Cell Cycle 2011;10(14):2255-2262.

158. Chopra P, Sethi G, Dastidar SG, Ray A. Polo-like kinase inhibitors: an emerging opportunity for cancer therapeutics. Expert Opin Investig Drugs 2010;19(1):27-43.

159. Strebhardt K. Multifaceted polo-like kinases: drug targets and antitargets for cancer therapy. Nat Rev Drug Discov 2010;9(8):643-660.

160. Takaki T, Trenz K, Costanzo V, Petronczki M. Polo-like kinase 1 reaches beyond mitosis--cytokinesis, DNA damage response, and development. Curr Opin Cell Biol 2008;20(6):650-660.

161. Liu XS, Song B, Liu X. The substrates of Plk1, beyond the functions in mitosis. Protein Cell

5

2010;1(11):999-1010.

162. Weichert W, Schmidt M, Gekeler V et al. Polo-like kinase 1 is overexpressed in prostate cancer and linked to higher tumor grades. Prostate 2004;60(3):240-245.

163. Deeraksa A, Pan J, Sha Y et al. Plk1 is upregulated in androgen-insensitive prostate cancer cells and its inhibition leads to necroptosis. Oncogene 2012.

164. Takagi M, Honmura T, Watanabe S et al. In vivo antitumor activity of a novel sulfonamide, HMN-214, against human tumor xenografts in mice and the spectrum of cytotoxicity of its active metabolite, HMN-176. Invest New Drugs 2003;21(4):387-399.

165. Garland LL, Taylor C, Pilkington DL, Cohen JL, Von Hoff DD. A phase I pharmacokinetic study of HMN-214, a novel oral stilbene derivative with polo-like kinase-1-interacting properties, in patients with advanced solid tumors. Clin Cancer Res 2006;12(17):5182-5189.

166. Patnaik A, Forero L, Goetz A et al. HMN-214, a novel oral antimicrotubular agent and inhibitor of pololike- and cyclin-dependent kinases: Clinical, pharmacokinetic (PK) and pharmacodynamic (PD) relationships observed in a phase I trial of a daily x 5 schedule every 28 days. [abstract]. J Clin Oncol 22, 2003 (suppl; abstr 514).

167. Steegmaier M, Hoffmann M, Baum A et al. BI 2536, a potent and selective inhibitor of polo-like kinase 1, inhibits tumor growth in vivo. Curr Biol 2007;17(4):316-322.

168. Rudolph D, Steegmaier M, Hoffmann M et al. BI 6727, a Polo-like kinase inhibitor with improved pharmacokinetic profile and broad antitumor activity. Clin Cancer Res 2009;15(9):3094-3102.

169. Wissing MD, Rosmus N, Gonzalez M et al. Targeting prostate cancer through a combination of Polo-like kinase inhibitors and histone deacetylase inhibitors. [abstract]. Proc Am Assoc Cancer Res (AACR), 2010 (abstr 5414).

170. Mross K, Frost A, Steinbild S et al. Phase I dose escalation and pharmacokinetic study of BI 2536, a novel Polo-like kinase 1 inhibitor, in patients with advanced solid tumors. J Clin Oncol 2008;26(34):5511-5517.

171. Hofheinz RD, Al-Batran SE, Hochhaus A et al. An open-label, phase I study of the polo-like kinase-1 inhibitor, BI 2536, in patients with advanced solid tumors. Clin Cancer Res 2010;16(18):4666-4674.

172. Pandha HS, Protheroe A, Wylie J et al. An open label phase II trial of BI 2536, a novel Plk1 inhibitor, in patients with metastatic hormone refractory prostate cancer (HRPC). [abstract]. J Clin Oncol 26, 2008 (May 20 suppl; abstr 14547).

173. Schoffski P, Awada A, Dumez H et al. A phase I, dose-escalation study of the novel Polo-like kinase inhibitor volasertib (BI 6727) in patients with advanced solid tumours. Eur J Cancer 2012;48(2):179-186.

