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CLINICAL TRIAL REPORT

A phase I study of HER1, HER2 dual kinase inhibitor lapatinib plus the proteasome inhibitor bortezomib in patients with advanced malignancies

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Abstract

Purpose This phase I trial evaluated the maximum tolerated dose, safety and preliminary efficacy of lapatinib, a HER1, HER2 dual kinase inhibitor plus bortezomib, a proteasome inhibitor, in adult patients with advanced malignancies.

Methods Patients were enrolled in a standard 3 + 3 design with lapatinib (L) 750, 1000, 1250 or 1500 mg daily, and bortezomib (B) 0.7, 1.0, 1.3 or 1.6 mg/m^2 for 3 weeks with 1 week off. Dose-limiting toxicities (DLT) were assessed during the first 28 days

Results Fifteen patients received the combination of lapatinib and bortezomib in three different cohorts and ten were evaluable for DLT. There were no DLTs. Anorexia was the most common adverse event. Biomarker analysis showed upregulation of p27 expression with lapatinib and the combination. No tumor response was observed and thus the study was closed early.

Conclusion The combination of lapatinib and bortezomib was well tolerated but no complete or partial tumor responses were observed at the dose levels tested.

ClinicalTrials.gov Identifier NCT01497626.

Keywords Bortezomib · Lapatinib · Phase I · EGFR · HER2 · Proteasome inhibitor

Introduction

The ErbB family of growth factor receptors is composed of classic membrane-bound tyrosine kinase receptors, whose activation initiates several cell signaling pathways [1]. These pathways include the Ras–Raf–MAPK pathway, the PI3K–AKT pathway, the protein kinase C pathway, the STAT pathway, and the src kinase pathway, all of which play important roles in tumor cell proliferation, invasion, migration, and inhibition of apoptosis [2]. Targeting of the ErbB family receptors has made a significant impact in cancer care [2].

Lapatinib (Tykerb®, Novartis) is a small molecule dual kinase inhibitor that targets the EGFR and HER2 [3]. Lapatinib received approval by the US Food and Drug Administration (FDA) to be used in combination with capecitabine or letrozole in patients with metastatic breast cancer, and lapatinib has showed significant promise in a variety of other cancers [4–6]. Despite the genuine promise and improved clinical outcome with agents that target the ErbB family, most patients' tumors are resistant to either the monoclonal

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antibodies (mAbs) or the small molecule inhibitors, suggesting the existence of resistant pathways in tumor cells.

Bortezomib (Velcade®, Millenium Pharmaceuticals, Inc.) is a proteasome inhibitor FDA approved for use in patients with multiple myeloma and mantle cell lymphoma [7]. While the ubiquitin–proteasome degradation pathway has been well described for a number of key regulatory proteins, the exact anti-tumor mechanisms of bortezomib have never been clearly understood, but may include effects on NFκB, the cell cycle proteins, and direct effects on the EGFR [8].

Preclinical data have demonstrated additive or even synergistic anti-tumor activity with the combination of an EGFR or HER2 antagonist and bortezomib. For example, Lorch et al. demonstrated synergistic anti-tumor activity with the combination of bortezomib and a small molecule inhibitor of the EGFR [9]. Kesarwala et al., proposed that one mechanism by which proteasome inhibition enhances the effects of the anti-EGFR mAbs could be through the prevention of the normal receptor internalization–degradation and recycling of the EGFR, thus "trapping" the EGFR at the cell membrane and maintaining a target for inactivation by the mAbs and tyrosine kinase inhibitors [10]. Similarly, Lorch et al. proposed that inhibition of the EGFR results in increased cell–cell adhesion, and that proteasome inhibition increases EGFR expression and thus increases the efficacy of a small molecule EGFR antagonist. An et al. demonstrated additive inactivation of NFκB as a mechanism for synergistic anti-cancer activity with bortezomib and a small molecule inhibitor of the EGFR in renal cell cancer cell lines [11]. Finally, Sloss and Cascone separately demonstrated a synergistic inhibition of the activation of downstream mediators of the EGFR signal, particularly phospho-AKT [12, 13]. Importantly, particularly in the context of colon cancer, activating mutations in the *RAS* gene confer an almost complete resistance to the EGFR mAbs. However, Luo et al. have elegantly demonstrated that bortezomib can overcome a constitutive Ras activation, thus rendering even *RAS*-mutated cells sensitive to EGFR inhibition [14]. The proof of concept justifying further study of the combination of an EGFR antagonist and bortezomib has also been demonstrated in humans. Dudek et al. performed a Phase I trial of a combination of cetuximab and bortezomib, with the bortezomib given on days 1 and 8 of a 21 day cycle at doses ranging from 1.3 to 2.0 mg/m^2. The MTD was not reached. Thirty-seven heavily pre-treated patients were enrolled with six patients (16.2%) achieving stable disease at 12 weeks. Surprisingly, none of the patients entered on the trial had colorectal cancer, a group for which single agent EGFR inhibition has proven activity [15].

