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3Q19 Solid Tumor – Greater Role for PARP Inhibitors

TABLE 1: Key Biotech/Pharma Companies in PARP Inhibitor Market – Key Valuation Metrics

Mkt. Cap (US$)		Mkt. Price 11/29/19	Fwd P/E	YTD	Viola Advisory Rating	Viola Advisory PT	Upside Potential 52-Week High	Upside Potential PT
217.5B	MRK	87.18	15.4	15.3%	Buy	93.00	-1%	12%
212.1B	PFE	38.52	14.1	-10.9%	Buy	41.00	21%	8%
125.4B	AZN	48.48	23.0	28.3%	Buy	50.00	2%	3%
113.0B	GSK	45.48	14.8	20.1%	Hold	45.00	1%	-1%
818.4M	CLVS	14.93	-2.7	-23.0%	Hold	13.00	115%	-13%

Source: Yahoo Finance, Ycharts.com, Viola Advisory LLC

Summary: **There is a growing role for PARP inhibitor drugs in solid tumors. First approved for ovarian cancer in 2014, PARP inhibitors have steadily gained ground from third-line recurrent setting to second-line maintenance treatment. This is due to impressive efficacy in germline BRCA mutations for both ovarian and breast cancer as well as for producing manageable side effects. The use of PARP inhibitors is now being investigated for other solid tumors that exhibit BRCA-like characteristics or homologous recombination-deficiency (HRD). Potential applications in breast cancer or in prostate cancer could expand their reach and the size of the market. We continue to see Lynparza (AstraZeneca/Merck) as the current market share gainer and potentially Talzenna (Pfizer) as a future blockbuster candidate.**

I. Greater Role for PARP Inhibitors in Solid Tumors

A. PARP proteins and BRCA1/BRCA2 proteins in repairing DNA damage

PARP (poly ADP ribose polymerase) inhibitors were designed to benefit women who have inherited a mutation in one of their BRCA genes and who have subsequently developed breast or ovarian cancer. PARP proteins help our body's cells repair single-strand breaks in the cell's DNA. DNA damage is often caused by oxygen free radicals – high energy oxygen atoms created by our cells as they produce energy. The creation of oxygen free radicals is unavoidable, and single-strand DNA breaks is a common occurrence in each of the billions of cells in our body.

Single-strand breaks that are not repaired can later cause a complete break in the chromosome (i.e., a double-strand DNA break). Double-strand breaks are very toxic to the body's cells and need to be repaired quickly.

There are two BRCA proteins in our cells: BRCA1 and BRCA2. Both are involved in repairing double-strand breaks in our DNA through a process called homologous recombination (HR). HR is very efficient and very accurate. It is the cells' preferred method of repairing double-strand DNA breaks.

Our cells have two genes – *BRCA1* and *BRCA2* – that have the genetic code for making BRCA1 and BRCA2 proteins. These two genes were discovered by scientists in the mid-1990s when they were researching why both breast and ovarian cancers sometimes run in families. They discovered that if a woman inherits a fault in one of her copies of either *BRCA1* or *BRCA2* gene, then her risk of developing breast and/or ovarian cancer is much higher than for other women. She is also likely to develop cancer at a relatively young age. Moreover, people who inherit BRCA1 and BRCA2 mutations are slightly more at risk of pancreatic cancer, stomach cancer, laryngeal cancer and prostate cancer (men only).

Women who have inherited a BRCA1 mutation (i.e., a germline BRCA1 mutation) have about a 40% risk of developing ovarian cancer and a 57% - 65% risk of developing breast cancer by age 70. Women with a germline BRCA2 mutation have an 11% - 18% risk of ovarian cancer and a 45% - 49% risk of breast cancer. What puzzles scientists is why mutations in *BRCA* genes cause breast and ovarian cancers but not any other type of cancer. Despite numerous investigations, there is still no agreement as to why this is the case.

B. PARP Inhibitors in Breast and Ovarian cancer

PARP inhibitors are highly effective in killing cancer cells, especially in women with germline BRCA1 or BRCA2 mutations because the PARP inhibitor prevents the tumor cells from repairing single-strand breaks. Scientists use the term "synthetic lethality" to refer to the use of PARP inhibitors in people with cancers linked to faulty BRCA genes. This refers to the combination (a synthesis) of the tumor cell's inability to perform HR plus the exposure to the PARP inhibitor, which causes the cancer cell to die.

The occurrence of cancer with germline BRCA defects account for about 5% - 10% of breast cancers and 10% - 15% of ovarian cancers. However, clinical trials have also shown PARP inhibitors to be effective in ovarian cancers that arise as a result of sporadic BRCA mutations – mutations that have occurred during the tumor cell's lifetime.

