COWEN AND COMPANY

Puma Biotechnology

Initiating With Outperform (1)

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The Cat With Nerat-(inib) Comes Back

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Conclusion: We are initiating coverage of Puma Biotechnology with an Outperform rating. Puma is developing neratinib, a small molecule HER2 inhibitor for select patients with breast and lung cancer. Neratinib has been studied in over 3,000 patients with clear demonstration of efficacy and safety. Puma's management team (formerly with Cougar Biotechnology) has a track record of efficient drug development, and consultants are optimistic for neratinib's success in a Phase III trial that will initiate in early 2013. We view PBYI shares as 40-50% undervalued based on our NPV analysis.

- **A Largely De-Risked Asset...** Neratinib came to Puma from Pfizer along with a plethora of Phase I and II data that suggest it is a best-in-class HER2 receptor tyrosine kinase inhibitor. Neratinib's efficacy as a monotherapy and in combination with chemotherapy appears substantially superior to that of Tykerb (GSK, sales of $372MM in 2011) with an acceptable safety profile. Additional Phase II data will be presented next month at the SABCS meeting.

- **...With A New Game Plan...** After gaining rights to neratinib, Puma and its advisors have re-focused and re-prioritized its development. We expect a head-to-head trial vs. Tykerb in 3rd-line HER2+ breast cancer patients to pave the way to approval while additional studies in breast cancer (neoadjuvant setting, salvage patients, patients with brain mets, and patients with a newly identified mutation) and lung cancer (patients with HER2 mutations) could substantially broaden the commercial opportunity.

- **...Has A Straight Path To Creation Of Shareholder Value.** With the exception of a 10-20% royalty to Pfizer, Puma owns worldwide rights to neratinib. We believe success vs. Tykerb could support 2020 sales of $600MM worldwide. Based upon an NPV estimate of neratinib's value and PBYI's cash on hand, we view shares as 40-50% undervalued.

PBYI (11/12)	**$20.01**
Mkt cap	**574.3MM**
Dil shares out	28.7MM
Avg daily vol	5.0K
52-wk range	$10.0-23.3
Dividend	Nil
Dividend yield	Nil
BV/sh	$1.40
Net cash/sh	$2.05
Debt/cap	NA
ROIC (LTM)	NA
5-yr fwd EPS growth (Norm)	NA
S&P 500	**1380.0**

Revenue $MM

FY Dec	2011 Actual	2012E Prior	2012E Current	2013E Prior	2013E Current	2014E Prior	2014E Current
Q1	—	—	0.0A	—	0.0	—	—
Q2	—	—	0.0A	—	0.0	—	—
Q3	—	—	0.0	—	0.0	—	—
Q4	—	—	0.0	—	0.0	—	—
Year	**0.0**	**—**	**0.0**	**—**	**0.0**	**—**	**0.0**
EV/S	—	—	—	—	—	—	—

EPS $

FY Dec	2011 Actual	2012E Prior	2012E Current	2013E Prior	2013E Current	2014E Prior	2014E Current
Q1	—	—	(0.59)A	—	(0.40)	—	—
Q2	—	—	(0.74)A	—	(0.41)	—	—
Q3	—	—	(0.58)	—	(0.43)	—	—
Q4	—	—	(0.43)	—	(0.45)	—	—
Year	**(1.32)**	**—**	**(2.30)**	**—**	**(1.70)**	**—**	**(1.75)**
P/E	—	—	—	—	—	—	—

Investment Summary

Puma Biotechnology was founded with the intent to in-license and develop novel drug candidates for cancer. The great majority of the company's resources are being directed to support of neratinib (PB272, formerly HKI-272), an oral, small molecule inhibitor of the HER2 receptor tyrosine kinase (RTK). Puma acquired neratinib from Pfizer in October 2011 along with a plethora of Phase II data that provides strong proof-of-concept efficacy. The company has refocused and narrowed neratinib's development within the HER2+ breast cancer landscape, and has identified a couple of additional cancer types that are of high developmental interest. The first pivotal trial in breast cancer (a head-to-head study versus GlaxoSmithKline's Tykerb) is expected to begin before year end, and could provide data in 2015. We view neratinib as a relatively low risk, majority owned oncology asset with $300MM+ potential, and expect PBYI shares to outperform the market as the candidate progresses forward in development.

PBYI: The Cat's Second Life

Puma Biotech was founded in 2011 by CEO Alan Auerbach, formerly the CEO of Cougar Biotechnology. Cougar was acquired by Johnson and Johnson in 2009 for approximately $1B after having advanced abiraterone (now marketed as Zytiga, estimated 2012 sales of $975MM) deep into Phase III trials for prostate cancer. Mr. Auerbach and much of his former Cougar team have moved on to Puma, where they are hoping to replay much of their game plan. The focus of their efforts will be neratinib, a drug that Pfizer sought to out-license due to escalating R&D costs. Pfizer retains a 10-20% royalty interest in neratinib and will be eligible for up to $187.5MM in milestones, the first of which is due upon approval. Neratinib is protected by a composition of matter patent that expires in 2025 and polymorph patents that expire in 2028.

Why We Like Neratinib

The HER2+ breast cancer market features multiple older (Roche's Herceptin, GlaxoSmithKline's Tykerb) and newer (Roche's Perjeta, Roche/Immunogen's T-DM1) therapeutic agents. Yet no patients with metastatic breast cancer are being cured, and even later line options like Tykerb bring in substantial sales ($372MM in 2011). Preclinical data suggest neratinib has a differentiated mechanism and best in class potency within the small molecule HER2 RTK inhibitor class. These factors appear to be translating into the clinical experience. Based upon much Phase I and II work conducted mostly by Pfizer, neratinib's efficacy and safety have been largely de-risked, and its overall profile appears superior to that of Tykerb. Puma and its advisors have mapped out an efficient development plan that attempts to (1) demonstrate the superiority of neratinib to Tykerb while (2) also expanding the small molecule HER2 RTK inhibitor market. Key components of the development plan are as follows:

1) Initiate a Phase III head-to-head trial on neratinib + chemotherapy vs. Tykerb + chemotherapy in 3rd line HER2+ breast cancer patients.

2) Initiate a Phase III trial of neratinib + Torisel in salvage (fourth line or later) Her2+ breast cancer patients.

3) Conduct a potential Phase III trial in HER2+ patients with brain metastases (dependent on the results from an ongoing Phase II trial).

4) Continued support of co-operative group trials on neratinib in the neoadjuvant setting in HER2+ patients.

5) Further exploration of neratinib's activity in the sub-population of lung cancer patients with HER2 mutations.

6) Investigation of neratinib's activity in a newly identified subset of breast cancer patients that harbor a novel genetic mutation.

While this plan is fairly ambitious, the track record of the Puma team makes us optimistic for timely and cost-efficient execution. Meanwhile, feedback from consultants on neratinib's profile indicates the molecule is up to the challenge. We expect success in the first indication (3rd-line HER2+ breast cancer) to allow neratinib to capture a majority of Tykerb's market. Subsequent trials could substantially broaden the drug's appeal.

Financials And Valuation

Puma Biotech was initially listed on the OTC Bulletin Board in April 2012 (another page from Cougar Biotechnology's playbook). Concurrent with a secondary stock offering, trading was transferred to the NYSE in October. In that offering, Puma raised $138MM, bringing its pro forma cash balance as of June 30 to approximately $170MM. Given a fairly modest burn rate of approximately $50MM, Puma appears well financed for the foreseeable future and has plenty of cash to see it through to the milestones noted below.

Puma Biotechnology - Upcoming Milestones

Milestone	Timing
Report additional data from neratinib + Torisel combination trial at San Antonio Breast Cancer Symposium	Dec 4 – 8
Report initial (safety) data from neratinib's brain met trial at SABCS	Dec 4 – 8
Preclinical data on novel mutation in HER2-negative breast cancer at SABCS	Dec 4 – 8
Initiate Phase II trial of neratinib in HER2-mutated NSCLC	Q4:12
Begin Phase III head to head trial of neratinib + chemo vs. Tykerb + chemo in 2nd/3rd line mBC	Q4:12/Q1:13
Initiate Phase II trial of neratinib in genetically defined mBC subset with novel mutation	Q4:12/Q1:13
Begin Phase III trial of neratinib + Torisel in 4th-line mBC	H1:13
Possible data from neratinib's Phase II brain met trial	2013
Possible data from neratinib's Phase II neoadjuvant trial(s)	2013
File IND for intravenous formulation of neratinib	2013

Source: Cowen and Company

The company has approximately 30M shares outstanding and a market capitalization of approximately $600MM. We base our valuation of Puma Biotechnology on neratinib in refractory HER2+ breast cancer, the opportunity we know most about and have the most confidence in. Assuming success in the head-to-head trial versus Tykerb, we believe neratinib can achieve revenues of $600MM+ in 2020. Our NPV analysis suggests this asset combined with Puma's cash are worth $29.50. Hence we view shares are nearly 50% undervalued relative to the market.

Neratinib NPV Model ($MM)

Financial Year End	12/31/2011
Valuation Date	11/9/2012
Discount Rate	**10.0%**

Puma Biotechnology: NPV Valuation Of Neratinib

Valuation Date: Friday, November 09, 2012

$MM	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026
Neratinib U.S. Sales	**0**	**0**	**0**	**0**	**25**	**140**	**235**	**255**	**275**	**294**	**312**	**328**	**341**	**351**	**70**
Growth (%)						*460%*	*68%*	*9%*	*8%*	*7%*	*6%*	*5%*	*4%*	*3%*	*2%*
Neratinib Ex-U.S. Sales	**0**	**0**	**0**	**0**	**0**	**80**	**250**	**350**	**410**	**472**	**533**	**597**	**656**	**709**	**142**
Growth (%)							*213%*	*40%*	*17%*	*15%*	*13%*	*12%*	*10%*	*8%*	*5%*
Total Revenues	**0**	**0**	**0**	**0**	**25**	**220**	**485**	**605**	**685**	**766**	**845**	**924**	**997**	**1060**	**212**
Growth (%)						*780%*	*120%*	*25%*	*13%*	*12%*	*10%*	*9%*	*8%*	*6%*	*-80%*
COGS	**0**	**0**	**0**	**0**	**1**	**20**	**78**	**103**	**116**	**138**	**152**	**166**	**179**	**191**	**38**
COGS as a % of sales					*2%*	*9%*	*16%*	*17%*	*17%*	*18%*	*18%*	*18%*	*18%*	*18%*	*18%*
R&D	**43**	**41**	**43**	**46**	**48**	**50**	**87**	**79**	**62**	**38**	**42**	**46**	**50**	**53**	**11**
R&D as a % of Revenues					*192%*	*23%*	*18%*	*13%*	*9%*	*5%*	*5%*	*5%*	*5%*	*5%*	*5%*
SG&A	**6**	**7**	**8**	**10**	**60**	**90**	**170**	**182**	**171**	**168**	**186**	**203**	**219**	**233**	**21**
SG&A as a % of Revenues					*240%*	*41%*	*35%*	*30%*	*25%*	*22%*	*22%*	*22%*	*22%*	*22%*	*10%*
Operating Income	**-49**	**-48**	**-51**	**-56**	**-84**	**60**	**150**	**242**	**336**	**421**	**465**	**508**	**548**	**583**	**142**
Tax	**0**	**0**	**0**	**0**	**0**	**0**	**45**	**73**	**101**	**126**	**139**	**152**	**165**	**175**	**43**
Tax rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*
Approx Free Cash Flow	**(49)**	**(48)**	**(51)**	**(56)**	**(84)**	**60**	**105**	**169**	**235**	**295**	**325**	**356**	**384**	**408**	**99**
Years	0.14	1.14	2.14	3.14	4.14	5.14	6.14	7.14	8.14	9.14	10.14	11.14	12.14	13.14	14.14
Discount Factor	0.99	0.90	0.82	0.74	0.67	0.61	0.56	0.51	0.46	0.42	0.38	0.35	0.31	0.29	0.26
NPV of Cash flows	**(49)**	**(43)**	**(41)**	**(41)**	**(56)**	**37**	**59**	**86**	**108**	**123**	**124**	**123**	**121**	**117**	**26**