Based on these data, we planned a Phase I trial of lapatinib plus bortezomib in patients with advanced malignancies. Both lapatinib and bortezomib are metabolized through the CYP 3A4 pathway, and pharmacokinetic interactions could exacerbate the toxicity of lapatinib, bortezomib, or both justifying a phase I trial. We also included extensive ErbB family and proteasome-related pathway analysis from fresh tumor biopsies critical to our understanding of the potential mechanisms of synergistic activity with combination therapy.

Materials and methods

Patients

Adult patients with refractory solid tumors were enrolled in an open label, dose-escalation phase I clinical study. Patients were required to have measurable disease, adequate organ function, an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, life expectancy of greater than 3 months, and adequate hepatic, bone marrow and renal function. All patients enrolled in the study provided written informed consent.

Trial design and objectives

The protocol was approved by the oncology-specific scientific review committee and the Georgetown Oncology Institutional Review Board and monitored by the Lombardi Comprehensive Cancer Center Data and Safety Monitoring Committee (DSMC).

The study was designed as a standard 3 + 3 dose-escalation study performed beginning at a reduced dose of both agents (Table 1). DLTs were defined as any of the following events that are possibly, probably, or definitely related

Table 1 Dose-escalation schema

Cohort	Lapatinib (mg daily)	Bortezomib (mg/m² weekly)
-2	750	0.7
-1	1000	0.7
1	1000	1.0
2	1250	1.0
3	1250	1.3
4	1500	1.3
5	1500	1.6

Cohort	Lapatinib (mg daily)	Bortezomib (mg/m² weekly)
Expansion Cohort 10 Patients	Recommended Phase II Doses	

to one or both agents and occur within the first cycle of therapy: (1) Grade 4 neutropenia lasting greater than 5 days or complicated by fever or infection. (2) Grade 4 anemia or thrombocytopenia. (3) Grade 3 or 4 non-hematologic toxicity. For patients with baseline grade 2 elevated liver enzymes (AST or ALT) due to known intrahepatic metastases, the DLT was defined only as a grade 4 elevation of AST or ALT. (4) Any toxicity, regardless of grade, which results in withholding of therapy for > 3 weeks. Any patient enrolled who received at least one dose was considered evaluable for DLTs provided: (1) the patient experienced a DLT; or (2) the patient is observed on protocol therapy for at least one cycle without a DLT. All other patients were considered non-evaluable and replaced. The DLT evaluation period was until the end of cycle 1 (i.e., − 7 to day 28 on study).

Patients were enrolled in cohorts of three patients. If there were no DLTs in the first cohort, then three patients were enrolled in the next cohort, as detailed in Table 1. Intra-patient dose escalation was not allowed. If one patient in any cohort experienced a DLT, then the cohort was expanded to six patients. If no additional patients experienced a DLT, then three patients were enrolled in the next cohort. If 2/6 or greater of the patients experienced a DLT, then the dose level below was considered the maximum tolerated dose (MTD). Dose de-escalation contingencies were also included (Table 1). Once the RP2D was established, an additional ten patients were planned to be treated at the RP2D to provide a more confident assessment of safety and tolerability, and to provide a preliminary assessment of treatment efficacy.

The primary objective of the study was to identify the maximally tolerated dose and recommended phase II dose of bortezomib to be used in combination with lapatinib in patients with advanced malignancies. Secondary clinical objectives included evaluation of toxicity, overall response rate and disease control rate of the combination of bortezomib plus lapatinib in patients with advanced malignancies. Secondary scientific objectives included assessment of pharmacodynamic effects of lapatinib alone, and in combination with bortezomib on the HER1, HER2 and proteasome pathways by phosphoprotein pathway analysis.

