COWEN AND COMPANY

Quick Take

Puma Biotechnology — Outperform (1)

PBYI: $19.38

Quick Take: Encouraging Progress On Multiple Programs Revealed At SABCS

December 10, 2012

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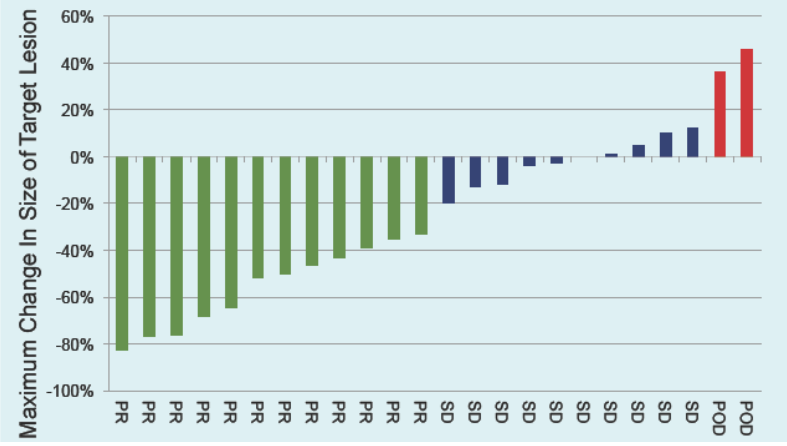
During the San Antonio Breast Cancer Symposium (December 4 – 8), encouraging updates were presented on multiple development programs for Puma's neratinib. We have spoken with management, and view the most important updates as: (1) a continued high response rate for neratinib + Torisel in salvage HER2+ breast cancer, and FDA sign-off on potential accelerated approval pending response data from the upcoming pivotal trial in this setting; and (2) greater clarity on potential utility of neratinib in a genetically defined subset of HER2-negative breast cancer. Neratinib also continues to move forward in several other settings, including HER2+ brain metastases and HER2-mutated NSCLC. We continue to view neratinib as an increasingly de-risked and attractive asset, and PBYI shares as undervalued.

Neratinib Plus Torisel Moving Into Pivotal Trial, Has Potential For Accelerated Approval. Updated data from the ongoing Phase I/II trial of neratinib in combination with Pfizer's Torisel (temsirolimus) in salvage breast cancer were presented at the meeting. Response rates were strong in these salvage patients, with 12 of 27 patients treated at the MTD (44%) showing a PR (vs. 9 of 15 patients in the 2011 SABCS update). Median PFS was 4.2 months. Regarding safety, the DLT in the Phase I was Grade 3 diarrhea; this was experienced by 6 patients (22%) in total. Three patients (11%) discontinued due to toxicity.

Neratinib + Torisel Phase II Efficacy



Source: SABCS 2012 poster

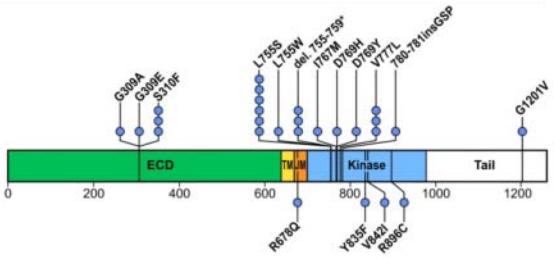
Management indicated that it had recently completed an end of Phase II meeting

with the FDA and gotten clarity on the design of a pivotal Phase III trial in this setting, to begin in H1:13. The trial will consist of three arms: (1) Neratinib + Torisel; (2) Neratinib alone (to verify additive utility of Torisel); and (3) investigator's choice of therapeutic regimen, which could include gemcitabine + Herceptin or Tykerb + Herceptin. There will be a dual primary endpoint of ORR and OS. Importantly, the FDA is receptive to potential accelerated approval based on response rate. Management indicated that the investigator's choice regimens might have response rates in the 10% range, and that doubling ORR vs. investigator's choice would likely support accelerated approval. With Phase II results suggesting ORR of approximately 4x best available therapy, we think accelerated approval of neratinib in this setting is looking quite likely. We believe success in this setting could support sales of $275MM+ in the U.S. and $1B globally.