Terminal Value Calculation

Final year FCF	99
Perpetual Growth Rate	
Terminal Value	**0**
Discount Factor	0.38
Present Value of Terminal Value	**0**
Present Value of Cash Flows	**729**
Enterprise Value	**729**
Add: Net cash	161
Market Value	**890**
Fully Diluted Shares Outstanding	30.2
Value per Fully Diluted Share	**$29.50**

Source: Cowen and Company

Puma Biotechnology Quarterly P&L Model ($MM)

	Q1:12A	Q2:12A	Q3:12E	Q4:12E	2012E	Q1:13E	Q2:13E	Q3:13E	Q4:13E	2013E
Neratinib Revenue	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total Contract/ Licensing/ Royalties	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total Revenues	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**
COGS	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
GMs										
R&D	10.6	13.0	10.0	9.5	43.1	9.5	10.0	10.5	11.0	41.0
SG&A	1.2	1.7	1.6	1.8	6.3	1.9	1.9	2.0	2.1	7.9
Other Expenses (Dep. and Amort.)	0.0	0.1	0.1	0.1	0.3	0.1	0.1	0.1	0.1	0.4
Total Operating Expenses	**11.9**	**14.8**	**11.7**	**11.4**	**49.7**	**11.5**	**12.0**	**12.6**	**13.2**	**49.3**
Operating Income/Loss	(11.9)	(14.8)	(11.7)	(11.4)	(49.7)	(11.5)	(12.0)	(12.6)	(13.2)	(49.3)
Net Interest and Other	0.0	0.0	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.4
Net Pre-Tax	(11.8)	(14.8)	(11.7)	(11.3)	(49.6)	(11.4)	(11.9)	(12.5)	(13.1)	(48.9)
Taxes	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Tax Rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Net Income (Loss)	(11.8)	(14.8)	(11.7)	(11.3)	(49.6)	(11.4)	(11.9)	(12.5)	(13.1)	(48.9)
GAAP EPS	**($0.59)**	**($0.74)**	**($0.58)**	**($0.43)**	**($2.30)**	**($0.40)**	**($0.41)**	**($0.43)**	**($0.45)**	**($1.70)**
Diluted Shares Outstanding	20.0	20.0	20.0	26.1	21.6	28.7	28.8	28.9	29.0	28.8

Source: Cowen and Company

Puma Biotechnology Annual P&L Model ($MM)

	2011A	2012E	2013E	2014E	2015E	2016E	2017E
Neratinib Revenue	0.0	0.0	0.0	0.0	0.0	25.0	220.0
Total Contract/ Licensing/ Royalties	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total Revenues	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**25.0**	**220.0**
COGS	0.0	0.0	0.0	0.0	0.0	3.5	26.4
GMs						*86%*	*88%*
R&D	0.8	43.1	41.0	43.0	45.0	48.0	50.0
SG&A	9.3	6.3	7.9	9.0	10.5	60.0	90.0
Total Operating Expenses	**10.2**	**49.7**	**49.3**	**52.5**	**56.0**	**112.0**	**166.9**
Operating Income/Loss	(10.2)	(49.7)	(49.3)	(52.5)	(56.0)	(87.0)	53.1
Net Interest and Other	(0.1)	0.1	0.4	0.0	0.0	0.0	0.0
Net Pre-Tax	(10.2)	(49.6)	(48.9)	(52.5)	(56.0)	(87.0)	53.1
Taxes	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Tax Rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Net Income (Loss)	(10.2)	(49.6)	(48.9)	(52.5)	(56.0)	(87.0)	53.1
GAAP EPS	**($1.32)**	**($2.30)**	**($1.70)**	**($1.75)**	**($1.65)**	**($2.35)**	**$1.35**
Diluted Shares Outstanding	7.7	21.6	28.8	30.0	34.0	37.0	39.4

Source: Cowen and Company

Treatment Paradigm For HER2+ Breast Cancer

Puma's neratinib is being developed primarily as a potential new treatment option for HER2+ metastatic breast cancer. Before discussing neratinib's specific opportunities, we believe it will be helpful to the reader to describe the treatment landscape that exists in HER2+ breast cancer today.

The American Cancer Society estimates that approximately 227,000 women will develop breast cancer in the U.S. in 2012, and approximately 39,500 patients will die of the disease. Breast cancer classification is based on the underlying oncogene, and depends on whether the tumor is driven by signaling through the estrogen receptor (ER+), the progesterone receptor (PR+), the HER2 receptor (HER2+; roughly 18-25% of patients), or none of these (triple-negative).

The treatment paradigm for breast cancer depends on the stage of the cancer at presentation (Stage I-IV), and on whether the tumor is hormone positive, HER2 positive, or triple negative. For HER2+ disease, a variety of HER2-receptor targeted agents have been developed that have improved the prognosis of the disease. These include Roche's Herceptin, an antibody that targets the HER2 ligand-binding domain; GSK's Tykerb, a small-molecule kinase inhibitor targeting the intracellular kinase domain; and Roche's Perjeta, an antibody targeting the dimerization domain.

In the U.S., the vast majority of breast cancer cases (90-95%) present at as early-stage (Stages I, II, or III). Patients diagnosed with early-stage breast cancer are typically treated with surgery to remove the tumor(s) and possibly some of the lymph nodes. Following surgery, a combination of radiation therapy and/or adjuvant chemotherapy and/or hormonal therapy is used to treat women with early-stage breast cancer. In HER2+ patients, a Herceptin-containing regimen, often with a taxane or other chemotherapy, is a typical adjuvant regimen. Such an adjuvant regimen might normally be continued for one year. Should a patient's disease recur as metastatic disease, there are several further treatment options available, including Roche's Perjeta (FDA approved June 2012) and GSK's Tykerb, with Roche's T-DM1 (now under regulatory review) likely to join the list in 2013.

The Adjuvant Setting: Of the ACS's estimated 227,000 women diagnosed with breast cancer in 2012 in the U.S., a number of literature sources estimate the percentage of HER2+ patients will be between 18% and 25%. The literature also suggests that between 90% and 95% of women are diagnosed with early stage breast cancer (stages I-III). Based on these assumptions, we estimate that approximately 42,000 breast cancer patients are HER2+ and are diagnosed with early stage disease. This is the patient population of HER2+ patients that would be eligible for treatment in the adjuvant setting in the U.S.

Our consultants note that a slightly higher percentage of patients present with metastatic disease in the E.U. and ROW, due to the lack of adequate screening programs ex-U.S., and especially ex-Western Europe. Assuming that approximately 87.5% of patients with HER2-positive breast cancer are diagnosed with early stage disease in the E.U., and approximately 75% of patients in ROW, we estimate that approximately 58,000 and 125,000 breast cancer patients are HER-2 positive and are diagnosed with early stage disease (stages I-III) in the E.U. and ROW, respectively.

Following positive data from four landmark Phase III trials (the NSABP, NCCTG, HERA and BCIRG 006) completed in 2005 and summarized in the table below, Herceptin is the gold standard for adjuvant HER2+ breast cancer. Herceptin has been approved

for use as a single agent or in combination with chemotherapy. Patients who are ER and/or PR-positive also receive treatment with hormonal therapies in addition to Herceptin and chemotherapy.

Herceptin Phase III Trials And Data In Adjuvant Setting

Trial name	Enrollment	Patient population	Arms of the trial	Initiation of trial	Data Announced	sBLA filed	FDA approval
NSABP	3,968	Patients with HER2-positive operable breast cancer	Arm 1: doxorubicin and cyclophosphamide followed by paclitaxel plus Herceptin (AC-TH), Arm 2: doxorubicin and cyclophosphamide followed by paclitaxel (AC-T)	December 2000	May 2005	February 2006	November 2006
NCCTG				December 2000	May 2005		
HERA	5,081	Early-stage HER2-positive breast cancer patients (both lymph node-positive and lymph node-negative patients were eligible for	Arm 1: Herceptin as monotherapy for 1 year, Arm 2: Herceptin as monotherapy for 2 years Arm 3: Observation only	March 2001	May 2005	December 2006	January 2008
BCIRG 006	3,222	HER2-positive early-stage breast cancer	Arm 1: doxorubicin and cyclophosphamide followed by docetaxel every 3 weeks (AC-T), Arm 2: AC-T plus trastuzumab Arm 3: docetaxel and carboplatin plus trastuzumab (TCH)	April 2001	September 2005	June 2007	May 2008

Source: Cowen and Company, Herceptin label

All of the four landmark trials listed above used 1 year of Herceptin treatment. Since that time, Roche has experimented with a longer treatment period (the HERA 2-year treatment trial arm, 8-year follow-up of which was presented at ESMO 2012), while cooperative groups have tried shorter periods (the PHARE and PEREPHONE trials). The net result of these studies has been that shorter treatment than 1 year may lead to inferior disease-free survival (DFS), while on the other hand, 2 years of treatment provides no better disease control than 1 year and leads to higher adverse event rates (e.g., cardiac issues). Therefore, it appears 1 year of Herceptin treatment is likely to remain standard of care in adjuvant treatment of HER2+ breast cancer.

1st-Line Metastatic Setting: HER2+ patients who progress to metastatic disease after adjuvant treatment, or present with metastatic disease, are typically treated with the combination of Herceptin and chemotherapy. However, this is changing following the June 2012 FDA approval of Roche's Perjeta (pertuzumab) for HER2-positive breast cancer. Perjeta showed impressive efficacy in the 1st-line setting when added to Herceptin and chemotherapy in the CLEOPATRA Phase III trial. Perjeta blocks the dimerization domain of HER2 (as opposed to the ligand-binding domain blocked by Herceptin) and thus provides additive efficacy. CLEOPATRA enrolled 808 patients who were randomized to receive Herceptin + docetaxel + pertuzumab or Herceptin + docetaxel + placebo. Roche announced success on the primary endpoint of PFS in July 2011. There was a 49% or 6.1-month improvement in median PFS in patients treated with Herceptin + docetaxel + pertuzumab, compared to patients treated with Herceptin + docetaxel (18.5 months vs. 12.4 months; HR=0.62, p<0.0001). Our consultants expect Perjeta to be widely used in this setting in combination with Herceptin and docetaxel.