Table 2 shows the FDA approved indications for all four PARP inhibitors – niraparib (Zejula), olaparib (Lynparza), rucaparib (Rubraca) and talazoparib (Talzenna). As of 2018, olaparib (Lynparza) is the only PARP inhibitor that is licensed for use in both ovarian and breast cancer. Lynparza is used in the second-line maintenance treatment of BRCA-mutated advanced ovarian cancer and in second-line maintenance setting for recurring ovarian cancer. It is also used to treat women with advanced ovarian cancer who have inherited *BRCA* gene mutations. Moreover, Lynparza is also used in BRCA mutated, HER2 negative metastatic breast cancer in combination with chemotherapy (see Table 2).

TABLE 2: FDA approved Indications for PARP Inhibitors

Generic	Brand	Manufacturer	Approved	Indication	Standard Dosage
Niraparib	Zejula	GlaxoSmithKline	2017	Maintenance treatment of recurrent EO/FT/PP cancer; Advanced EO/FT/PP cancer	300 mg once daily
Olaparib	Lynparza	AstraZeneca/ Merck	2014	Maintenance treatment of BRCA-mutated advanced EO/FT/PP cancer; maintenance treatment of recurrent EO/FT/PP cancer; Germline BRCA-mutated advanced ovarian cancer; BRCA-mutated, HER2- MBC treated with chemotherapy	300 mg twice daily

Rucaparib	Rubraca	Clovis Oncology	2016	Maintenance treatment of recurrent EO/FT/PP cancer; BRCA-mutated EO/FT/PP cancer	600 mg twice daily
Talazoparib	Talzenna	Pfizer	2018	Germline BRCA-mutated, HER2-, locally advanced MBC	1 mg once daily

Note: EO = epithelial ovarian; FT = fallopian tube; HER2- = HER2 negative; MBC = metastatic breast cancer; PP = primary peritoneal
Source: Melton, C.L., "Recent Studies Point to a Greater Role for PARP Inhibitors in Solid Tumors", www.targetedonc.com

All four PARP inhibitors in Table 2 have produced relatively similar response rates and side effects in clinical trials. However, researchers have yet to determine which cancers and which patients will benefit most from PARP inhibitors. Currently, there is interest in expanding the use of PARP inhibitors to other settings like:

- Other cancers, such as prostrate cancers, malignant melanomas and pancreatic cancers occurring in men and women with germline BRCA mutations;
- Cancers that don't have defective BRCA proteins but have some other problem that makes them unable to perform HR. These cancers are said to exhibit "BRCA-like," or "BRCAness" or be homologous recombination-deficient (HRD). For example, around 20% of prostate cancers have defects in various DNA repair proteins; in addition, around 50% of high-grade ovarian cancers contain defects in HR,
- For patients whose cancer is sensitive to platinum-based chemotherapy, as this is a sign that the cancer has difficulty in repairing DNA damage and might therefore be sensitive to a PARP inhibitor,
- To increase the effectiveness of chemotherapy and radiotherapy by preventing cancer cells from repairing the DNA damage that these treatments cause, and
- For cancers that lack PTEN (PTEN suppresses the PI3K/AKT/mTOR pathway). This is one of the reasons that PARP inhibitors are being studied in prostate and endometrial cancers – these cancers often lack PTEN.

Most clinical trials are recruiting women with breast or ovarian cancer. However, trials are also evaluating PARP inhibitor's usefulness in prostate, lung, pancreatic, cervical, endometrial, gastric and many other cancer types.

C. Pivotal PARP Inhibitor Clinical Trials

Many new experimental drugs are first tested in the recurrent setting, and when they demonstrate efficacy in that setting, they are then moved up into the front-line setting. That is currently the case in pivotal clinical trials with PARP inhibitors.

At the 2019 European Society for Medical Oncology (ESMO) meeting in Barcelona, AstraZeneca, AbbVie and GlaxoSmithKline all presented clinical trial data of their PARP inhibitor drugs in the first-line ovarian cancer maintenance setting (see Table 3).

TABLE 3: Progression-free survival (months) and risk reduction vs. control: 3 Ovarian cancer trials

Drug	Study	BRCA mutation	HRD	Overall population
Veliparib	VELIA	34.7 months, 56%	31.9 months, 43%	23.5 months, 32%
Zejula	PRIMA	(PFS: n/a), 60%	21.9 months, 57%	13.8 months, 38%
Lynparza	PAOLA-1	37.2 months, 69%	37.2 months, 67%	22.1 months, 41%

Source: ESMO, New England Journal of Medicine

Phase 3 PAOLA-1: Trial data showed that frontline maintenance therapy with the combination of olaparib (Lynparza) and bevacizumab (Avastin) improved PFS to 23.5 months versus bevacizumab and placebo in women with newly diagnosed, advanced ovarian cancer following prior treatment with platinum-based chemotherapy and bevacizumab. The benefit with olaparib was seen across all patient subsets but was more pronounced in patients with BRCA1 and BRCA2 mutations and homologous recombination deficiency (HRD).

