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Ticker	Price	Rating
ARVN	17.26	Buy
AZN LN	12,018.00	Buy
LLY	905.16	Buy
NOVN-SWX	97.61	Neutral
PFE	26.10	Buy

Biotechnology

February 27, 2025

Guggenheim Grand Rounds Recap: Takeaways from Our Expert Call on SERDs, ER+ Breast Cancer

Key Message: We hosted an investor call with a breast cancer expert as part of our weekly Guggenheim Grand Rounds series, focusing on estrogen receptor (ER)-positive BC. Key highlights include: **(1)** treatment for 2L+ HR+/HER2- mBC patients depends on prior response to 1L therapy and expression of biomarkers, including ESR1-mutations, **(2)** our KOL believes that **Menarini's** (private) elacestrant and **LLY's** imlunestrant have relatively similar efficacy as monotherapy in 2L HR+ BC, after factoring in differences in patient baseline characteristics, **(3)** imlunestrant is likely to be approved for 2L patients as monotherapy, but the regulatory path for CDK4/6 combo regimens is uncertain and may depend on survival data, **(4) AZN-LON**'s SERENA-6 study in 1L has potential to validate the use of continued surveillance to detect endocrine resistance without radiologic progression; our KOL hopes to see "doubling" of PFS in SEREENA-6 from an estimated ~4-6 months for continued AI therapy, **(5)** for **ARVN**'s VERITAC-2 study, our KOL sees ≥2mo PFS improvement over fulvestrant as clinically relevant, and sees potential for a win in the all comers setting, **(6)** 1L combination of vepdegestrant with **PFE**'s atirmociclib (CDK4i) could potentially avoid hematological toxicities associated with CDK4/6 inhibitors.

Current Treatment for 2L+ HR+ mBC

Treatment for 2L+ HR+/HER2- mBC patients depends prior on response to 1L therapy and expression of biomarkers, including ESR1-mutations. Our KOL noted that most of the clinical benefit from the novel oral SERD class has been seen in ESR1-mutated patients, and that expanding to the all-comers population of 2L+ HR+/HER2- metastatic BC remains a significant area of unmet need. He outlined several factors to consider when evaluating treatment options in 2L patients, including the durability of response to frontline therapy and/or presence of HER2 expression. For patients who progress within 12 months on CDK4/6 inhibitors (~25%-30% of all ER+ patients), our KOL discontinues endocrine therapy and administers either HER2 ADCs for HER2-low/-ultra low patients or chemotherapy for HER2-zero patients. He expects the proportion of patients falling into this group to increase over time given the increasing use of LLY's abemaciclib and NOVN-SWX's ribociclib in the adjuvant setting. For patients who respond to CDK4/6 inhibitors beyond 12 months (~70%), our KOL evaluates biomarkers via some form of sequencing (e.g. NGS) to evaluate the presence of ESR1-mutations, which are present in ~1/3 of patients and enables the patients to receive Menarini's (private) elacestrant. The remaining "slow" progressors include ~1/3 with PIK3CA mutations, ~5%-10% with AKT/PTEN alterations, and ~20%-25% that are wild-type for both.

LLY's Phase III EMBER-3 Study

Our KOL believes that elacestrant and imlunestrant have relatively similar efficacy as monotherapy in 2L HR+ BC, after factoring in differences in patient baseline characteristics. On the recently presented data from the Ph. III EMBER-3 study of LLY's oral SERD imlunestrant, our KOL noted that the study recruited from global sites and may not be as representative of the US population. For instance, in EMBER-3 35%-40% of patients had not been exposed to a CDK4/6 inhibitor compared to <10%-15% for the US, and in EMBER-3 the majority of patients (65%-70%) had been treated with palbociclib whereas in the US most patients are treated with ribociclib. He noted that the PFS for imlunestrant monotherapy in 2L all comers was exactly the same as the SoC, but showed superiority in ESR1-mutant patients with a HR=0.62 which validates the role of ESR1 as a predictive biomarker for SERD activity. He added that the presence of ESR1 mutations is a known resistance factor for aromatase inhibitors. When comparing with elacestrant, he noted that the Phase III EMERALD study enrolled more heavily pretreated patients with more aggressive biology, but overall believes that the two compounds have similar efficacy.

Imlunestrant is likely to be approved for 2L patients as monotherapy, but was less confident in the combination pending survival data. Our KOL was not surprised by the

positive abemaciclib + imlunestrant combo data in EMBER-3 in all-comers, although he noted that the magnitude of benefit was somewhat unexpected (9.4mo mPFS vs. 5.5mo for imlunestrant alone; HR=0.57) when factoring in that 40% of patients had not yet seen a prior CDK4/6 inhibitor. He expects that imlunestrant will be approved as monotherapy for ESR1-mutant patients with a similar label as elacestrant, although he does not expect any combos with CDK4/6 inhibitors to be approved in the near term given that the OS is not yet mature, while also noting that the control group in the EMBER-3 study was not standard. On safety, our KOL noted higher rates of diarrhea and GI toxicity relative to elacestrant, but believes that the adverse events appear manageable as a tradeoff for ~9-10 months of benefit in the 2L setting.