2nd-line Metastatic Setting: When patients progress on Herceptin and chemotherapy in 1st-line setting, they typically continue to be treated with a HER2-targeted regimen. Most patients continue to receive Herceptin, but in combination

with a different chemotherapeutic partner. For example, if the Herceptin + Taxol combination is used in the 1st-line setting and a patient progress, oncologists may replace Taxol with a different chemotherapy and continue treatment with Herceptin. Standard of care is likely to change soon in the second line setting as well, however, following the Phase III success of Roche's T-DM1 (trastuzumab emtansine) in second-line (after Herceptin) HER2+ breast cancer. T-DM1 is an antibody-drug conjugate consisting of Herceptin linked to emtansine, a cytotoxic agent. Thus T-DM1 should selectively kill HER2-overexpressing tumor cells. In the EMILIA trial in second-line mBC, 991 HER2+ patients who had progressed on Herceptin and a taxane were randomized to receive either T-DM1 or GSK's Tykerb + Xeloda (the latter regimen being FDA-approved in this setting). The trial succeeded on its co-primary endpoints of PFS and OS. There was a 50% or 3.2-month improvement in median PFS in patients treated with T-DM1, compared to patients treated with Tykerb and Xeloda (9.6 months vs. 6.4 months) in the ITT patient group (HR= 0.65, p< 0.0001). The survival analysis showed a nearly 6-month benefit for T-DM1 on median OS vs. Tykerb + Xeloda (30.9 months vs. 25.1 months; HR = 0.68, p = 0.0006). T-DM1 also showed a better side effect profile compared to the Tykerb and Xeloda combination. T-DM1 has received FDA priority review and has a PDUFA date of February 26, 2013. We expect approval and rapid adoption as the standard of care for second-line metastatic HER2+ breast cancer.

3rd-line (and later) Metastatic Setting: HER2+ patients in the 3rd-line metastatic setting may be treated with GSK's Tykerb in combination with Xeloda, or alternately with additional lines of Herceptin + chemotherapy. Tykerb + Xeloda is actually approved for second line use (after a patient has progressed on prior therapy including Herceptin, a taxane, and an anthracycline). However, Tykerb is more commonly used in the third line setting, after a patient has received two lines of Herceptin-containing therapy. Tykerb works by inhibiting the intracellular kinase domain of the HER2 receptor. FDA approval was supported by a single Phase III trial in 392 refractory HER positive metastatic breast cancer patients. The study showed a time to disease progression benefit for Tykerb plus Xeloda (36.9 weeks) versus Xeloda monotherapy (19.7 weeks, p=0.00016). Our U.S.-based consultants report limited use of Tykerb in their HER2 positive metastatic breast cancer patients. While they note that Tykerb is a viable alternative in patients no longer benefiting from Herceptin, they have tended to continue using Herceptin in the majority of their patients post-progression as they see no reason to switch to Tykerb and note Tykerb's safety profile may on the margin be differentially worse than that of Herceptin. However, off-label use of Herceptin in combination with Xeloda in place of Tykerb plus Xeloda is an option not as readily available to ex-U.S. physicians due to reimbursement constraints. Tykerb does hold theoretical advantages over Herceptin such as oral administration, lower cardiotoxicity, and efficacy in treating CNS metastases. However, consultants note that these advantages are unproven. Consultants assert that oral dosing is not a significant advantage in the treatment setting as compliance with a five pills/day regimen cannot be assured, and every three week Herceptin infusions are hardly inconvenient. As a result, patients have not clamored for Tykerb.

Despite Competition in Breast Cancer, Neratinib Likely To Find A Niche

As the preceding section illustrates, HER2+ breast cancer is a competitive space. Roche's Herceptin plus chemotherapy is the dominant first line treatment for metastatic disease, with the addition of Roche's Perjeta to that regimen likely to rapidly gaining first-line share. GSK's Tykerb plus Xeloda regimen is approved for patients who progress on Herceptin, although is more typically used as a third-line agent following a second Herceptin-containing treatment regimen. Roche's Phase III success with T-DM1 in patients progressing on Herceptin will likely win approval by mid-2013 and slot into the second line position, perhaps also replacing Herceptin in the first line over time.

Puma's neratinib is a HER2-family kinase domain inhibitor that is essentially being developed as a better version of Tykerb. While we do not believe neratinib will ever displace the entrenched anti-HER2 antibodies such as Herceptin in early-line disease, we do think the drug offers substantial improvements over Tykerb that could allow it to take over Tykerb's opportunity ($370MM in 2011 sales), as well as grow the opportunity through higher pricing and penetration. Further market opportunity may come from expansion into opportunities Tykerb has not accessed. Neratinib offers potential superiority to Tykerb in several respects, including:

1) Irreversible binding to the HER-kinase target, vs. Tykerb's reversible binding.

2) Evidence of better preclinical and clinical activity.

3) Potential for lower pill burden, vs. Tykerb's 5- or 6-pill per day dosing.

4) A potentially more tolerable safety profile (in combination with prophylactic anti-diarrheals).

Specifically, we think the most straightforward paths to market that Puma is pursuing are (1) a head-to-head trial against Tykerb in 3rd-line mBC and (2) a combination trial with Pfizer's Torisel (temsirolimus) in 4th-line or greater mBC. Other development paths that provide potential upside include (1) treatment of mBC with brain metastases; (2) use in the neoadjuvant setting; (3) treatment of HER2+ lung cancer; and (4) treatment of a molecularly-defined subset of HER2-negative breast cancer.

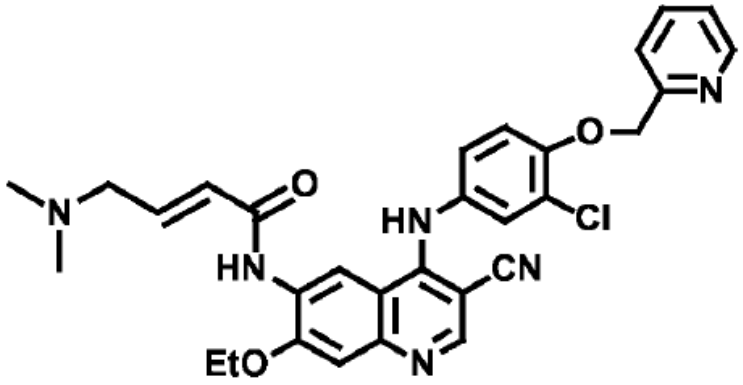
Our breast cancer consultants have commented positively on neratinib. One consultant believes that there is "no question that neratinib is the best anti-HER2 tyrosine kinase inhibitor out there." He feels that neratinib's development had not been optimally handled by its prior stewards, and believes the CEO of Puma is capable of bringing the drug to market efficiently. Another consultant, who is participating in clinical trials with neratinib, echoed the enthusiasm for the drug, although she cautioned that neratinib can cause troublesome diarrhea, which physicians are still learning how best to manage.

Neratinib: An Irreversible Pan-HER Kinase Inhibitor

Neratinib (PB-272; formerly HKI-272) is a tyrosine kinase inhibitor targeting the human EGF receptor family members EGFR (HER1, ErbB1), HER2 (ErbB2) and, according to Pfizer, HER4 (ErbB4). Neratinib was initially developed in the

laboratories of Wyeth in the early 2000's, before passing to Pfizer in the 2009 merger. Over the years, these pharmaceutical companies generated significant preclinical and clinical data on neratinib, going so far as to begin a Phase III trial in HER2+ breast cancer, before Pfizer out-licensed the rights to Puma in October 2011. Puma is now developing neratinib in several treatment settings for HER2+ breast cancer, as well as certain genetically defined forms of lung cancer and non-HER2+ breast cancer.

Structure Of Neratinib



Source: Puma Biotechnology

In vitro, neratinib was shown to selectively inhibit HER-2 and EGFR kinase activity with an IC50 of less than 100nM. GSK's Tykerb (lapatinib) has a similar mechanism of action and selectivity profile. However, unlike Tykerb, neratinib inhibits these targets irreversibly by forming a covalent bond with a cysteine residue in the ATP binding pocket of the receptor. This property may lead to superior *in vivo* efficacy. In preclinical xenograft models, neratinib was shown to inhibit growth of HER2-overexpressing tumors with once-daily oral dosing. Neratinib was also active in EGFR-driven xenografts, albeit less so than in HER2-driven ones. The drug had little to no effect in xenografts of tumors expressing low levels of both receptors.

Kinase Inhibition Selectivity Of Neratinib And Tykerb

Kinase	Neratinib IC_{50} (nM)	Tykerb IC_{50} (nM)
HER1 (EGFR1, ErbB1)	92	11
HER2 (ErbB2)	59	9
HER4 (ERbB4)	NR	367
Akt	>20,000	
CDK4	>50,000	
CDK1	>18,000	>10,000
CDK2	>18,000	>10,000
IKK-2	>9,000	
KDR	800	
c-Met	>35,000	
MK2	>45,000	
PDK1	>5,000	
c-Raf	>18,000	>10,000
Src	1,400	3,500
Tpl-2	>18,000	

Source: Rusnak et al 2001; Rabindran et al 2004; Cowen and Company

Neratinib Has Already Undergone Extensive Clinical Development

While under the stewardship of Wyeth and Pfizer, neratinib was tested in a number of Phase I and II trials, and one 2,800 Phase III trial was initiated. The drug has been given to over 3,000 patients in all, primarily in HER2+ breast cancer. Neratinib has demonstrated compelling efficacy as a single agent, as well as in combination with chemotherapy (including capecitabine, vinorelbine, or paclitaxel), Herceptin (trastuzumab), and Torisel (temsirolimus). The single-agent maximum tolerated dose (MTD) was found to be 320mg QD, with the DLT (at 400mg QD) being grade 3 diarrhea. The most prominent AE has continued to be diarrhea, though studies suggest this tends to be transient, and our consultants indicate it is manageable with the aid of (ideally prophylactic) anti-diarrheals and/or dose modifications.

Neratinib's Clinical Trial Experience In HER2+ Breast Cancer

ClinicalTrials.gov ID	Phase	Patient Population	n	Regimen	Initiated	Status
NCT01423123	Phase I	HER2+ mBC	15	neratinib + paclitaxel + Herceptin	May 2011	presented (ASCO 2012)
NCT01111825	Phase I/II	HER2+ or triple negative mBC	50	neratinib + Torisel	April 2010	presented (SABCS 2011)
NCT00741260	Phase I/II	HER2+ mBC (Phase II portion)	110	neratinib + Xeloda	December 2008	presented (SABCS 2011)
NCT00706030	Phase I/II	HER2+ mBC (Phase II portion)	92	neratinib + vinorelbine	April 2008	presented (SABCS 2010)
NCT00445458	Phase I/II	HER2+ mBC (Phase II portion)	115	neratinib + paclitaxel vs. Herceptin + paclitaxel	September 2007	presented (SABCS 2010)
NCT00398567	Phase I/II	HER2+ mBC	45	neratinib + Herceptin	April 2007	enrollment complete
NCT00300781	Phase II	HER2+ mBC with or without prior Herceptin	137	neratinib	August 2006	published (JCO 2010)
NCT01494662	Phase II	HER2+ mBC and brain mets	45	neratinib	January 2012	enrolling
NCT00777101	Phase II	HER2+ mBC	233	neratinib vs. Tykerb + Xeloda	February 2009	presented (SABCS 2011)
NCT00915018	Phase II	First-line HER2+ mBC	480	neratinib + paclitaxel vs. Herceptin + paclitaxel	August 2009	winding down
NCT01008150	Phase II	neoadjuvant therapy for HER2+ BC	129	taxol + Herceptin; taxol + neratinib; taxol + Herceptin + neratinib	October 2010	enrolling
NCT01042379	Phase II	neoadjuvant therapy for HER2+ BC	20 - 120 per arm	paclitaxel + Herceptin; paclitaxel + neratinib; paclitaxel + Herceptin + neratinib	March 2010	enrolling
NCT00878709	Phase III	HER2+ BC after adjuvant Herceptin	2842	neratinib vs. placebo	July 2009	winding down

Source: Cowen and Company

Puma Licensed Neratinib From Pfizer In Late 2011…

In October 2011, Puma announced the licensing of neratinib from Pfizer. The deal includes the oral form of neratinib, the (preclinical) IV form, a structurally related pan-HER TKI, PB357 (Phase I), and certain related compounds. There was no upfront payment, though Puma is obligated to pay up to $187.5MM in contingent milestones, as well as incremental royalties on net sales ranging from approximately 10% - 20%. However, no milestone payments required until after the first marketing approval of neratinib. Moreover, Puma's obligation to contribute funding to ongoing neratinib trials started under Pfizer was subject to a cap that was reached in October 2012, and Puma has no further obligation to fund these trials.