Treatment

The starting dose of lapatinib was 1000 mg/day continuously for 28 days of each 28-day cycle, including an initial run-in of lapatinib alone (Fig. 1). The run-in dose was started on day − 7. Patients also received bortezomib IV on days 1, 8, and 15 of a 28 day cycle. The standard starting dose of bortezomib used in patients with multiple myeloma is 1.3 mg/m^2 on days 1, 4, 8 and 11 of a 21-day cycle. However, bortezomib has also been used on a weekly schedule in patients with solid tumors (e.g. 1.6 mg/m^2 days 1, 8, 15 of a 28 day cycle in patients with lung cancer [16]). Therefore, the starting dose of bortezomib used in this study was 1.0 mg/m^2. Patients were enrolled in a standard 3 + 3 alternating dose-escalating fashion to an intended maximal dose of lapatinib of 1500 mg/day, and a maximal dose of bortezomib of 1.6 mg/m^2, as detailed in Table 1.

Response and toxicity

Patients were evaluated, including laboratory testing, every 2 weeks until the first restaging analysis. Restaging occurred every 8 weeks. If at restaging there was no evidence of progression of disease, as determined by RECIST 1.1 criteria and the patient was tolerating therapy, then patients could be seen only every 4 weeks, unless clinically indicated. Patients remained in the study as long as there was no evidence of progression of disease (according to RECIST 1.1 criteria) and the therapy was adequately tolerated.

Adverse events were monitored continuously from the time of enrolment through 30 days after the last dose of study drug or until resolution of treatment-related events whichever was longer. These events were graded using the NCI CTCAE version 4.0. A drug-related toxicity was defined as an adverse event or laboratory value outside of the reference range that was judged by the investigator to be either "possibly related" or "probably related" to the study drug. For the purposes of this study, causality assessments were attributed to lapatinib, bortezomib, or both. Toxicity was deemed "clinically significant" based on the medical judgment of the investigator.

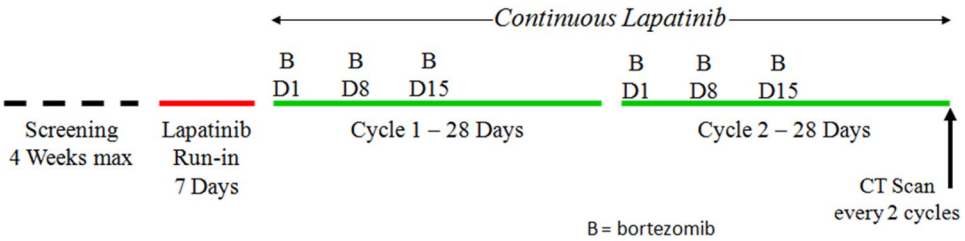

Fig. 1 Treatment schedule

Correlative studies

All patients were required to undergo serial biopsies: prior to treatment, repeated biopsy after single agent lapatinib and final biopsy after combination therapy with lapatinib and bortezomib. Three-core biopsy specimens were collected in formalin, liquid nitrogen, and a Proprietary Universal Fixative, developed by Theranostics Health to block fluctuation in kinases and phosphatases [17]. Reverse phase protein array (RPPA)-based protein drug target activation mapping testing and analysis were performed as a joint collaboration with Theranostics Health in Rockville, MD.

Statistical methods

This was a phase 1 dose-escalation study with a standard 3 + 3 dose escalation. Therefore, the final sample size would depend on the number of dose levels and DLTs in the study. Descriptive statistics were used to summarize patients' demographic factors. Evaluation of the toxicities of the combination of lapatinib and bortezomib were also only descriptive in nature. Analyses of adverse events (and serious adverse events) included only "treatment-emergent" events, i.e., those that have an onset on or after the day of the first dose of study drug. Analyses did not include those that have an onset greater than 30 days after the last dose of study drug. Treatment-emergent adverse events were summarized by system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA) adverse event coding dictionary.