AZN-LON's Phase III SERENA-6 Study

Positive SERENA-6 study in 1L has potential to validate the use of continued surveillance to detect endocrine resistance without radiologic progression; our KOL hopes to see "doubling" of PFS from current ~4-6 months. AZN-LON recently announced that the Phase III SERENA-6 study evaluating camizestrant + CDK4/6i vs. SoC in 1L HR+ BC with ESR1-mutation reported "highly statistically significant and clinically meaningful improvement" in the primary PFS endpoint. Our KOL noted that the study included ctDNA-guided testing to detect the emergence of endocrine resistance without radiologic progression, and was based on a prior study showing patients who had an ESR1 mutation and switched to fulvestrant had ~6mo improvement in PFS relative to those who stayed on SoC. He noted that longer time on treatment with an endocrine therapy is associated with higher likelihood of acquiring a resistance mutation, and believes that this study can validate the use of continuous surveillance with Guardant (GH; covered by Subbu Nambi) or liquid biopsies to achieve deeper and more durable responses. He noted that ESR1 mutations are acquired over time, and may only have an incidence of ~2-3% after 1L treatment that could increase significantly over time to ~30% or greater. However, he noted that pushback may come from the payer side who would be resistant to paying for several liquid biopsies, and also wants to be confident that the treatment is not associated with sustained bradycardia that will require EKG monitoring. Overall, he sees a doubling of PFS from ~4-6 months as a goal for the study, and noted overall that he would like to see ~6 month improvement over control to justify using oral SERDs in the frontline setting rather than saving them for 2L.

ARVN's Phase III VERITAC-2 Study

For ARVN's VERITAC-2 study, our KOL sees ≥2mo PFS improvement over fulvestrant as clinically meaningful in 2L mBC, and sees potential for a win in the all comers setting as well. Our KOL noted that ARVN's vepdegestrant (ER degrader, partnered w/ PFE) has a differentiated mechanism where activity is less dependent on the presence of ESR1 mutations relative to SERDs. He does expect higher efficacy in ESR1 mutant patients given that alteration indicates the cancer is still dependent on the estrogen pathway for survival and proliferation, but could also see benefit in all comers. Our KOL believes that the VERITAC-2 would have to show ~2 months improvement over fulvestrant to be a "clean" win, and noted that benefit <2 months would require further digging into subgroups. He also noted that the HR will be more useful when comparing between trials given differences in baseline characteristics, adding that the VERITAC-2 study does a better job than EMBER-3 of capturing patients who reflect the real world US population. In order to be best in class, the HR for vepdegestrant would have to be 0.5 or better in ESR1 mutant patients, but our KOL believes that the best way to be differentiated is to have a positive outcome and/or approval in all comers (e.g. ~2 months or greater improvement in PFS).

Frontline combination of vepdegestrant with PFE's atirmociclib (CDK4i) could potentially avoid hematological toxicities associated with CDK4/6 inhibitors. Our KOL noted that ARVN's plans to combine vepdegestrant with PFE's CDK4 inhibitor atirmociclib in 1L is an interesting way to potentially avoid some hematological toxicities (e.g. neutropenia, thrombocytopenia) associated with CDK6 inhibition. However, he is cautious about moving new mechanisms immediately into the 1L setting when they could also be beneficial in 2L or later, and noted that ultimate treatment decision will depend on the clinical data.

Our recent coverage of ARVN and the breast cancer space:

ARVN - BUY - Low Street Expectations & Poor Sentiment Provide Favorable Risk/Reward Heading into VERITAC-2 Phase 3 Data this Quarter

ARVN - BUY - LLY's EMBER-3 Data Weighs on oral SERDs, Though Sets Low Competitive Bar Heading Into VERITAC-2, In Our View

ARVN - BUY - Abemaciclib Combo Data At SABCS Highlights Good Safety, Absence of Drug-Drug Interaction; Efficacy Still Early; Ph. 3 VERITAC-2 Data Next

Highlights From Our Life Science Tools & Liquid Biopsy and Oncology (Heme & Breast/Lung) KOL Panel Discussions at the Guggenheim Healthcare Innovation Conference

ARVN - BUY - SABCS Abstracts Highlight Upcoming Vepdegestrant Combination Data; LLY's EMBER-3 Likely to Set New Efficacy Bar in 2L mBC