Proof Of Concept Trial Now Open In Genetically Defined HER2-Negative Breast Cancer. An oral presentation at the meeting revealed details of new findings from the Cancer Genome Project, a whole-genome sequencing effort to identify novel mutations in cancer. The presentation reported novel mutations in HER2-negative breast cancer, which may be drivers of these tumors' proliferation. Specifically, 25 breast cancer patients (of 1,499 sequenced, 1.7%) were found to have one of 16 novel somatic mutations in the HER2 gene, in the absence of significant HER2 gene amplification. The majority of these (over two-thirds) were clustered in the kinase domain. Many of the mutations tested were found to be activating mutations *in vitro* (seven of 13, according to a *Cancer Discovery* publication of these data on Friday). Moreover, all of the activating mutations were sensitive to neratinib inhibition, despite the fact that some were insensitive to Tykerb.

Neratinib's *In Vitro* Activity Against Novel HER2 Mutations

25 Patients with HER2 Somatic Mutations



- Each blue circle represents a patient.
- From 8 publications with a total of 1,499 patients.
- 20% of patients have mutations at amino acids 309 or 310.
- 68% of patients have mutations at amino acids 755-781.

Cell Growth Inhibition by Neratinib and Lapatinib

	IC_{50} (nM)	
	Neratinib	Lapatinib
MCF10A - Her2 WT	<2	400 ± 60
G309A	<2	470 ± 50
V777L	<2	1,040 ± 570
D769H	<2	980 ± 950
V842I	<2	650 ± 210
Del755-759	2.1 ± 0.2	660 ± 90
L755S	15 ± 6	> 10,000
BT474 cells	<2	31 ± 2
MCF7 cells	> 3,000	> 10,000

Source: SABCS 2012 presentation

A Phase II proof of concept trial is now open to examine the clinical benefit of neratinib in metastatic breast cancer patients carrying these mutations. The trial initially opened with four U.S. centers, but management indicates that following the SABCS presentation, 12 more U.S. sites plan to sign on, along with others in the E.U. Generally, these sites are already aware of patients in their care that carry the mutations of interest, and will enroll from this prevalent pool without regard to line of therapy, so we would expect that proof of concept can be gathered quite rapidly. Management estimates that about 4,000 breast cancer patients (all stages) may carry these HER2 mutations in the U.S. today. We believe this opportunity looks promising, but await further data on (1) which of these mutations are primary drivers of cancers

in metastatic patients, and (2) the clinical effect of neratinib, before estimating the commercial size of this opportunity.

Updates From Management On Brain Met Trial, NSCLC Trial. Specifics on neratinib's HER2+ brain metastasis trial were disclosed in the SABCS abstracts. The trial will enroll two cohorts: (1) 40 patients with new or progressive CNS disease, and (2) 5 patients with CNS disease amenable to surgery. According to the investigator, 27 patients have been enrolled thus far in Cohort 1. The abstract states that there was an efficacy hurdle of at least 1 response in the first 18 patients to enroll further patients, so we deduce that response(s) are being observed in this trial. At least 5 responses in the full 40 patients is the bar to deem the drug worthy of further study, according to the abstract, and the trial is 92% powered to detect a CNS ORR of 20%, assuming a null hypothesis of 6% response (the rate observed with single-agent Tykerb). This trial is also one of the first to use prophylactic loperamide (an anti-diarrheal), given that neratinib causes Grade 3 diarrhea in approximately 30% of patients across trials. The investigator reports this approach appears beneficial, with only 2 of 27 patients (7%) experiencing Grade 3 diarrhea.