Table 2 Patient characteristics

Demographic	Result
Total enrolled	15
Age—median (years), range	56.5 (29–74)
Gender—male/female	5 M/10F
Race	
White	8
Black	6
Asian	1
Primary disease	
Gastrointestinal	10
Gynecological	1
Breast	2
Sarcoma	2

Results

Patients

Between September 2011 and December 2015, a total of 17 patients signed consent. Fifteen patients received at least one dose of study drug and two patients failed screening. Demographics for these patients are summarized in Table 2. Duration of treatment ranged from 1 to 6 cycles. Patients were enrolled in three different cohorts. Of the ten patients evaluable for DLTs, three were treated with lapatinib 1000 mg daily and bortezomib 1 mg/m^2 weekly for 3 weeks with 1 week off (L1000/B1), six with lapatinib 1250 mg daily and bortezomib 1 mg/m^2 (L1250/B1), and one with lapatinib 1250 mg daily and bortezomib 1.3 mg/m^2 (L1250/B1.3).

Toxicities by dose level

Of the 15 patients enrolled, 10 patients were evaluable for DLTs, with no DLTs confirmed. Four of the five patients who did not complete the DLT evaluation period had progressive disease in that period (Table 3). The combination of lapatinib and bortezomib was generally well tolerated, with no grade 4 toxicities occuring. Treatment-related toxicities that were experienced by ≥ 10% of subjects are summarized in Table 4. Anorexia was the most common side event, occurring in 30% of patients, followed by diarrhea, fatigue, mucositis, nausea, headaches and rash, all experienced by 20% of patients. Patient 009 was initially considered to have experienced a DLT in cohort 2 with hyponatremia and dehydration in the setting of diarrhea. For that reason, this cohort was expanded to six patients. At the time of the DSMC meeting, the event was reviewed and adjudicated as not being a DLT and instead attributed

Table 3 Patients who did not complete the DLT evaluation period

Patient	Gender	Primary disease	Description
003	M	Ampullary adenocarcinoma	Nausea and vomiting due to disease progression
007	M	Gastric cancer	Disease progression in the brain, enrolled in hospice
010	F	Colon cancer	Decline in performance status due to disease progression, enrolled in hospice
011	F	Colon cancer	Decline in performance status after hospitalization due to urinary tract infection, enrolled in hospice
016	F	Breast cancer	Elevated liver function tests due to disease progression, decline in performance status

Table 4 Incidence and grade of treatment-related toxicities that were experienced by > 10% of subjects

CTC term	CTC grade				Number of patients who experienced this AE	Incidence (%)
	1	2	3	Total		
Anorexia	1	2	0	3	3	30
Dehydration	0	0	1	1	1	10
Diarrhea	1	1	0	2	2	20
Fatigue (asthenia, lethargy, malaise)	2	0	0	2	2	20
Mucositis/stomatitis (clinical exam)	2	0	0	2	2	20
Nausea	1	0	1	2	2	20
Pain: head/headache	2	0	0	2	2	20
Rash: acne/acneiform	2	0	0	2	2	20
Sodium, serum low (hyponatremia)	0	0	1	1	1	10
Total	11	3	3	17		

to a pre-existing condition. For that reason the following patient to go on study was enrolled in cohort 3.

Response

Of the 15 patients enrolled, all were evaluable for response. There were no objective responses by RECIST criteria to the combination of lapatinib and bortezomib. Two patients had stable disease, one with rectal cancer in cohort 1 and the other with breast cancer in cohort 2, for 2 and 6 cycles, respectively. The second patient had HER2 positive breast cancer determined by tumor overexpression of HER2 (IHC 3+) and Her-2/neu gene amplification. She had previously received eight lines of therapy for metastatic disease including anti-HER2 monoclonal antibodies (trastuzumab and pertuzumab) and an antibody drug conjugate consisting of trastuzumab covalently linked to the cytotoxic agent DM1 (ado-trastuzumab emtansine). There was evidence of EGFR and ERBB2 amplification on liquid biopsy. After enrolling 15 patients and given limited activity of the combination, the trial was terminated by the funding entity.

Pharmacodynamics

Serial tumor biopsies were evaluable for 12 patients. RPPA-based analysis evaluated 36 key protein and phosphoproteins directly related to drug mechanism of action. Phosphoprotein pathway analysis was performed in patient tumor samples to assess the pharmacodynamic effect of lapatinib alone and in combination with bortezomib on the HER1 and HER2 pathways (Fig. 2). Compared to baseline, lapatinib alone resulted in an increase in p27 expression by 1.68. The combination of lapatinib and bortezomib resulted in an increase in p27 expression by 1.89-fold (p 0.069 compared to baseline). Both with lapatinib and the combination, there was also a significant increase in the amount of HER2 activation/phosphorylation (Y1248) [1.32 and 1.29, respectively, ($p = 0.047$ compared to baseline)].