Puma received worldwide exclusive license to four issued or allowed U.S. patents and nine pending applications, as well as foreign counterparts. These include an issued U.S. patent on the composition of matter of neratinib, expiring 2025, exclusive of possible extensions. In addition, Puma holds issued U.S., E.U. and Japan patents covering a family of compounds that include neratinib, expiring 2019. Puma also has an issued U.S. method of use patent for neratinib in breast cancer (expiring 2025) and two allowed U.S. polymorph patents for neratinib (expiring 2028). The polymorph patents include one each on anhydrous and hydrous forms of neratinib; both forms are present in the drug product.

Pfizer's motivation for out-licensing neratinib seems to have been a need to rationalize R&D programs in the wake of the Wyeth acquisition. Neratinib, though a highly active drug, had been embroiled in a large, unfocused, expensive quagmire of trials, and Pfizer seems to have recognized that it could be brought to market more quickly by a more nimble, focused steward. Puma's team was chosen to license the molecule in large part on the strength of its CEO's track record in developing Zytiga for prostate cancer. Moreover, the deal structure enables Pfizer to retain an economic interest in the drug.

...And Refocused Pfizer's Development Program

Puma is focusing its development efforts for neratinib mainly in HER2+, Herceptin-experienced, locally advanced or metastatic breast cancer, as this could be an efficient potential path to market. At the time of the transfer from Pfizer, Pfizer had been conducting two large trials with neratinib: (1) NEfERTT, a Phase II trial of neratinib plus paclitaxel vs. Herceptin plus paclitaxel in previously untreated HER2+ mBC; and (2) ExteNET, a Phase III trial testing maintenance neratinib monotherapy after adjuvant Herceptin in patients with early-stage breast cancer (this trial had enrolled 2,050 patients by January 2011). Puma has stopped enrollment and is winding down these trials, consistent with the company's refocused development plans. We view the termination of these trials as sensible. Roche's CLEOPATRA trial of pertuzumab plus Herceptin and docetaxel in front-line patients will likely render irrelevant the comparator used in NEfERTT, and certainly makes the path to market in front-line disease more challenging. Meanwhile, the high FDA bar for approval of maintenance therapies, as well as the discontinuation of the Tykerb-only arm for futility in GSK's ALTTO trial and the failure of the TEACH study of Tykerb in adjuvant HER2+ breast cancer, suggest that the expense and time commitment of ExteNET may not have been justified for any firm focused on an expedient, capital- and time-efficient path to market.

Puma Exploring Several Efficient Paths To Market In HER2+ Breast Cancer

Puma's primary development focus for neratinib will be third-line or later HER2+ metastatic breast cancer. The company is pursuing three main avenues in this regard. First, neratinib has shown compelling activity in Phase II trials in combination with paclitaxel, capecitabine, and vinorelbine. Therefore Puma plans to initiate a Phase III trial of neratinib plus Xeloda (capecitabine) head to head vs. Tykerb plus Xeloda (currently the only approved regimen for Herceptin failure breast cancer). In addition, an investigator sponsored Phase II trial has produced impressive initial efficacy with neratinib in combination with Pfizer's Torisel (temsirolimus), an mTOR inhibitor. Further data from this trial will be released at San Antonio Breast Cancer Symposium (SABCS) in December 2012, and Puma plans to continue development in this setting in a Phase III trial. Lastly, Puma has begun a Phase II trial in HER2+ breast cancer patients with brain metastases, a distinct unmet need, and will pursue development in this setting if initial data warrants.

Outside of refractory breast cancer, two Phase II investigator studies are currently evaluating neratinib in the neoadjuvant setting. FDA guidance released in May 2012 indicate that pathological complete response (pCR) may be an acceptable surrogate endpoint for accelerated approval in this setting, so Puma could have a fairly rapid path to market if these studies show promising initial results.

Finally, Puma intends to begin Phase I/II studies of neratinib in two additional genetically defined settings where the drug has shown activity: (1) HER2-mutant lung cancer and (2) breast cancer with a mutation in a non-HER2 gene.

Neratinib's Development Program

Drug	Indication	Pre-clinical	I	II	III	Registration
PB272 (oral) Combination w/ chemotherapy	Metastatic Breast Cancer					
PB272 (oral) Combination w/ Torisel	Metastatic Breast Cancer					
PB272 (oral) Single agent	Metastatic Breast Cancer with Brain Mets					
PB272 (oral) Combination with chemotherapy	Neoadjuvant Breast Cancer					
PB272 (oral) Combination	HER2 Mutated NSCLC					
PB272 (oral)	Mutated Breast Cancer					

Source: Puma Biotechnology

Approach #1: Head To Head Vs. Tykerb

Perhaps the most important potential path to market that Puma is pursuing is to prove neratinib plus chemotherapy is superior to Tykerb plus chemotherapy. In early 2013, Puma intends to begin a randomized Phase III pivotal trial of neratinib vs. Tykerb, both on background Xeloda, for Herceptin-refractory HER2+ breast cancer. Puma is currently negotiating final details with the FDA, but expects the trial to enroll around 400-500 patients and to have a primary endpoint of PFS. Tykerb's trial in that setting led to an FDA approval exactly three years after the trial began, so we believe Puma's trial could support FDA approval in 2016.

We believe this head-to-head trial has a good chance of success, for three main reasons: (1) cross-trial Phase II comparisons suggest that neratinib is more potent as a monotherapy and in chemotherapy combinations than Tykerb; (2) Phase II uncontrolled neratinib + Xeloda data specifically showed a response rate greater than that seen in Tykerb + Xeloda trials; and (3) in addition to these cross-trial comparisons, there has been one trial testing a neratinib regimen vs. a Tykerb regimen directly. This trial was not apples-to-apples, in that it compared neratinib monotherapy to the Tykerb + Xeloda combination, but is encouraging because it showed that neratinib by itself is almost as effective as the Tykerb plus chemo combination.

Neratinib Looks More Effective Than Tykerb In Cross-Trial Monotherapy And Chemo Combination Comparisons…

Though no head-to-head comparisons of neratinib's and Tykerb's efficacy have been conducted, with the usual caveats regarding cross-trial comparisons, it does appear that neratinib is more efficacious than Tykerb in all clinical settings in which both have been tested. This conclusion is based on comparisons of ORR and PFS in Phase II trials enrolling HER2+ breast cancer patients in several settings: (1) Herceptin-naïve, treated with monotherapy neratinib or Tykerb; (2) Herceptin-refractory, treated with monotherapy neratinib or Tykerb); and (3) Herceptin refractory, treated with neratinib or Tykerb in combination with vinorelbine. Note that all these trials were conducted while neratinib was under Pfizer's/Wyeth's control.

Neratinib's and Tykerb's Efficacy In Herceptin-Naive HER2+ mBC

Treatment	n	Response Rate	PFS (weeks)	References
Tykerb (single agent)	138	245	22	Gomez, JCO 2008
Neratinib (single agent)	70	56%	40	Burstein, JCO 2010

Source: Cowen and Company

As a monotherapy, 240mg QD neratinib produced a 56% ORR and 40-week PFS in 70 Herceptin-naïve breast cancer patients, as compared to a 24% ORR and 22 week PFS for a similarly-designed trial with lapatinib monotherapy. Meanwhile, in two trials treating a total of 183 Herceptin-refractory patients, neratinib produced a 24% - 29% ORR and 18 – 22 week PFS, as compared to a 4 - 8% ORR and 8 - 15 week PFS in three similar trials for lapatinib (n=366 patients altogether).

Neratinib's and Tykerb's Efficacy In Herceptin-Experienced HER2+ mBC

Treatment	n	Response Rate	PFS (weeks)	References
Tykerb (single agent)	78-148	4-8%	8-15	Blackwell, Ann. Oncol 2009; Burstein Ann. Oncol 2008; Blackwell, JCO 2010
Neratinib (single agent)	66-117	18-24%	18-22	Burstein, JCO 2010; Martin, SABCS 2011 meeting
Tykerb plus Xeloda	198	24%	27	Tykerb FDA label
Neratinib plus Xeloda	65	64%	40	Saura, SABCS 2011 meeting
Tykerb plus vinorelbine	19	42%	20	Saip, ASCO 2011 meeting
Neratinib plus vinorelbine	56	57%	44	Staroslawska, ASCO 2011 meeting

Source: Puma Biotechnology, Cowen and Company

A trial of neratinib plus vinorelbine in 56 HER2+ metastatic breast cancer patients who had progressed after prior Herceptin produced a 57% ORR and 44-week PFS, as compared to 42% ORR and 20-week PFS in a similar trial using Tykerb plus vinorelbine. Additionally, at SABCS 2010, Pfizer presented Phase II data on neratinib plus paclitaxel in HER2+ breast cancer patients (first to fourth line). In 99 evaluable patients treated with 240 mg QD neratinib and 80 mg/m2 paclitaxel weekly, ORR was 71% and PFS was 56 weeks (results were similar for first- and later-line patient subgroups). Neratinib also looked better than Tykerb in combination with Xeloda (see next section).

Neratinib's and Tykerb's Monotherapy Safety In Herceptin-Experienced Patients

Most Common AEs	Any Grade	Grade 3+
Diarrhea		
Tykerb	46-59%	7-11%
Neratinib	85-97%	28-30%
Nausea		
Tykerb	23-31%	0-2%
Neratinib	35-42%	3-4%
Vomiting		
Tykerb	10-18%	0-1%
Neratinib	24-26%	3-4%
Rash		
Tykerb	29-47%	1-4%
Neratinib	13-19%	0%

Source: Burstein, 2008 and 2010; Blackwell, 2009 and 2010; Martin, 2011; Cowen and Company

Neratinib is reasonably well tolerated as monotherapy. While most patients experienced diarrhea in Phase II trials, only 1-2% of patients had to be discontinued as a result of this AE. Diarrhea tended to be transient, with episodes typically occurring early in treatment (median time to onset around 3 days) and lasting a median 3 to 7 days. Anti-diarrheals and dose modification allowed treatment to continue in nearly all cases. (Recent trials of neratinib are beginning to employ prophylactic anti-diarrheals). In the Burstein, *et al*, trial publication in *JCO* in 2010, it was reported that diarrhea episodes decreased from 70–90% of patients during the first week of treatment to 10-15% of patients by the end of two months. No other Grade 3 AE occurred in more than 5% of patients; the most common other AEs were nausea, vomiting, fatigue, headache, anorexia, and rash.