174. Dumez H, Gombos A, Schöffski P et al. Phase I trial of the polo-like kinase (Plk) inhibitor volasertib (BI 6727) combined with cisplatin or carboplatin in patients with advanced solid tumors. [abstract]. J Clin Oncol 30, 2012 (suppl; abstr 3018^).

175. Stadler WM, Vaughn DJ, Sonpavde G et al. Phase II study of single-agent volasertib (BI 6727) for second-line treatment of urothelial cancer (UC). [abstract]. J Clin Oncol 29, 2011 (suppl 7; abstr 253).

176. Combination of BI6727 (Volasertib) and BIBF1120 in Solid Tumors. Bethesda, MD: US National Institute of Health, 2012. Available at: http://clinicaltrial.gov/ct2/show/NCT01022853 [Last accessed 12 December 2012].

177. BI 6727 (Volasertib) Randomised Trial in Ovarian Cancer. Bethesda, MD: US National Institute of Health, 2012. Available at: http://clinicaltrial.gov/ct2/show/NCT01121406 [Last accessed

12 December 2012].

178. An Open Label Phase I Dose Escalation Trial of Intravenous BI 6727 (Volasertib)in Combination With Oral BIBW 2992 (Afatinib) in Patients With Advanced Solid Tumours. Bethesda, MD: US National Institute of Health, 2012. Available at: http://clinicaltrial.gov/ct2/show/NCT01206816 [Last accessed 12 December 2012].

179. BI 6727 (Volasertib) Monotherapy Phase I Trial in Japanese Patients With Advanced Solid Tumours. Bethesda, MD: US National Institute of Health, 2012. Available at: http://clinicaltrial.gov/ct2/show/NCT01348347 [Last accessed 12 December 2012].

180. Gilmartin AG, Bleam MR, Richter MC et al. Distinct concentration-dependent effects of the polo-like kinase 1-specific inhibitor GSK461364A, including differential effect on apoptosis. Cancer Res 2009;69(17):6969-6977.

181. Laquerre S, Sung C, Gilmartin A et al. A potent and selective Polo-like kinase 1 (Plk1) Inhibitor (GSK461364) induces cell cycle arrest and growth inhibition of cancer cell. [abstract]. Proc Am Assoc Cancer Res (AACR), 2007 (abstr 5389).

182. Olmos D, Barker D, Sharma R et al. Phase I study of GSK461364, a specific and competitive Polo-like kinase 1 inhibitor, in patients with advanced solid malignancies. Clin Cancer Res 2011;17(10):3420-3430.

183. Study of NMS-1286937 in Adult Patients With Advanced/Metastatic Solid Tumors. Bethesda, MD: US National Institute of Health, 2012. Available at: http://clinicaltrial.gov/ct2/show/NCT01014429 [Last accessed 12 December 2012].

184. Dose Escalation Study to Determine Safety, Pharmacokinetics, and Pharmacodynamics of Intravenous TKM-080301. Bethesda, MD: US National Institute of Health, 2012. Available at: http://clinicaltrial.gov/ct2/show/NCT01262235 [Last accessed 12 December 2012].

185. Study of Orally Administered TAK-960 in Patients With Advanced Nonhematologic Malignancies. Bethesda, MD: US National Institute of Health, 2012. Available at: http://clinicaltrial.gov/ct2/show/NCT01179399 [Last accessed 12 December 2012].

186. Beria I, Bossi RT, Brasca MG et al. NMS-P937, a 4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline derivative as potent and selective Polo-like kinase 1 inhibitor. Bioorg Med Chem Lett 2011;21(10):2969-2974.

187. Valsasina B, Beria I, Alli C et al. NMS-P937, an orally available, specific, small molecule Polo-Like Kinase 1 inhibitor with antitumor activity in solid and haematological malignancies. Mol Cancer Ther 2012.