ARVN - BUY - 3Q Recap; Vepdegestrant Key Near-Term Value Driver Heading into SABCS, VERITAC-2 Top-line Data; LRRK2 Phase I Advancing; PT to $57 on Model Maintenance

Read-Through from RHHBY Pharma Day to Our Biotech Coverage: RLAY, ARVN, BGNE, INCY, GLUE, AMGN, IGMS

2024 ASCO Field Report – Highlights from Our Physician KOL Panel Discussion on Emerging Landscape in Lung, Breast, GU Cancers, and Melanoma

ARVN - BUY - Ph. Ib Update Highlights Consistent Strong Safety/Efficacy & Vepdegestrant Opp'ty In Combination With CDK4/6 Inhibitors In Breast Cancer

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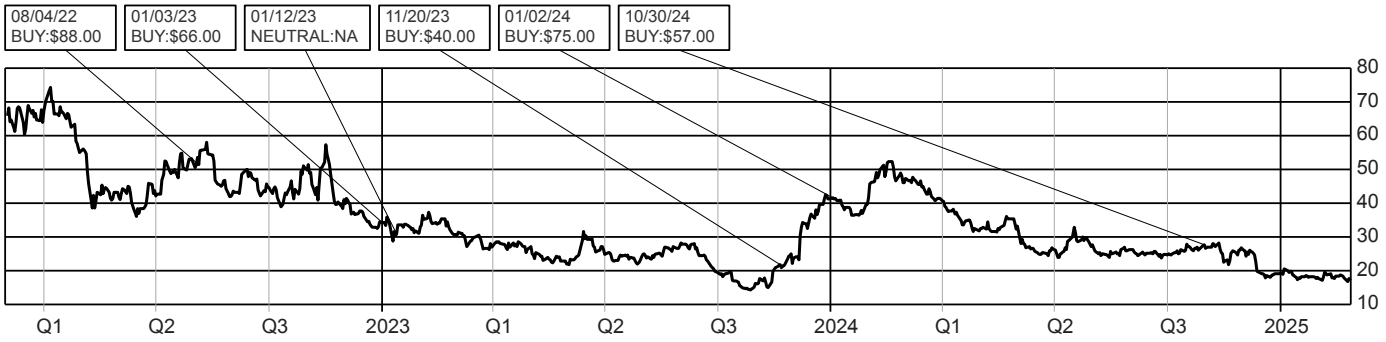

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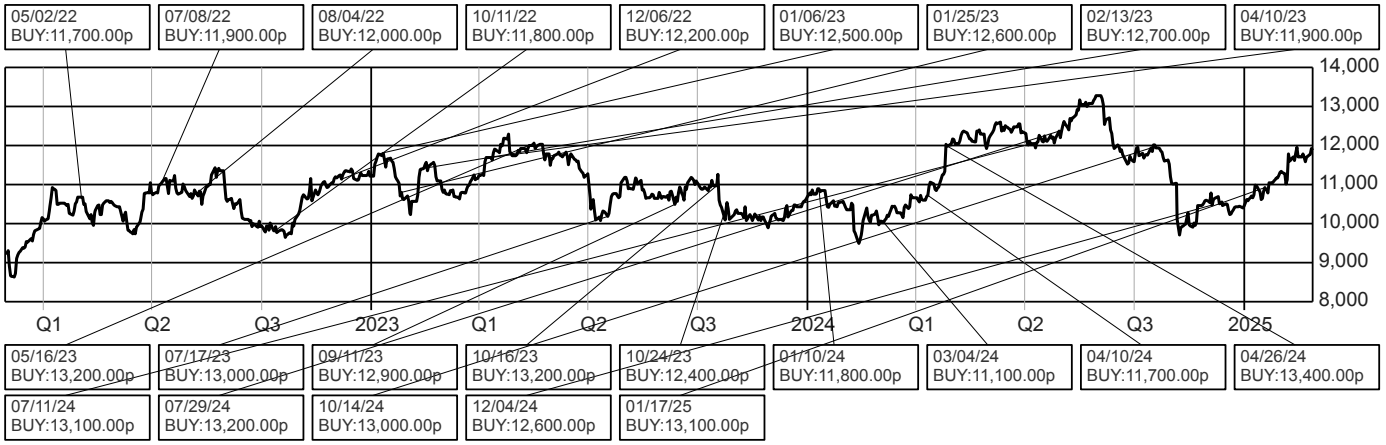