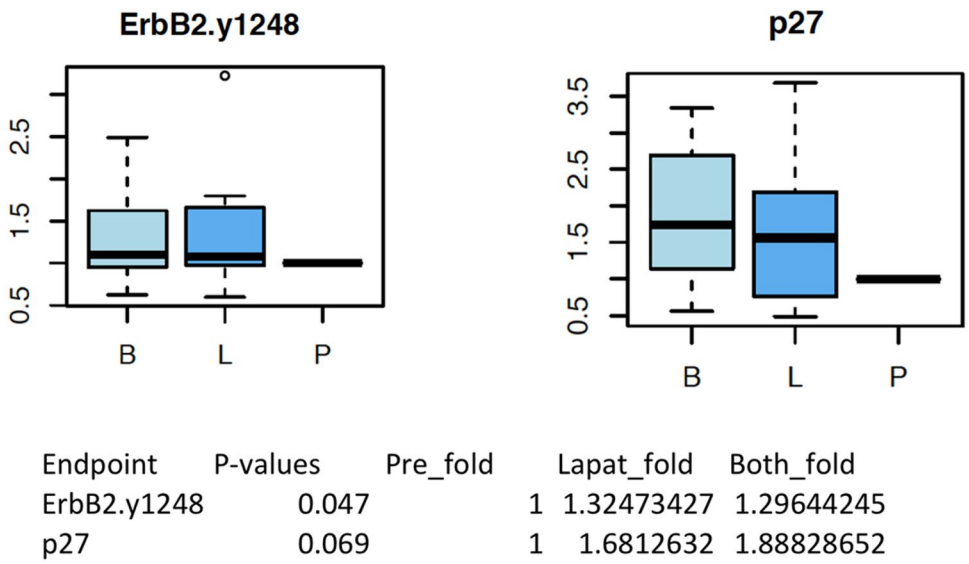

Fig. 2 Changes in phosphorylated peptides of HER2 (y1248) and p27 with exposure to lapatinib and bortezomib + lapatinib. *B* both, *L* lapatinib alone, *P* baseline, *ErbB2.y1248* HER2 activation/phosphorylation (Y1248)

Discussion

Numerous investigations over the past decades have demonstrated that targeting the ErbB family receptors has anticancer properties both in preclinical and clinical studies. However, only a small number of tumors respond to monoclonal antibodies (mAbs) or small molecule inhibitors targeting the ErbB family receptors and resistance eventually develops. Proteasome inhibitors appeared as a potential way of overcoming resistance to ErbB receptors through different mechanisms that include prevention of the normal receptor internalization–degradation and recycling of the EGFR [10] or increase of EGFR expression [9]. There is also evidence that lapatinib induces constitutive activation of NF-kB rendering the tumor cells more vulnerable to NF-KB inhibition by bortezomib. This effect was seen with lapatinib but not with other EGFR inhibitors [18].

In our study, the combination was well tolerated and the MTD was not reached. The toxicity profile observed in our patients was less than expected and there were no DLTs. Unfortunately, 33% (5/15) of the patients enrolled were not evaluable for DLT period which is likely related to the nature of phase 1 studies where some patients participate in a period too advanced of their malignancy. This is higher than the 16.5% rate of early discontinuation reported by Hyman et al. [19], although the small sample size of this study doesn't allow us to draw any further conclusions.

At the studied doses, there was no evidence of significant clinical efficacy. Only two patients had stable disease. In the patient with HER2 positive breast cancer who had stable disease for 24 weeks, lapatinib is known to have single agent activity therefore raising the question of whether bortezomib had any synergistic effect. Certainly, it did not appear at the studied doses. The HER2 status of other patients was unknown. The lack of significant responses was disappointing, given the robust findings from previous in vitro and in vivo experiments [11–14]. One of the strengths of this study was the success in obtaining serial biopsies in most patients. With these biopsies we confirmed that, as expected, the addition of lapatinib led to an upregulation in p27 expression, further potentiated with the addition of bortezomib. p27 is a negative regulator of the protein kinase CDK2/cyclin E and can block the cell cycle at G0/G1 phase [20]. Previous studies have also demonstrated that lapatinib upregulates p27 expression through both transcriptional and post-translational mechanisms and induces G1 cell cycle arrest in various types of cancer cells [21].