Comparing neratinib's tolerability profile to that of Tykerb, based on cross-trial comparisons in Herceptin experienced patients, it appears that neratinib may be associated with more diarrhea and other GI symptoms, but less rash. Specifically, diarrhea has been seen in 85%+ of patients in neratinib's monotherapy trials, compared to 45–60% of patients in Tykerb's trials, while rash has been seen in about 15-20% of neratinib patients vs. 30-50% of Tykerb patients. Discontinuations due to AEs were low in these trials and seemingly comparable for neratinib vs. Tykerb (3-8% for neratinib vs. 6-7% for Tykerb).

…And Neratinib + Xeloda Produced Better Efficacy Than Tykerb + Xeloda A Cross Trial Comparison…

Of particular note, data presented at SABCS 2011 from a single-arm Phase II trial of neratinib plus Xeloda in 65 Herceptin-refractory, HER2+ breast cancer patients showed a 64% ORR and PFS of 40.3 weeks, better than any reported trials of Tykerb plus Xeloda, including the pivotal trial (which reported a TTP of 27.1 weeks and ORR of 23.7% in 198 patients). Importantly, the patient populations in the SABCS trial and the Tykerb pivotal trial appear comparable, with essentially all subjects having

received multiple prior lines of therapy including exposure to taxane(s), anthracycline(s), and Herceptin.

Phase II Efficacy of Neratinib Plus Xeloda

Parameter, n (%)	N + C No prior L (n = 61)	N + C Prior L (n = 7)
Clinical benefit rate[a]	44 (72)	5 (71)
ORR[b]	39 (64)	4 (57)
Complete response	7 (11)	1 (14)
Partial response	32 (52)	3 (43)
Stable disease <24 weeks	12 (20)	2 (29)
Stable disease ≥ 24 weeks	5 (8)	1 (14)
Progressive disease	5 (8)	0

N, neratinib; C, capecitabine; L, lapatinib; ORR, objective response rate.
[a]Clinical benefit rate includes objective response and stable disease ≥ 24 weeks.
[b]ORR includes complete and partial responses.

Source: SABCS 2011

Tolerability also looked acceptable in the neratinib + Xeloda Phase II. The most common AEs were diarrhea (89%), hand-foot syndrome (57%), nausea (36%), and vomiting (28%). The frequency of diarrhea appears, typically, somewhat worse than Tykerb + Xeloda, while the other AEs are roughly similar in frequency. Importantly, dose reductions and delays were less frequent with neratinib + Xeloda than with Tykerb + Xeloda (at 34% reductions and 48% delays with neratinib, vs. 53% and 74%, respectively, with Tykerb). Neratinib's apparently greater potency and tolerability at higher dose density than Tykerb appear to give neratinib a good chance of outperforming Tykerb in the Xeloda combination setting.

Phase II Safety And Tolerability Of Neratinib + Tykerb

Table 3. Treatment-related AEs Reported for ≥15% of Patients[a] (Phase 2)

	N + C No prior L (n = 65)		N + C Prior L (n = 7)		Total (N = 72)	
AE, n (%)	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Diarrhea	58 (89)	17 (26)	6 (86)	2 (29)	64 (89)	19 (26)
PPE	36 (55)	10 (15)	5 (71)	0	41 (57)	10 (14)
Nausea	23 (35)	1 (2)	3 (43)	0	26 (36)	1 (1)
Vomiting	16 (25)	3 (5)	4 (57)	0	20 (28)	3 (4)
Decreased appetite	15 (23)	2 (3)	2 (29)	0	17 (24)	2 (3)
Rash	11 (17)	0	2 (29)	0	13 (18)	1 (1)
Dyspepsia	6 (9)	0	0	0	6 (8)	0
Increased ALT	10 (15)	1 (2)	2 (29)	0	12 (17)	1 (1)
Increased AST	9 (14)	2 (3)	2 (29)	0	11 (15)	2 (3)
Fatigue	10 (15)	0	1 (14)	0	11 (15)	0
Neutropenia	10 (15)	1 (2)	1 (14)	0	11 (15)	1 (1)
Stomatitis	11 (17)	0	0	0	11 (15)	0
Constipation	2 (3)	0	2 (29)	0	4 (6)	0
Hypokalemia	1 (2)	0	3 (43)	3 (43)	4 (6)	3 (4)

AE, adverse event; N, neratinib; C, capecitabine; L, lapatinib; PPE, palmar-plantar erythrodysesthesia syndrome; ALT, alanine aminotransferase; AST, aspartate aminotransferase.
[a]All treatment-related grade 3/4 AEs reported in > 2 patients are shown. Additional treatment-related grade 3/4 AEs include asthenia (n = 2), abdominal pain, anemia, decreased hemoglobin, decreased weight, general physical health deterioration, herpes zoster, increased blood alkaline phosphatase, lymphopenia, mucosal inflammation, nail avulsion, prolonged electrocardiogram QT interval, prothrombin time ratio, rash macular, and thrombocytopenia (n = 1 each).

Table 4. Treatment Modifications and Discontinuations Due to AEs (Phase 2)

Event, n (%)	N + C No prior L (n = 65)	N + C Prior L (n = 7)	Total (N = 72)
Dose reductions	22 (34)	3 (43)	25 (35)
Capecitabine	21	3	24
Neratinib	8	1	9
Dose delays	31 (48)	5 (71)	36 (50)
Capecitabine	29	4	33
Neratinib	20	3	23
Treatment discontinuations	7 (11)	1 (14)	8 (11)

AE, adverse event; N, neratinib; C, capecitabine; L, lapatinib.

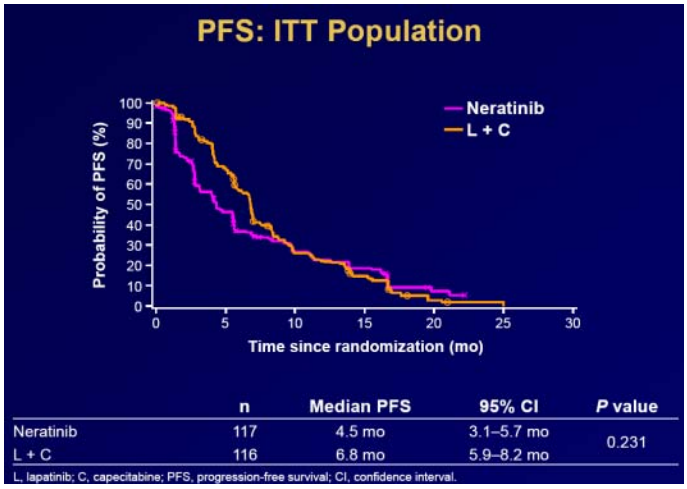
Source: SABCS 2011

… And Neratinib Monotherapy Is Nearly As Effective As Tykerb PLUS Xeloda In A Direct Comparison

A Phase II trial in second/third-line Herceptin-experienced, HER2+ breast cancer compared neratinib monotherapy to Tykerb plus Xeloda (an approved regimen in this setting). The trial was designed to assess non-inferiority of neratinib vs. Tykerb + Xeloda on PFS. The trial randomized 117 patients to the neratinib arm and 116 patients to the Tykerb + Xeloda arm. Results were reported at SABCS 2011. The trial failed to demonstrate non-inferiority of neratinib vs. Tykerb + Xeloda; PFS was

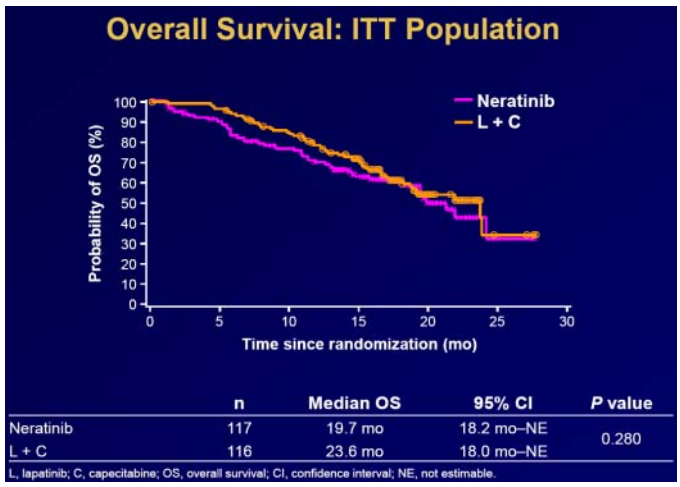
numerically (though not statistically) shorter on the neratinib arm (4.5 months vs. 6.8 months). Moreover, OS was numerically lower on neratinib, at 19.7 months vs. 23.6 mo. ORR response rate was 29% on the neratinib arm vs. 40% on the Tykerb + Xeloda arm.

Efficacy of Neratinib Monotherapy Vs. Tykerb Plus Xeloda



	n	Median PFS	95% CI	*P* value
Neratinib	117	4.5 mo	3.1–5.7 mo	0.231
L + C	116	6.8 mo	5.9–8.2 mo	

L, lapatinib; C, capecitabine; PFS, progression-free survival; CI, confidence interval.



	n	Median OS	95% CI	*P* value
Neratinib	117	19.7 mo	18.2 mo–NE	0.280
L + C	116	23.6 mo	18.0 mo–NE	

L, lapatinib; C, capecitabine; OS, overall survival; CI, confidence interval; NE, not estimable.

Source: SABCS 2011

Neratinib was reasonably well tolerated in this trial, with more diarrhea than the Tykerb + Xeloda arm (85% of patients vs. 68%), but less PPE (palmar-plantar erythrodysesthesia, a.k.a hand-foot syndrome; 5% vs. 65%). The neratinib arm had numerically fewer dose reductions (19% vs. 53% of patients), dose delays (32% vs. 74%), and discontinuations due to AEs (6% vs. 17%). (Note that these safety data should be interpreted bearing in mind that Xeloda may be responsible for many of the safety effects seen in the Tykerb combination arm).

Tolerability of Neratinib Monotherapy Vs. Tykerb Plus Xeloda

Treatment-related Adverse Events Reported for >10% of Patients, All Grades: Safety Population

Adverse event, %	Neratinib (n = 116)	L + C (n = 115)
Diarrhea	85	68
PPE	5	65
Nausea	35	38
Vomiting	24	17
Rash	19	34
Fatigue	16	23
Decreased appetite	23	15
Hyperbilirubinemia	1	23
Stomatitis	8	22
Paronychia	4	20
Increased AST	6	17
Mucosal inflammation	4	16
Asthenia	14	7
Increased ALT	7	13
Neutropenia	5	12
Pruritis	3	11

L, lapatinib; C, capecitabine; PPE, palmar-plantar erythrodysesthesia syndrome; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Treatment Modifications, Discontinuations, and Deaths Due to Adverse Events

Modification, %	Neratinib (n = 116)	L + C (n = 115)
Dose reduction	19	53
Dose delay	32	74
Treatment discontinuations[a]	6	17
Diarrhea	2	4
Nausea	0	2
Stomatitis	0	2
PPE	0	4
Dizziness	0	2
Metastasis to central nervous system	0	2
Respiratory failure	2	1
Deaths	0	0

L, lapatinib; C, capecitabine; PPE, palmar-plantar erythrodysesthesia syndrome.
[a]Adverse events leading to ≥2 discontinuations are listed in the table.

Source: SABCS 2011

In this monotherapy neratinib vs. Tykerb/Xeloda combination trial, neratinib alone came fairly close to replicating the efficacy of the combination, despite lacking a chemotherapeutic backbone. We think these results provide some support for the head-to-head trial of neratinib plus Xeloda vs. Tykerb plus Xeloda in Herceptin-refractory, HER2+ second/third-line breast cancer.