188. Hikichi Y, Honda K, Hikami K et al. TAK-960, a novel, orally available, selective inhibitor of Polo-like kinase 1, shows broad-spectrum preclinical antitumor activity in multiple dosing regimens. Mol Cancer Ther 2011.

189. Judge AD, Robbins M, Tavakoli I et al. Confirming the RNAi-mediated mechanism of action of siRNA-based cancer therapeutics in mice. J Clin Invest 2009;119(3):661-673.

190. Semple SC, Judge AD, Robbins M et al. Preclinical characterization of TKM-080301, a lipid nanoparticle formulation of a small interfering RNA directed against polo-like kinase 1. [abstract]. Proc Am Assoc Cancer Res (AACR); Cancer Res 71, 2011 (suppl 8; abstr 2829).

191. Gumireddy K, Reddy MV, Cosenza SC et al. ON01910, a non-ATP-competitive small molecule inhibitor of Plk1, is a potent anticancer agent. Cancer Cell 2005;7(3):275-286.

192. Chapman CM, Sun X, Roschewski M et al. ON 01910.Na is selectively cytotoxic for chronic lymphocytic leukemia cells through a dual mechanism of action involving PI3K/AKT inhibition and induction of oxidative stress. Clin Cancer Res 2012;18(7):1979-1991.

193. Ma WW, Messersmith WA, Dy GK et al. Phase I study of Rigosertib, an inhibitor of the

phosphatidylinositol 3-kinase and Polo-like kinase 1 pathways, combined with gemcitabine in patients with solid tumors and pancreatic cancer. Clin Cancer Res 2012;18(7):2048-2055.

194. Riggs BL, Hartmann LC. Selective estrogen-receptor modulators -- mechanisms of action and application to clinical practice. N Engl J Med 2003;348(7):618-629.

195. Valabrega G, Montemurro F, Aglietta M. Trastuzumab: mechanism of action, resistance and future perspectives in HER2-overexpressing breast cancer. Ann Oncol 2007;18(6):977-984.

196. Qi W, Liu X, Cooke LS et al. AT9283, a novel aurora kinase inhibitor, suppresses tumor growth in aggressive B-cell lymphomas. Int J Cancer 2011.

197. Qi W, Cooke LS, Liu X et al. Aurora inhibitor MLN8237 in combination with docetaxel enhances apoptosis and anti-tumor activity in mantle cell lymphoma. Biochem Pharmacol 2011;81(7):881-890.

198. Feng B, Wang R, Chen LB. MiR-100 resensitizes docetaxel-resistant human lung adenocarcinoma cells (SPC-A1) to docetaxel by targeting Plk1. Cancer Lett 2012;317(2):184-191.

199. Kachhap SK, Rosmus N, Collis SJ et al. Downregulation of homologous recombination DNA repair genes by HDAC inhibition in prostate cancer is mediated through the E2F1 transcription factor. PLoS One 2010;5(6):e11208.

200. Paller C, Wissing M, Kim E, et al. Preclinical profile of AMG900 in combination with HDACIs in prostate cancer. [abstract]. Proc Am Assoc Cancer Res (AACR), 2012 (abstr 2049).

201. Marin-Aguilera M, Codony-Servat J, Kalko SG et al. Identification of docetaxel resistance genes in castration-resistant prostate cancer. Mol Cancer Ther 2012;11(2):329-339.

202. Domingo-Domenech J, Vidal SJ, Rodriguez-Bravo V et al. Suppression of acquired docetaxel resistance in prostate cancer through depletion of notch- and hedgehog-dependent tumor-initiating cells. Cancer Cell 2012;22(3):373-388.

203. Madan RA, Pal SK, Sartor O, Dahut WL. Overcoming chemotherapy resistance in prostate cancer. Clin Cancer Res 2011;17(12):3892-3902.

204. Beer TM, Javle MM, Ryan CW et al. Phase I study of weekly DN-101, a new formulation of calcitriol, in patients with cancer. Cancer Chemother Pharmacol 2007;59(5):581-587.