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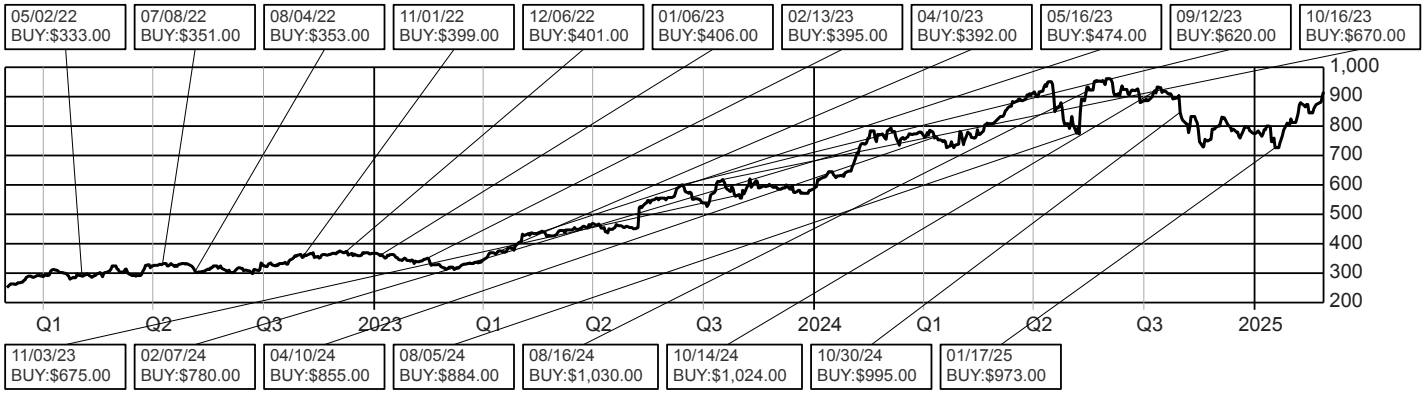

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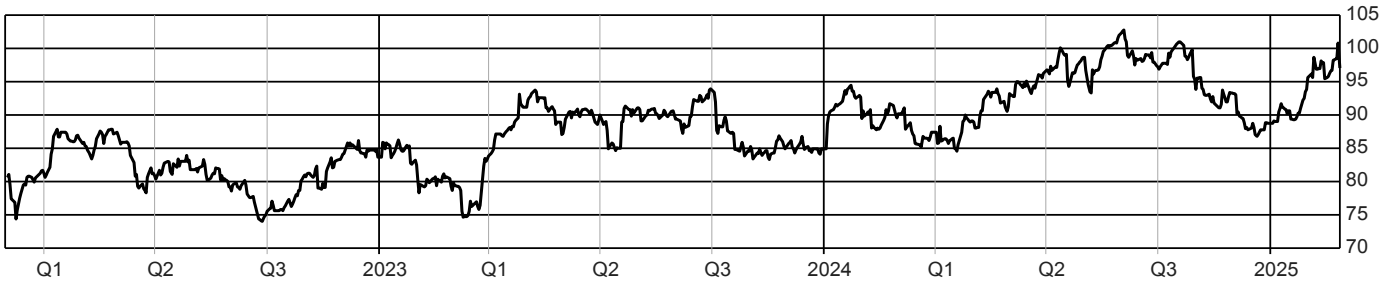

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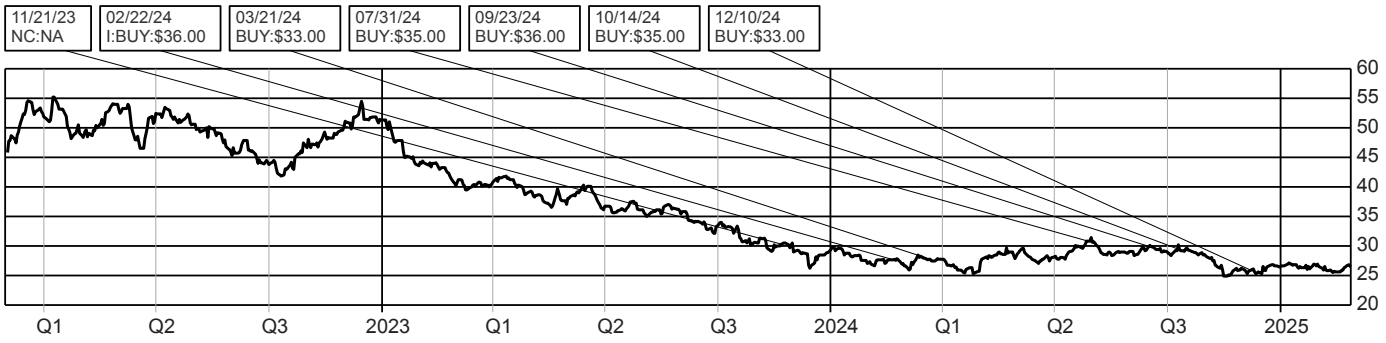

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