We Forecast Adoption Of Neratinib In Place Of Tykerb

Our consultants expect neratinib to quickly replace Tykerb assuming success in the head-to-head trial. Tykerb is currently approved for two settings: (1) in combination with Xeloda in second line HER2+ breast cancer after Herceptin failure, and (2) in combination with letrozole in first-line HER2+, HR+ breast cancer. However, we believe Tykerb's use in practice is primarily in the third-line setting, after patients have failed two Herceptin-containing regimens. In 2011, Tykerb sold approximately $100MM in the U.S. (£64MM) and $370MM globally (£231MM). Our model suggests that approximately 53% of an estimated 8.6K U.S. third-line or later HER2+ breast cancer patients are receiving Tykerb today.

To arrive at our estimate of 8.6K third-line or greater HER2+ U.S. mBC patients, we make the following assumptions, based on government data sources, scientific literature, and consultant checks: (1) There are approximately 230K new breast cancer cases in the U.S. annually, about 20% of whom are HER2+ (230K x 20% = 46K incident HER2+ breast cancer patients), (2) Of these, 92.5% present in Stage I-III and get adjuvant treatment, of which 20% eventually progress to metastatic disease. Additionally, 4% of patients present with metastatic disease initially and go straight to that treatment setting, (3) Of the approximately 10K patients thus initiating first-line treatment for metastatic disease, we model 95% progressing to second-line treatment, and 95% of those progressing to third-line treatment, yielding about 8.6K annual third-line metastatic, HER2+ breast cancer patients annually as candidates for neratinib treatment.

Tykerb has a current U.S. WAC price of about $4K per month. TTP was about 6 months in Tykerb's pivotal trial, so we believe this translates into around $24K in gross mean revenue per patient. We believe Tykerb is underpriced, particularly given the price point of Roche's Perjeta, approved for earlier line use in 2012, which costs about $6K per patient per month. Therefore, we think neratinib could command a price premium to Tykerb, especially if armed with superiority data.

Neratinib Sales Could Reach $600MM+ By 2020

Assuming neratinib launches in 2016, captures most of the 8.5K third-line patients, and is priced at a 25% premium to Tykerb, we estimate U.S. sales of $25MM in 2016 rising to $275MM by 2020, based solely on replacing Tykerb in this setting. In the U.S., some physicians use a Herceptin + Xeloda combination instead of Tykerb, based on cooperative group data suggesting comparable efficacy of these regimens. Patients treated with Herceptin + Xeloda would not typically go on to receive Tykerb + Xeloda, as doctors generally do not repeat chemotherapeutic backbones in subsequent lines of therapy. Superiority data for neratinib vs. Tykerb could allow neratinib to capture this group of patients as well, suggesting a potential source of upside to our U.S. estimates. We believe the ex-U.S. opportunity could also be substantial, based on the fact that Tykerb is currently getting over 70% of its sales from ex-U.S. geographies (possibly a consequence of less physician freedom ex-U.S. to use off-label Herceptin + Xeloda in place of Tykerb + Xeloda). However, to be conservative, we estimate that neratinib's peak ex-U.S. sales might be only 1.5x its U.S sales. Our assumptions suggest global peak sales of approximately $1B in 2025, the year of neratinib's composition patent expiration.

Tykerb's last Orange Book listed U.S. patent (#7,157,466) expires in 2021, and there are four other Orange Book listed patents expiring 2017-2020. Nevertheless,

assuming neratinib produces superior efficacy data, we do not expect generic Tykerb to meaningfully impact U.S. sales.

Neratinib Revenue Model In Third-Line mBC

U.S. BREAST CANCER	2015E	2016E	2017E	2018E	2019E	2020E
ADJUVANT HER2+ BREAST CANCER						
# of newly-diagnosed breast cancer patients	235,161	237,230	239,318	241,424	243,548	245,691
Population growth	*0.88%*	*0.88%*	*0.88%*	*0.88%*	*0.88%*	*0.88%*
% of patients with HER2+ breast cancer	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*
# of patients with HER2+ breast cancer	47,032	47,446	47,864	48,285	48,710	49,138
% diagnosed with early stage disease (Stage I-III)	*93%*	*93%*	*93%*	*93%*	*93%*	*93%*
# diagnosed with early stage disease (Stage I-III)	43,505	43,888	44,274	44,663	45,056	45,453
% of patients treated in the adjuvant setting	*98%*	*98%*	*98%*	*98%*	*98%*	*98%*
# of patients treated in the adjuvant setting	**42,635**	**43,010**	**43,388**	**43,770**	**44,155**	**44,544**
1st LINE METASTATIC HER2+ BREAST CANCER						
% of Stage I-III patients that recur (metastatic)	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*
# of Stage I-III patients that recur (metastatic)	8,527	8,602	8,678	8,754	8,831	8,909
# of patients that present as Stage IV, HER2+	1,881	1,898	1,915	1,931	1,948	1,966
# of total Stage IV, HER2+ 1st line patients	10,408	10,500	10,592	10,685	10,779	10,874
% of patients treated in 1st-line setting	*98%*	*98%*	*98%*	*98%*	*98%*	*98%*
# of patients treated in the 1st line setting	**10,200**	**10,290**	**10,380**	**10,472**	**10,564**	**10,657**
2nd LINE METASTATIC HER2+ BREAST CANCER						
% of patients that progress to 2nd-line	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*
# of patients that progress to 2nd-line	9,690	9,775	9,861	9,948	10,036	10,124
% of patients treated in 2nd-line setting	*98%*	*98%*	*98%*	*98%*	*98%*	*98%*
# of patients treated in 2nd-line setting	**9,496**	**9,580**	**9,664**	**9,749**	**9,835**	**9,921**
3rd LINE METASTATIC HER2+ BREAST CANCER						
% of patients that progress to 3rd-line	*95%*	*95%*	*95%*	*95%*	*95%*	*95%*
# of patients that progress to 3rd-line	9,021	9,101	9,181	9,262	9,343	9,425
% of patients treated in the 3rd-line setting	*96%*	*96%*	*96%*	*96%*	*96%*	*96%*
# of patients treated in 3rd-line (or greater) setting	**8,661**	**8,737**	**8,814**	**8,891**	**8,969**	**9,048**
% Tykerb penetration	*65%*	*50%*	*27%*	*5%*	*4%*	*4%*
# patients treated (000)	5,629.4	4,410.7	2,379.0	474.6	399.8	356.7
Price per month of treatment ($)	$4,959	$5,257	$5,572	$5,907	$6,261	$6,637
Average months of treatment per patient	*6*	*6*	*6*	*6*	*6*	*6*
Revenue Per Patient Treated ($)	$29,756	$31,542	$33,434	$35,440	$37,567	$39,821
Tykerb Sales ($MM)	**$168**	**$139**	**$80**	**$17**	**$15**	**$14**
USD/GBP exchange rate	*0.60*	*0.60*	*0.60*	*0.60*	*0.60*	*0.60*
Tykerb Sales (GBP MM)	***£101***	***£83***	***£48***	***£10***	***£9***	***£9***
% Neratinib penetration		*15%*	*38%*	*60%*	*61%*	*61%*
# patients treated (000)		1,268.2	3,349.9	5,304.7	5,430.3	5,524.8
Price per month of treatment ($)		$6,571	$6,965	$7,383	$7,826	$8,296
Average months of treatment per patient		*3*	*6*	*6*	*6*	*6*
Revenue Per Patient Treated ($)		$19,714	$41,793	$44,300	$46,958	$49,776
Neratinib U.S. 3rd Line+ Her2+ Breast Cancer Sales ($MM)	**$0**	**$25**	**$140**	**$235**	**$255**	**$275**
Neratinib Ex-U.S. 3rd Line+ Her2+ Breast Cancer Sales ($MM)	**$0**	**$0**	**$80**	**$250**	**$350**	**$410**
Neratinib WW 3rd Line+ Her2+ Breast Cancer Sales ($MM)	**$0**	**$25**	**$220**	**$485**	**$605**	**$685**

Source: Cowen and Company

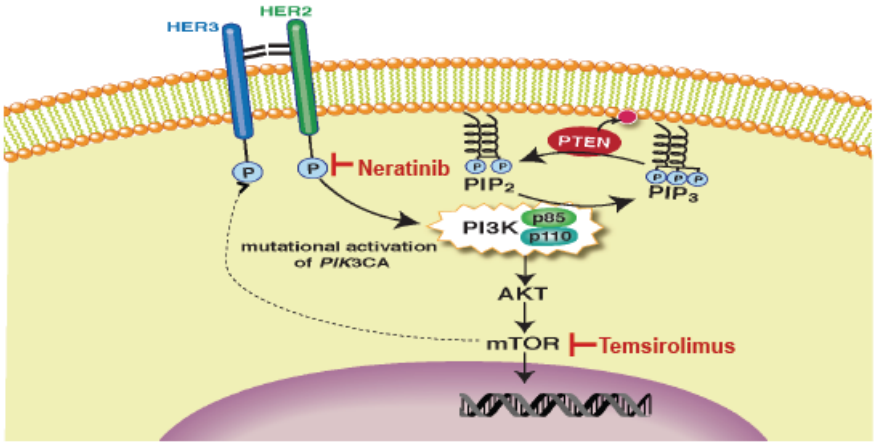
Approach #2: Neratinib + Torisel

Based on promising Phase II data, Puma intends to begin a pivotal Phase III trial of neratinib combined with Pfizer's mTOR inhibitor, Torisel (temsirolimus), in salvage HER2+ breast cancer. Preliminary discussions with the FDA have suggested that accelerated approval may be possible in this setting, supported by a surrogate endpoint of PFS or perhaps even ORR in a randomized Phase III trial. Management has suggested that a >20% ORR and DOR of at least 6 months in Phase III would likely be an improvement over the standard of care. The trial will likely enroll 400-500 patients and is planned to begin in H1:13. Based on compelling Phase II data, we think this approach has a good chance of success.

Combination Is Supported By Solid Scientific Rationale…

In 2010, Pfizer initiated a Phase I/II trial of neratinib in combination with Torisel in HER2+ mBC. The rationale for this approach was the hope that dual inhibition of the HER2-PI3K-Akt-mTOR signaling cascade might have synergistic effects, especially in patients with acquired resistance to HER receptor-directed therapy. It is thought that an important mechanism of acquired resistance to HER2-directed therapy is downstream mutational activation of the PI3K-Akt-mTOR signaling cascade activated by HER2. This downstream activation is thought to re-activate the oncogenic signaling pathway, allowing tumors to resume growth despite HER2-directed therapy. Torisel inhibits mTOR but has been found to have little single-agent activity in metastatic breast cancer. The explanation for this is thought to be that inhibition of mTOR relieves feedback inhibition of HER2 signaling, resulting in upregulation of the pathway and defeating Torisel's inhibitory effect. The theory is that simultaneous treatment with neratinib and Torisel would both inhibit mTOR signaling and prevent activation of HER2 after the consequent relief of feedback inhibition on HER2, thus efficiently blocking the oncogenic pathway. These concepts are illustrated in the figure below.