205. Coleman RL, Duska LR, Ramirez PT et al. Phase 1-2 study of docetaxel plus aflibercept in patients with recurrent ovarian, primary peritoneal, or fallopian tube cancer. Lancet Oncol 2011;12(12):1109-1117.

206. Isambert N, Freyer G, Zanetta S et al. Phase I dose-escalation study of intravenous aflibercept in combination with docetaxel in patients with advanced solid tumors. Clin Cancer Res 2012;18(6):1743-1750.

207. Demetri GD, Lo RP, MacPherson IR et al. Phase I dose-escalation and pharmacokinetic study of dasatinib in patients with advanced solid tumors. Clin Cancer Res 2009;15(19):6232-6240.

208. Eisenberger MA, Hardy-Bessard A, Mourey L, et al. Comparison of two doses of cabazitaxel plus prednisone in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) previously treated with a docetaxel (D)-containing regimen. [abstract]. J Clin Oncol 30, 2012 (suppl; abstr TPS4692^).

209. Study of Weekly Cabazitaxel for Advanced Prostate Cancer. Bethesda, MD: US National Institute of Health, 2012. Available at: http://clinicaltrial.gov/ct2/show/NCT01518283 [Last accessed 21 December 2012].

210. A Study Looking at Novel Scheduling of Cabazitaxel for Patients With Metastatic Prostate Cancer (ConCab). Bethesda, MD: US National Institute of Health, 2012. Available at: http://

clinicaltrial.gov/ct2/show/NCT01541007 [Last accessed 21 December 2012].

211. Second-line Chemotherapy in Castration Resistant Prostate Cancer (ProstyII). Bethesda, MD: US National Institute of Health, 2012. Available at: http://clinicaltrial.gov/ct2/show/ NCT01558219 [Last accessed 21 December 2012].

212. Cabazitaxel Plus Prednisone With Octreotide For Castration-Resistant Prostate Cancer (CRPC) Previously Treated With Docetaxel. Bethesda, MD: US National Institute of Health, 2012. Available at: http://clinicaltrial.gov/ct2/show/NCT01469338 [Last accessed 21 December 2012].

213. Cabaresc NL. Rotterdam, NL: Stichting DUOS, 2012. Available at: http://www.stichtingduos. nl/studies/cabaresc-nl/ [Last accessed 21 December 2012].

214. Cabazitaxel Versus Docetaxel Both With Prednisone in Patients With Metastatic Castration Resistant Prostate Cancer (FIRSTANA). Bethesda, MD: US National Institute of Health, 2012. Available at: http://clinicaltrial.gov/ct2/show/NCT01308567 [Last accessed 21 December 2012].

215. Comparison of Cabazitaxel/Prednisone Alone or in Combination With Custirsen for 2nd Line Chemotherapy in Prostate Cancer (AFFINITY). Bethesda, MD: US National Institute of Health, 2012. Available at: http://clinicaltrial.gov/ct2/show/NCT01578655 [Last accessed 21 December 2012].

216. The CATCH Prostate Cancer Trial: Cabazitaxel And Tasquinimod in Men With Prostate Cancer. Bethesda, MD: US National Institute of Health, 2012. Available at: http:// clinicaltrial.gov/ct2/show/NCT01513733 [Last accessed 21 December 2012].

217. Cabazitaxel and Abiraterone Acetate in Patients With Metastatic Castrate-Resistant Prostate Cancer. Bethesda, MD: US National Institute of Health, 2012. Available at: http:// clinicaltrial.gov/ct2/show/NCT01511536 [Last accessed 21 December 2012].

218. Ph Ib/IIa Study of Cabazitaxel Plus Bavituximab in Castration-resistant Prostate Cancer. Bethesda, MD: US National Institute of Health, 2012. Available at: http://clinicaltrial.gov/ ct2/show/NCT01335204 [Last accessed 21 December 2012].