Meanwhile, Puma's Phase II trial in HER2-mutated NSCLC (2-4% of NSCLC) should begin enrolling in early Q1:13. In the U.S., the trial protocol is in a final 30-day approval stage with the FDA. Meanwhile, an EU consortium has approached Puma with 120 identified patients on hand, and will also be participating in the trial, which should lead to proof of concept in the minimum of time.

Addendum

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Ticker	Company Name
PBYI	Puma Biotechnology

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(a) Assumptions: Time horizon is 12 months; S&P 500 is flat over forecast period.

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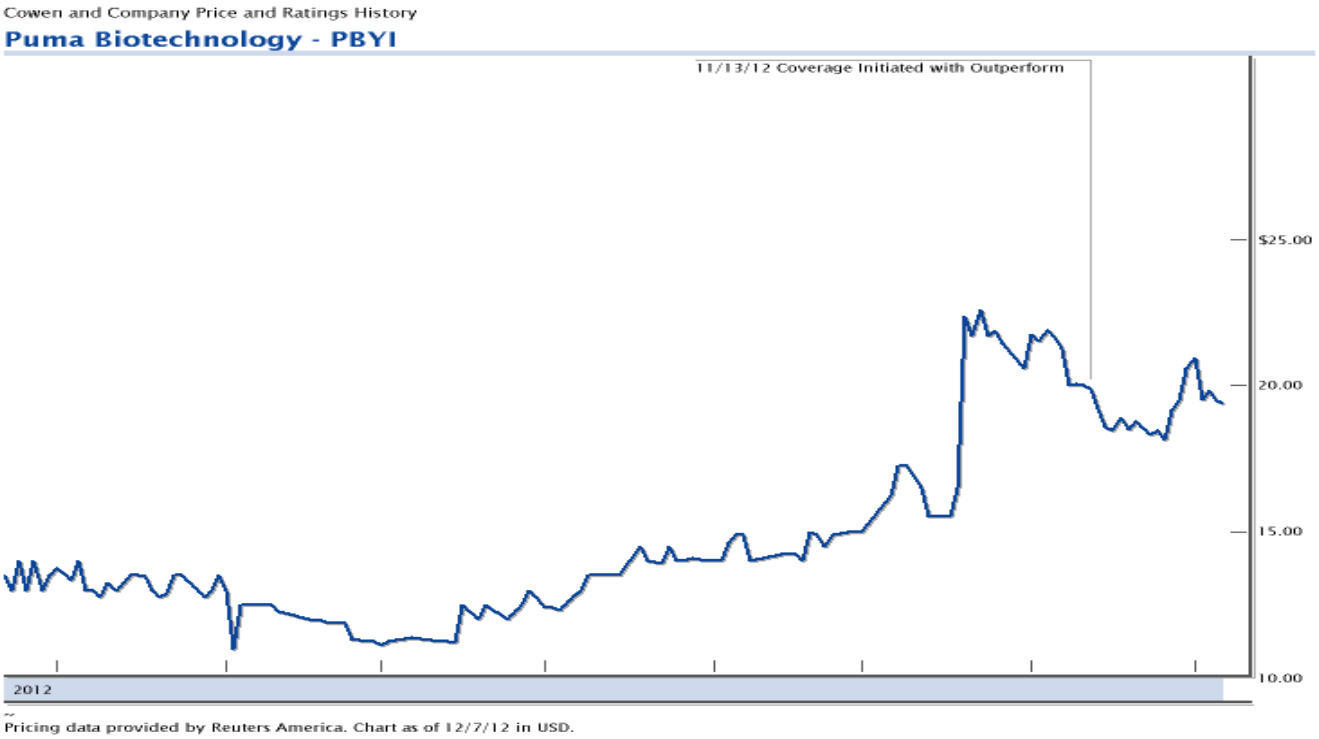
Cowen and Company Price and Ratings History
Puma Biotechnology - PBYI
11/13/12 Coverage Initiated with Outperform
$25.00
20.00
15.00
10.00
2012
Pricing data provided by Reuters America. Chart as of 12/7/12 in USD.