Intracellular Impact Of Neratinib And Torisel

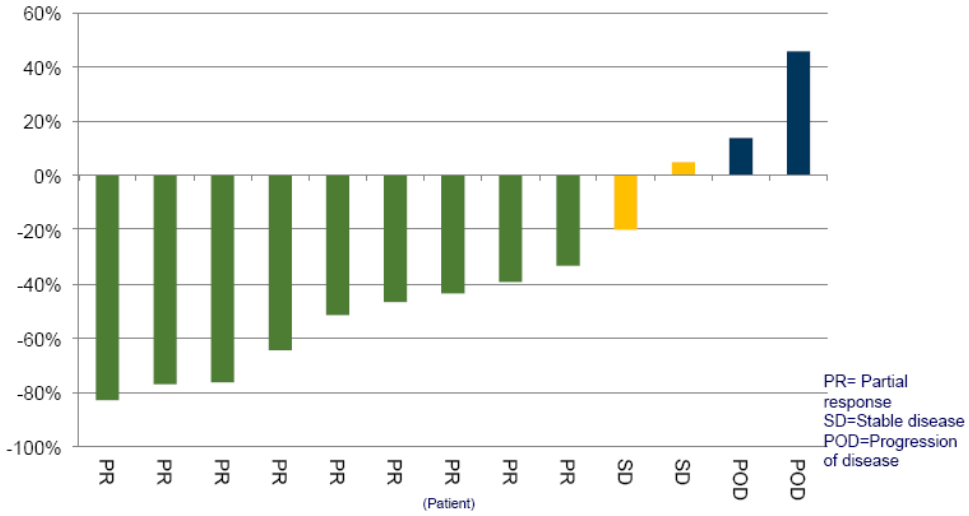


Source: SABCS 2011

…And Strong Early Data

Preliminary data from the Phase II portion of the Pfizer HER2+ breast cancer trial were presented at SABCS in December 2011. The presentation included results for 15 fourth-line and later HER2+ mBC patients treated with 240mg QD neratinib and 8mg Torisel (IV) weekly. Remarkably, 10 of 15 of these heavily pretreated patients showed clinical benefit, including 9 PRs (60% ORR) and 1 SD of greater than 6 months. The patient group showing benefit included individuals previously treated with all of Herceptin, Tykerb, and T-DM1. Five triple-negative patients were also treated in this trial, but no responses were noted in these patients.

Phase II Efficacy Data For Neratinib/Torisel Combination – HER2+ Patients



Source: Puma Biotechnology, SABCS 2011

Grade 3 diarrhea was the dose-limiting toxicity in Phase I part of this trial. In 20 patients treated at the maximum tolerated dose of 240mg neratinib QD plus 8mg Torisel IV weekly, 11 patients (55%) experienced drug-related diarrhea (nine patients at Grade 2 and two patients at Grade 3). Other common treatment-related AEs included hyperglycemia, mucositis, leukopenia, fatigue, and rash. The trial continues to enroll patients, and additional data on n=34 patients is expected at SABCS in December 2012.

Phase II Safety Data For Neratinib/Torisel Combination

Toxicity	Grade 2 N (%)	Grade 3 N (%)	Grade 4 N (%)
Temsirolimus 8 mg + Neratinib 240 mg (N=20)			
Diarrhea	9 (45%)	2 (10%)	-
Hyperglycemia	8 (40%)	1 (5%)	-
Mucositis	8 (40%)	1 (5%)	-
Leukopenia	4 (20%)	1 (5%)	-
Fatigue	2 (10%)	1 (5%)	-
Rash-acneiform	4 (20%)	-	-
Temsirolimus 15 mg + Neratinib 240 mg (N=2)			
Diarrhea	-	2 (25%)*	-
* DLT experienced: MTD is Temsirolimus 8 mg + Neratinib 240 mg			

Source: SABCS 2011

These initial efficacy data are impressive in these advanced patients. Two breast cancer consultants we checked in with considered the >50% response rate "fantastic" in this heavily pretreated setting. One of our consultants participated in this trial, and considers the scientific rationale "beautiful science." She noted that each of the drugs in this combination has drawbacks in terms of toxicity (mucositis for temsirolimus, diarrhea for neratinib), but felt comfortable that with more experience, physicians could learn to manage these effectively.

We view the post-Tykerb, fourth-line or greater setting as approximately the same size opportunity for neratinib as the potential third-line setting discussed above. Of course, the two opportunities are mutually exclusive, not additive, as one would cannibalize the other. On the other hand, one of our consultants commented that he would expect neratinib to rapidly supplant Tykerb through off-label use once it reached the market in any indication, so the opportunity may not be greatly affected by the precise labeled indication. Should neratinib succeed in the Torisel combination approach, we would expect peak sales of $275MM+ in the U.S. and $1B globally.

Approach #3: Breast Cancer Brain Metastases

A third approach that Puma is investigating for neratinib is the potential treatment of brain metastases in HER2+ breast cancer. About 15-55% of HER2+ breast cancer patients develop brain mets during their disease, according to various literature reports. This number has been on the rise since the advent of Herceptin, which is effective at prolonging survival and controlling disease outside the brain; unfortunately, antibodies such as Herceptin and pertuzumab do not cross the blood brain barrier and are ineffective at controlling metastases within the brain. Brain metastases in patients with controlled systemic disease are typically treated with surgical resection and/or whole brain radiation therapy. Due to the efficacy of HER2-directed therapies outside the CNS, up to 50% of HER2+ mBC patients today die of CNS progression, rather than extracranial disease. Clearly the unmet need in this indication is great.

Proof-Of Concept Data In The Works

It is unclear whether Tykerb can cross the intact blood-brain barrier. A 242-patient Phase II Tykerb monotherapy trial showed just a 6% CNS objective response in HER2+ mBC patients with brain mets. However, it should be noted that it is not easy to say whether the low response rate is due to poor penetration into the CNS or some intrinsic difference in sensitivity of brain mets to Tykerb, relative to systemic mets.

Puma is not aware of data characterizing the ability of neratinib to cross the blood brain barrier in humans. However, there is reason to suppose its greater potency might translate into more meaningful clinical efficacy for brain mets, assuming it can get into the CNS in sufficient quantity. Therefore, Puma and the Translational Breast Cancer Research Consortium began a Phase II trial of neratinib monotherapy in HER2+ mBC patients with brain mets in January 2012. The trial is enrolling a planned 45 patients. The primary endpoint is CNS objective response rate, with secondary endpoints including PFS, OS, and safety.

Importantly, Puma's brain met trial included an undisclosed efficacy hurdle that had to be reached within the first 20 patients before the trial would be permitted to proceed to full enrollment. This hurdle is undisclosed, but is presumably above the than the 6% CNS response rate that monotherapy Tykerb has reported. Indeed, Puma has indicated that it reached the efficacy hurdle within the first 5 or 10 patients enrolled. Therefore even one response would imply at least a 10% response rate, and we think a higher response rate is likely.

The SABCS 2012 meeting will feature a data update from this trial, though it is expected to be focused mainly on safety rather than efficacy. The most significant element of the safety data is that it will be the first public presentation of the use of

prophylactic anti-diarrheals with neratinib. Given the 20-30%+ Grade 3 or higher diarrhea routinely observed with neratinib, a meaningful reduction would be noteworthy.

This trial continues to enroll patients, and efficacy data are expected in 2013. Puma's initial discussions with the FDA have suggested that a follow-up trial of neratinib + Xeloda vs. Tykerb + Xeloda in patients with brain mets may be required for registration. However, we think it is not out of the question that very compelling data from the current trial could support a faster path to market. We would note that prior Phase II trials of Tykerb in combination with Xeloda have shown more robust CNS responses on the order of 20% and up. We therefore believe neratinib (as monotherapy or, later, in combination with chemotherapy) will need to exceed this bar to excite physicians.

Brain Mets Represent A Large Unmet Need

Our expert consultants agree that breast cancer with brain metastases is perhaps the greatest unmet need that Puma is targeting, so this could potentially represent the quickest path to market if neratinib proves effective. However we view this trial as relatively high risk. There is little or no public data to support neratinib's ability to enter the brain and its efficacy on CNS mets, so handicapping the trial result is difficult. However, Puma's disclosure that it has observed responses sufficient to expand enrollment in the trial is encouraging.

Given annual incidence of approximately 55,000 HER2+ breast cancer cases in the U.S. and the estimate that approximately 20%-50% of these may go on to develop brain metastases, the incidence of HER2+ patients developing brain mets may be in the range of 11-25K per year in the U.S. alone. This setting could thus represent an opportunity 1.5-3 times as large as the third-line or greater setting described above, suggesting possible U.S. peak sales in the $400-800MM range.

Approach #4: Neoadjuvant Setting

A relatively new approach to treating early stage breast cancer patients is the use of "neoadjuvant" chemotherapy and/or targeted therapy prior to surgery. Neoadjuvant therapy is given with the goal of reducing tumor burden prior to surgical treatment. Neoadjuvant treatment can shrink the tumor enough to reduce the invasiveness of the surgery required. In some cases, neoadjuvant treatment may even eliminate the tumor entirely, such that no tumor is evident at surgery, a so-called pathologic complete response (pCR). Herceptin, Perjeta+Herceptin, and Tykerb+Herceptin have all produced positive pCR data in neoadjuvant trials. However, no drug has won FDA approval for neoadjuvant use in breast cancer, so this approach remains largely limited to clinical trials and academic centers due to reimbursement constraints.

FDA Approval Pathway Still Coming Into Focus

The reason no drug has ever been FDA approved based on a neoadjuvant trial is that it was not until May 2012 that FDA draft guidance first acknowledged pCR as an potentially approvable surrogate endpoint, noting its predictive relationship to DFS and OS in HER2+ and triple-negative breast cancer (though not in hormone receptor-positive breast cancer). This development raises the possibility of a relatively short accelerated approval pathway in the neoadjuvant setting based on increased pCR. However, the FDA guidance also suggests that conditional approvals using pCR as a surrogate endpoint should be based on ongoing trials that are large enough to be

followed for DFS and/or OS to confirm clinical benefit. Thus, it appears that the new guidelines call for trials requiring substantial resources to run.

Neratinib is being tested in two cooperative group trials in the neoadjuvant setting for HER2+ breast cancer. There is a reasonable rationale for this approach, given that in the NeoALTTO neoadjuvant trial, Tykerb added to Herceptin and paclitaxel showed an approximate doubling of pathological complete response (pCR) rate in HER2+ breast cancer vs. Herceptin and paclitaxel alone. Specifically, the Tykerb + Herceptin + paclitaxel combination showed a 51.3% pCR rate, vs. 29.5% for Herceptin + paclitaxel and 24.7% for Tykerb + paclitaxel. It is therefore reasonable to suppose neratinib could do even better.

Two Cooperative Group Trials Ongoing

The first of the two cooperative group trials studying neratinib in the neoadjuvant setting is the NSABP FB-8 trial. This is a Phase II, three-arm trial that is comparing Herceptin vs. neratinib vs. Herceptin + neratinib, all on a paclitaxel chemotherapeutic background. The trial is enrolling 129 total patients, with a primary endpoint of pCR rate. Puma expects enrollment to be complete around YE:12 and initial data to be presented in 2013.

With regard to the triple combination arm in the NSABP FP-7 trial, it is notable that at ASCO 2012, a Phase I dose escalation study in post-Herceptin breast cancer (NSABP FP-8) showed that a neratinib, paclitaxel, and Herceptin combination regimen was tolerable, and that 5 of 15 patients showed a RECIST response. Importantly, neratinib appeared tolerable in this combination at nearly the full monotherapy dose of 240 mg QD, in contrast to the significant dose reductions required when Tykerb is combined with Herceptin (as in NeoALTTO). This increased dose intensity for neratinib, in addition to its intrinsically greater potency, may support even better results than were observed in NeoALTTO.