219. Cabazitaxel With or Without Carboplatin in Patients With Metastatic Castration-Resistant Prostate Cancer Previously Treated With Docetaxel-Based Therapy. Bethesda, MD: US National Institute of Health, 2012. Available at: http://clinicaltrial.gov/ct2/show/ NCT01505868 [Last accessed 21 December 2012].

220. De Souza PL, Mellado B, Pfister C, et al. Randomized phase II trial of patupilone plus prednisone versus docetaxel plus prednisone in patients with chemotherapy-naïve, metastatic, castrate-resistant prostate cancer (CRPC). [abstract]. J Clin Oncol 28:15s, 2010 (suppl; abstr 4553).

221. Gerecitano JF, Stephenson JJ, Lewis NL et al. A Phase I trial of the kinesin spindle protein (Eg5) inhibitor AZD4877 in patients with solid and lymphoid malignancies. Invest New Drugs 2012.

222. Macarulla T, Cervantes A, Elez E et al. Phase I study of the selective Aurora A kinase inhibitor MLN8054 in patients with advanced solid tumors: safety, pharmacokinetics, and pharmacodynamics. Mol Cancer Ther 2010;9(10):2844-2852.

223. Dees EC, Infante JR, Cohen RB et al. Phase 1 study of MLN8054, a selective inhibitor of Aurora A kinase in patients with advanced solid tumors. Cancer Chemother Pharmacol 2011;67(4):945-954.

224. Cervantes A, Elez E, Roda D et al. Phase I pharmacokinetic/pharmacodynamic study of MLN8237, an investigational, oral, selective aurora a kinase inhibitor, in patients with

5

advanced solid tumors. Clin Cancer Res 2012;18(17):4764-4774.

225. Mosse YP, Lipsitz E, Fox E et al. Pediatric Phase I Trial and Pharmacokinetic Study of MLN8237, an Investigational Oral Selective Small-Molecule Inhibitor of Aurora Kinase A: A Children's Oncology Group Phase I Consortium Study. Clin Cancer Res 2012;18(21):6058-6064.

226. Matulonis UA, Sharma S, Ghamande S et al. Phase II study of MLN8237 (alisertib), an investigational Aurora A kinase inhibitor, in patients with platinum-resistant or -refractory epithelial ovarian, fallopian tube, or primary peritoneal carcinoma. Gynecol Oncol 2012;127(1):63-69.

227. Lee P, Alvarez RH, Melichar B, et al. Phase I/II study of the investigational aurora A kinase (AAK) inhibitor MLN8237 (alisertib) in patients (pts) with non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), breast cancer (BrC), head/neck cancer (H&N), and gastroesophageal (GE) adenocarcinoma: Preliminary phase II results.. [abstract]. J Clin Oncol 30, 2012 (suppl; abstr 3010).

228. Falchook GS, Goff BA, Kurzrock R, et al. Phase I/II study of weekly paclitaxel with or without MLN8237 (alisertib), an investigational aurora A kinase inhibitor, in patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer (OC), or breast cancer (BrC): Phase I results. [abstract]. J Clin Oncol 30, 2012 (suppl; abstr 5021).

229. Frost A, Mross K, Steinbild S et al. Phase i study of the Plk1 inhibitor BI 2536 administered intravenously on three consecutive days in advanced solid tumours. Curr Oncol 2012;19(1):e28-e35.

230. Ellis PM, Chu QS, Leighl N et al. A Phase I Open-Label Dose-Escalation Study of Intravenous BI 2536 Together With Pemetrexed in Previously Treated Patients With Non-Small-Cell Lung Cancer. Clin Lung Cancer 2012.

231. Schoffski P, Blay JY, De Greve J et al. Multicentric parallel phase II trial of the polo-like kinase 1 inhibitor BI 2536 in patients with advanced head and neck cancer, breast cancer, ovarian cancer, soft tissue sarcoma and melanoma. The first protocol of the European Organization for Research and Treatment of Cancer (EORTC) Network Of Core Institutes (NOCI). Eur J Cancer 2010;46(12):2206-2215.