It is intriguing, however, that lapatinib and the combination with bortezomib led to an increase in the amount of HER2 activation/phosphorylation (Y1248). Previous experiences have shown that lapatinib effectively suppressed activation of HER2 given that lapatinib is a known HER2 kinase inhibitor [22]. Our results showed increased activity of HER2 in the on-treatment biopsy compared to the matched pretreatment sample, and could represent a resistance mechanism within the tumor cells wherein a compensatory response to kinase inhibition is obtained through the upregulating of the substrate itself as a feedback mechanism. The study predefined biopsies only offer us a few time-dependent molecular "snapshots" that do not allow us to fully understand the temporal perturbation of the phosphoproteome-based dynamics induced by lapatinib treatment [23]. On the other hand, these findings could be reflective of the fact that the drugs did not inhibit the target effectively at the studied doses, which could therefore explain the lack of clinical efficacy. Of interest, at the studied doses, the addition of bortezomib to lapatinib only slightly increased the p27 expression or HER2 activation/phosphorylation (Y1248) compared to lapatinib alone.

The slow accrual of this study was a limitation and it is possible that we would have seen evidence of synergy at higher doses. This may have been in part explained by the challenge to perform serial biopsies. The absence of clinical efficacy may also be justified by the lack of patient selection based on HER2 or EGFR status.

In conclusion, the combination of lapatinib and bortezomib was well tolerated but it lacked evidence of clinical activity and does not support further clinical investigation of this combination. Currently there are no ongoing trials exploring this combination in any solid tumor. New generation of proteasome inhibitors with higher clinical efficacy in combination with inhibitors of the ErbB family along with better patient selection may be considered in the future.

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Compliance with ethical standards

Conflict of Interest FL has received research grants from BMS, Pfizer, Genentech/Roche, Immunomedics, Calithera, Chugai, Regeneron, Tesaro and Inivata; has participated in advisory boards (non-paid) with BMS, Jounce and AstraZeneca and travel expenses from BMS, Genentech and Jounce. EFP has a leadership role in Ceres Nanosciences and Perthera; has stock and other ownership interests in Avant Diagnostics, Ceres Nanosicences and Perthera; has consulting or advisory roles with Avant Diagnostics, AZGen, Ceres Nanosciences and Perthera; has received research funding from Abbvie, Ceres Na-