Phase 3 PRIMA: Trial data from this study is important since niraparib (Zejula) is currently under priority review by the FDA. Frontline maintenance therapy with niraparib improved median PFS to 13.8 months versus placebo in patients with newly diagnosed, platinum-sensitive disease, irrespective of biomarker status. The risk reduction benefit was more pronounced in patients with BRCA mutations who were 60% less likely to die versus the overall population of 38%.

Phase 3 VELIA: Trial data demonstrated that the frontline combination of veliparib and chemotherapy followed by veliparib maintenance resulted in a PFS benefit versus placebo and chemotherapy in patients with high-grade serous ovarian cancer. Median PFS was 23.5 months in the veliparib/chemotherapy treatment group compared with 17.3 months in the placebo/chemotherapy group. VELIA marks the first randomized trial exploring platinum-based chemotherapy plus a PARP inhibitor. The combination is thought to have a synergistic effect whereby chemotherapy damages circulating tumor DNA and PARP blocks cell repair.

II. Overview of the PARP Inhibitor Market

A. PARP Inhibitor Market: Market Participants, Annual Sales and Y/Y Growth Rates

Table 4 examines the size of the PARP inhibitor market, how quickly the space is growing on a Y/Y basis as well as who the companies are in the PARP inhibitor space. Moreover, it shows which companies are taking share and which companies are giving up share. The data points were collected from company financial statements (SEC filings) and were consolidated into our proprietary database for further analysis. The data will be updated annually at the end of the 4Q reporting period and will comprise of annual sales figures of all FDA approved oncology drugs for that year.

TABLE 4: Pharma/Biotech Players in PARP Inhibitor Market (by Sales, 2016 - 2018)

				Sales (US$ Million)								
Generic	**Sub-Type**	**Brand**	**Manufacturer**	**FY 2016**	**Y/Y chg.**	**% of Total**	**FY 2017**	**Y/Y chg.**	**% of Total**	**FY 2018**	**Y/Y chg.**	**% of Total**
olaparib	ovarian, breast	Lynparza	AstraZeneca	218	132%	100%	297	36%	62%	647	118%	56%
olaparib	breast	Lynparza	Merck & Co.	--	--	--	20	--	4%	187	*	16%
niraparib	ovarian	Zejula	GlaxoSmithKline	--	--	--	110	--	23%	235	114%	20%
rucaparib	ovarian	Rubraca	Clovis Oncology	--	--	--	56	--	12%	95	72%	8%
talazoparib	breast	Talzenna	Pfizer	--	--	--	--	--	--	--	--	--
			Total	**218**	**132%**	**100%**	**483**	**121%**	**100%**	**1,164**	**141%**	**100%**

Source: Viola Advisory Oncology database
* = over 100%
Note: on July 27, 2017, AstraZeneca and Merck to share development, marketing costs and gross profits equally on Lynparza.

The PARP inhibitor market has grown steadily from $218 million in sales (+132% y/y) in 2016 to $1.16 billion in sales (+141% y/y) in 2018. AstraZeneca's Lynparza was the only PARP inhibitor drug in the space in 2016 that

was approved for ovarian cancer. Since then, four other companies came up with their own PARP treatments which steadily reduced AstraZeneca's market share from 100% in 2016 to around 56% in 2018.

B. PARP Inhibitor Market: Potential Share Gainers and Losers

The collaboration between AstraZeneca and Merck in Lynparza continues to outperform as both companies' combined market share grew to 72% in 2018 from 66% in 2017. Despite robust growth in 2017 by both Zejula and Rubraca, both drugs lost market share in 2018 with Zejula losing ground by 3 percentage points and Rubraca losing share by 4 percentage points.

Both Zejula and Rubraca are approved for ovarian cancer which is a smaller indication compared to breast cancer. Currently, both Lynparza and Talzenna are approved for breast cancer in different subtypes with Talzenna receiving approval in 2018. Both Lynparza and Talzenna are also currently being explored as treatment for patients with triple-negative breast cancer (TNBC). In addition, veliparib (from AbbVie), although not yet FDA approved, is also being evaluated for TNBC.

There is currently a lot of interest in expanding the reach of PARP inhibitors outside of patients with germline *BRCA* mutations as well as improving the response in patients with *BRCA* mutations. One crucial trial to watch is the OLYMPIA adjuvant trial which completed accrual this year. That trial is looking at adjuvant olaparib with germline BRCA mutations. Another set of data that looks intriguing is in the neoadjuvant setting investigating single agent talazoparib in patients with germline BRCA mutations. That trial is now in Phase 2 and is producing relatively high pathologic complete response rates (pCR) with talazoparib as a monotherapy.

If either Lynparza or Talzenna produces positive trial results in TNBC, then both AstraZeneca/Merck (Lynparza) and Pfizer (Talzenna) can build on and secure a market leading position in the PARP inhibitor space. Unless Zejula or Rubraca can expand their indication outside of ovarian cancer, then both companies could continue to see a steady decline in their market share.

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