232. Sebastian M, Reck M, Waller CF et al. The efficacy and safety of BI 2536, a novel Plk-1 inhibitor, in patients with stage IIIB/IV non-small cell lung cancer who had relapsed after, or failed, chemotherapy: results from an open-label, randomized phase II clinical trial. J Thorac Oncol 2010;5(7):1060-1067.

233. Mross K, Dittrich C, Aulitzky WE et al. A randomised phase II trial of the Polo-like kinase inhibitor BI 2536 in chemo-naive patients with unresectable exocrine adenocarcinoma of the pancreas - a study within the Central European Society Anticancer Drug Research (CESAR) collaborative network. Br J Cancer 2012;107(2):280-286.

234. BI 6727 (Volasertib) Human ADME Trial in Various Solid Tumours. Bethesda, MD: US National Institute of Health, 2012. Available at: http://clinicaltrials.gov/ct2/show/NCT01145885 [Last accessed 21 December 2012].

235. Dose Finding Study of BI 6727 (Volasertib) in Patients With Various Solid Cancers. Bethesda, MD: US National Institute of Health, 2012. Available at: http://clinicaltrial.gov/ct2/show/NCT00969553 [Last accessed 21 December 2012].

236. Trial of BI 6727 (Volasertib) Monotherapy and BI 6727 in Combination With Pemetrexed Compared to Pemetrexed Monotherapy in Advanced NSCLC. Bethesda, MD: US National Institute of Health, 2012. Available at: http://clinicaltrial.gov/ct2/show/NCT00824408 [Last

accessed 21 December 2012].

237.   Jimeno A, Li J, Messersmith WA et al. Phase I study of ON 01910.Na, a novel modulator of the Polo-like kinase 1 pathway, in adult patients with solid tumors. J Clin Oncol 2008;26(34):5504-5510.

238.   Ohnuma T, Holland JF, Goel S, et al. Final results of a phase I dose-escalation study of ON 01910.Na in combination with oxaliplatin in patients with advanced solid tumors. [abstract]. J Clin Oncol 29, 2011 (suppl; abstr e13584).

239.   Bowles DW, Diamond JR, Lam ET, et al. Phase I study of oral rigosertib in patients with advanced solid tumors. [abstract]. J Clin Oncol 30, 2012 (suppl; abstr 3017).

240.   Vainshtein JM, Ghalib MH, Kumar M, et al. Phase I study of ON 01910.Na, a novel polo-like kinase 1 pathway modulator, administered as a weekly 24-hour continuous infusion in patients with advanced cancer. [abstract]. J Clin Oncol 26, 2008 (May 20 suppl; abstr 2515).

241.   Ohnuma T, Cho SY, ROboz J, et al. Phase I study of ON 01910.Na by 3-day continuous infusion (CI) in patients (pts) with advanced cancer. [abstract]. J Clin Oncol 24:18S, 2006 (June 20 suppl; abstr 13137).

242.   Safety, Pharmacokinetics and Clinical Activity of Oral Rigosertib in Solid Tumors. Bethesda, MD: US National Institute of Health, 2012. Available at: http://clinicaltrial.gov/ct2/show/ NCT01168011 [Last accessed 21 December 2012].

243.   Effect of 2-h Infusion of ON 01910.Na in Ovarian Cancer Patients. Bethesda, MD: US National Institute of Health, 2012. Available at: http://clinicaltrial.gov/ct2/show/ NCT00856791 [Last accessed 21 December 2012].

244.   Gemcitabine and ON 01910.Na in Previously Untreated Metastatic Pancreatic Cancer (ONTRAC). Bethesda, MD: US National Institute of Health, 2012. Available at: http:// clinicaltrial.gov/ct2/show/NCT01360853 [Last accessed 21 December 2012].

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