nosciences, GSK and Symphogen; has intellectual property rights in NIH Patents Licensing Fee Distribution/Royalty and University assigned patent licensing fee/royalty; has received travel expenses by Ceres Nanoscience and Perthera. PRP has intellectual property rights (United States Patents no. 8,486,413; no. 8,501,417; 9,023,362 and 9,745,377: Immunological Compositions as Cancer Biomarkers and/or Therapeutics); has ownership interests in Immunonet BioSciences; has consulted for Heron, Personalized Cancer Therapy, PUMA, Pfizer, Oncoplex Dx, CARIS, Sirtex; has received financial support for educational programs (non-CME teaching) from ASCO, Dava Oncology, Roche; has received research grants to the institution from Immunonet BioSciences, Genentech/Roche, Pfizer, Cascadian therapeutics/Seattle Genetics, Fabre-Kramer, Advanced Cancer Therapeutics, Pieris. BS has received honoraria for speaking for TAIHO. DSS is an employee and has stock and other ownership interests in AZ; DSS was on speakers' bureau for AZ and Genentech until June 2019. JD has received research grants from Merck, BMS and Loxo Oncology and has outside income/royalties from UpToDate. JM has been a speaker/consultant and received honoraria from Genentech, Amgen, Celgene, Taiho, Bayer, Merck, Caris and Indivumed. MP has been a speaker/consultant for AstraZeneca/MedImmune, Caris Life Sciences, Celgene, Merrimack, Perthera, RenovoRx and Sirtex Medical; has received travel, accommodations and expenses Support from AstraZeneca/MedImmune, Merck, Caris Life Sciences, Perthera and Sirtex Medical and has Stock interests in Perthera.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Pishvaian M, Marshall JL, He R, Wang D (2011) Epidermal growth factor inhibitors. In: Schwab M (ed) Encyclopedia of cancer. Springer, Berlin
2. Marshall J (2006) Clinical implications of the mechanism of epidermal growth factor receptor inhibitors. Cancer 107:1207–1218
3. Tykerb [package insert]. Novartis, 2013
4. Opdam FL, Guchelaar HJ, Beijnen JH, Schellens JH (2012) Lapatinib for advanced or metastatic breast cancer. Oncologist 17(4):536–542
5. Wisinski KB, Tevaarwek AJ, Burkard ME et al (2016) Phase I Study of an AKT inhibitor (MK-2206) combined with lapatinib in adults solid tumors followed by dose expansion in advanced HER2 + breast cancer. Clin Cancer Res 22(11):2659–2667
6. Deeken JF, Wang H, Subramaniam D et al (2015) A phase 1 study of cetuximab and lapatinib in patients with advanced solid tumor malignancies. Cancer 121(10):1645–1653
7. Velcade [package insert]. Millennium Pharmaceuticals, Inc., 2014
8. Adams J (2004) The proteasome: a suitable antineoplastic target. Nat Rev Cancer 4:349–360
9. Lorch JH, Thomas TO, Schmoll HJ (2007) Bortezomib inhibits cell–cell adhesion and cell migration and enhances epidermal growth factor receptor inhibitor-induced cell death in squamous cell cancer. Cancer Res 67:727–734
10. Kesarwala AH, Samrakandi MM, Piwnica-Worms D (2009) Proteasome inhibition blocks ligand-induced dynamic processing and internalization of epidermal growth factor receptor via altered receptor ubiquitination and phosphorylation. Cancer Res 69:976–983
11. An J, Rettig MB (2007) Epidermal growth factor receptor inhibition sensitizes renal cell carcinoma cells to the cytotoxic effects of bortezomib. Mol Cancer Ther 6:61–69
12. Cascone T, Morelli MP, Morgillo F et al (2008) Synergistic antiproliferative and pro-apoptotic activity of combined therapy with bortezomib, a proteasome inhibitor, with anti-epidermal growth factor receptor (EGFR) drugs in human cancer cells. J Cell Physiol 216:698–707
13. Sloss CM, Wang F, Liu R et al (2008) Proteasome inhibition activates epidermal growth factor receptor (EGFR) and EGFR-independent mitogenic kinase signaling pathways in pancreatic cancer cells. Clin Cancer Res 14:5116–5123
14. Luo J, Emanuele MJ, Li D et al (2009) A genome-wide RNAi screen identifies multiple synthetic lethal interactions with the Ras oncogene. Cell 137:835–848
15. Dudek AZ, Lesniewski-Kmak K, Shehadeh NJ et al (2009) Phase I study of bortezomib and cetuximab in patients with solid tumours expressing epidermal growth factor receptor. Br J Cancer 100:1379–1384
16. Lilenbaum R, Wang X, Gu L et al (2009) Randomized phase II trial of docetaxel plus cetuximab or docetaxel plus bortezomib in patients with advanced non-small-cell lung cancer and a performance status of 2: CALGB 30402. J Clin Oncol 27:4487–4491
17. Mueller C, Edmiston KH, Carpenter C et al (2011) One-step preservation of phosphoproteins and tissue morphology at room temperature for diagnostic and research specimens. PLoS One 6(8):e23780
18. Chen Y-J, Yeh M-H, Yu M-C et al (2013) Lapatinib-induced NF-kappaB activation sensitizes triple-negative breast cancer cells to proteasome inhibitors. Breast Cancer Res 15:R108
19. Hyman DM, Eaton AA, Gounder MM et al (2015) Predictors of early treatment discontinuation in patients enrolled on phase I oncology trials. Oncotarget 6:19316–19327
20. Akli S, Zhang XQ, Bondaruk J et al (2012) Low molecular weight cyclin E is associated with p27-resistant, high grade, high stage and invasive bladder cancer. Cell Cycle 11:1468–1476
21. Tang L, Wang Y, Strom A et al (2013) Lapatinib induces p27(Kip1)-dependent G1 arrest through both transcriptional and post-translational mechanisms. Cell Cycle 12(16):2665–2674
22. Zhang D, Pal A, Bornmann WG et al (2008) Activity of lapatinib is independent of EGFR expression level in HER2-overexpressing breast cancer cells. Mol Cancer Ther 7(7):1846–1850
23. Imami K, Sugiyama N, Imamura H et al (2012) Temporal Profiling of lapatinib-suppressed phosphorylation signals in EGFR/HER2 pathways. Mol Cell Proteomics 11:1741–1757