The second cooperative group study of neratinib in neoadjuvant breast cancer is the Investigation of Serial Studies to Predict Your Therapeutic Response With Imaging And Molecular Analysis 2 (I-SPY2) trial. An NIH-led study with university backing from the University of California at San Francisco (UCSF), this study is designed to advance the concept of “personalized medicine” by testing which drugs are most effective against different breast cancer types. Furthermore, this study is designed to learn more about early indicators of response (via tumor analysis prior to surgery with MRI and blood/tissue samples) and their predictive value for treatment success. Patients are being randomized to receive either neratinib or Herceptin, each on background paclitaxel, prior to tumor resection. Puma expects a third regimen of neratinib + Herceptin + paclitaxel to be added during 2012. The trial uses an adaptive design that may enroll anywhere from 20 to 120 patients per arm. The primary endpoint is pCR rate when experimental neoadjuvant therapy is added to standard neoadjuvant chemotherapy for each established biomarker signature. The study is currently enrolling patients and is expected to read out in 2014.

Puma could, in principle, seek to be the first to pioneer a neoadjuvant approval under the new FDA draft guidance. However, we think this development path is less capital-efficient and bears greater regulatory risk relative to others open to the company. Though Puma could perhaps also win an eventual approval for an adjuvant indication based on a trial begun to support the neoadjuvant indication, we are skeptical that a neratinib-based regimen will ever displace Herceptin-based regimens in the adjuvant setting. That said, as the two trials are being run by

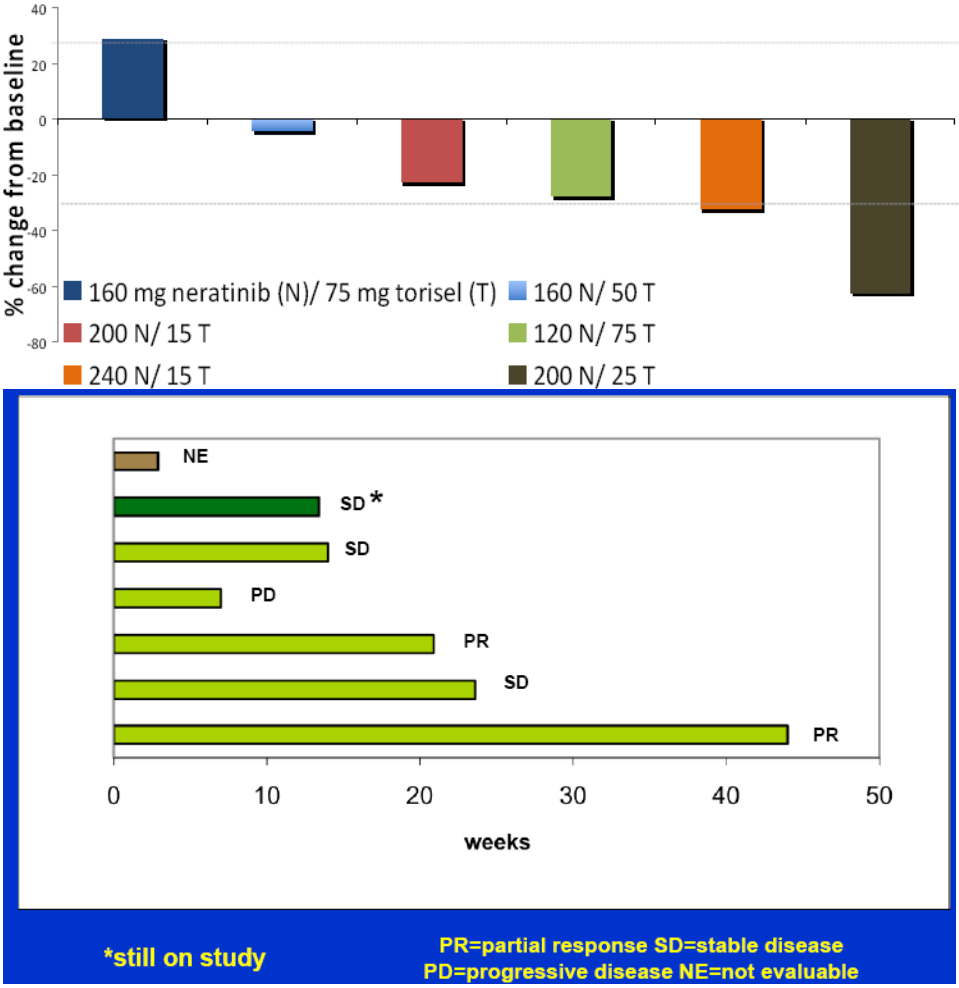
cooperative groups, Puma's future funding commitment is less than $2MM altogether. The company intends to wait for data from both of these trials and then evaluate option in consultation with the FDA, which seems reasonable enough to us. Clearly, though, other paths to market are potentially quicker and are appropriately receiving higher prioritization at the company.

Other Potential Neratinib Indications Being Explored

Puma is planning initial trials in two other molecularly defined cancer indications, one in NSCLC and one in breast cancer.

HER2-Mutant NSCLC. Approximately 2-4% of NSCLC patients harbor a mutation in the HER2 gene exon 20, corresponding to the kinase domain (this is similar to the percentage of patients with mutated ALK kinase, the target of Pfizer's Xalkori). Literature reports suggest that patients with the HER2 mutation are resistant to paclitaxel chemotherapy and EGFR inhibitors. Neratinib showed early promise in a Phase I combination trial with Torisel that Pfizer had previously conducted, which enrolled a variety of solid tumors. This trial included seven patients with HER2-mutated NSCLC. Results from these patients were presented at ASCO 2011 and International Association for the Study of Lung Cancer 2012. Of the six evaluable patients, two (33%) had a partial response and three had SD (lasting several months), with tumor shrinkage of 5-28%. These data imply an impressive 83% clinical benefit rate. Moreover, responses were durable, lasting 8-40+ weeks (one might normally expect a three week PFS in third-line and greater NSCLC patients such as these). Furthermore, a European group has tried Tykerb in these patients (n=5) and seen some responses, but of short duration (1-2 months). Importantly, as shown in the figure below, the responses appear to deepen at the higher doses of neratinib and Torisel, suggesting that the Phase I data may underestimate the benefit of an optimally-dosed regimen.

Phase I Efficacy Data For Neratinib/Torisel Combination in NSCLC



Source: Puma Biotechnology

Puma plans to begin a Phase II randomized trial in HER2-mutated NSCLC in Q4:12. The trial will include two arms, consisting of neratinib with or without Torisel, in order to assess the contribution of Torisel. The trial will initially enroll 12 patients per arm, and each arm may be expanded to 36 if initial efficacy is encouraging. Puma expects to report initial data in 2013. If the responses are as profound as the Phase I data suggest, we believe this trial could support accelerated approval.

Genetically Defined HER2-Negative Breast Cancer. The Cancer Genome Atlas (*Nature*, September 2012) identified a novel mutation found in about 2% of all breast cancer cases. Puma is aware of third party preclinical results that suggest neratinib is active in cells bearing this mutation, and to a greater degree than either Tykerb or Herceptin. The exact nature of this mutation is presently undisclosed, but Puma expects the preclinical data to be presented at SABCS 2012 in December. Puma plans to begin a pilot trial in about ten HER2-negative breast cancer patients carrying this mutation in Q1:13. While this approach also appears promising, we await more data on the causative role of this new mutation in breast cancer.

Two Earlier-Stage Candidates In Puma's Stable

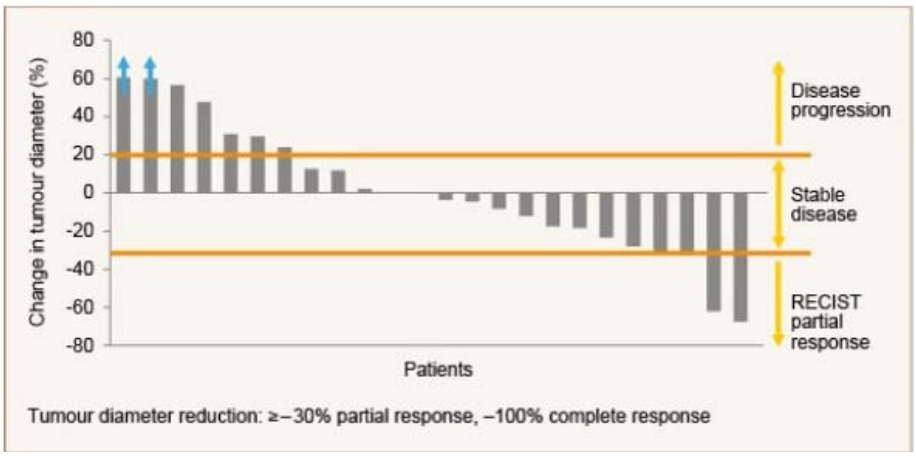
Puma has two additional candidates in-licensed from Pfizer. The first is an IV formulation of neratinib, which in preclinical models has shown higher blood exposure than the oral form. Puma is hopeful that this might translate into superior efficacy in humans, and plans to file an IND for IV neratinib in 2013.

The second candidate is PB357, a potential backup compound for neratinib. Like neratinib, PB357 is an oral, pan-HER kinase inhibitor with structural similarities to neratinib. Pfizer previously completed single dose Phase I trials with PB357. Puma is still weighing its options as regards development of this asset.

Afatinib May Be Neratinib's Only Competitor

Boehringer's afatanib is a small-molecule, irreversible inhibitor of the kinase domains of EGFR and HER-2, including resistance mutants of EGFR. A multi-institutional, open-label, single-arm Phase II study of stage IIIB/IV HER-2+ metastatic breast cancer patients was presented at ASCO 2009. Eligible patients were those with progression following trastuzumab treatment or trastuzumab intolerance, and who had not received prior EGFR-targeted therapy. Patients received 50 mg afatanib daily until treatment progression. The primary endpoint was objective response rate. Of the evaluable patients (n=34), four had a partial response (PR) and eight had stable disease through at least four cycles. The main side effects were manageable (including cutaneous adverse events and diarrhea).

Best Responses To Afatanib – 2009 ASCO Phase II Trial (Hickish et al)



Source: Boehringer Ingelheim Pharma GmbH & Co

Currently, afatanib is in a 780-patient Phase III trial (LUX-Breast 1) in combination with Vinorelbine vs. Vinorelbine + Herceptin for second line treatment of HER2+ metastatic breast cancer. Enrollment is ongoing and the estimated primary completion date is 2016.

We believe the LUX-Breast 1 trial design will disadvantage afatinib relative to neratinib, even assuming LUX-Breast 1 is successful. By the time LUX-Breast 1 reads out, standard of care in second-line disease will almost certainly have shifted to T-DM1, rendering the comparator arm in afatinib's trial irrelevant and essentially placing afatinib in competition with Tykerb for third-line patients. Neratinib, meanwhile, would have superiority data vs. Tykerb, assuming success in its head-to-head trial, which would place the drug in a much stronger position to gain share.

Addendum

STOCKS MENTIONED IN IMPORTANT DISCLOSURES

Ticker	Company Name
PBYI	Puma Biotechnology

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