ChatGPT

Drug Summary

Olaparib is an oral small-molecule **poly(ADP-ribose) polymerase (PARP) inhibitor** indicated for certain breast cancers with DNA-repair deficiencies. By exploiting the concept of **synthetic lethality** in tumors harboring homologous recombination repair defects (e.g. **BRCA1/2** mutations), olaparib selectively kills cancer cells with impaired double-strand DNA break repair while sparing normal cells [1] [2]. In breast cancer, olaparib has demonstrated improved progression-free survival in **HER2-negative, germline BRCA-mutated** metastatic disease and significantly improved invasive disease-free and overall survival as adjuvant therapy in **high-risk, BRCA-mutated early breast cancer** [3] [4]. Olaparib was first FDA-approved in 2014 and is marketed under the brand name **Lynparza** [5]. It targets key DNA repair enzymes to induce lethal DNA damage accumulation in cancer cells with homologous recombination deficiency (HRD) [1].

Identifiers & Synonyms

- **ChEMBL ID:** CHEMBL521686 [6]
- **DrugBank ID:** DB09074 [7]
- **Synonyms / Trade Names:** AZD-2281 (AZD2281); KU-0059436 (KU59436); **Lynparza®** [5]

Mechanism of Action (Breast Cancer–Specific)

Olaparib binds to and inhibits **PARP1, PARP2**, and to some extent **PARP3**, enzymes that detect and repair single-strand DNA breaks via the base excision repair pathway [1]. In BRCA1/2-mutant or other **HR-deficient** breast cancer cells, PARP inhibition leads to unrepaired single-strand breaks that collapse replication forks, causing irreparable **double-strand breaks** [8]. Lacking functional BRCA-mediated homologous recombination, these cancer cells cannot faithfully repair double-strand breaks, resulting in genomic catastrophe and cell death – a **synthetic lethal** effect [9] [2]. Olaparib not only blocks PARP catalytic activity but also **traps PARP-DNA complexes**, preventing release of the repair enzymes and intensifying DNA damage [8]. This mechanism is highly **breast cancer subtype-specific**: tumors with **germline BRCA1/2 mutations or HRD+ status** (often **basal-like/triple-negative** cancers) are exquisitely sensitive, whereas HR-proficient tumors (e.g. without BRCA mutations) are typically not responsive [2] [10]. In summary, olaparib's cytotoxicity in breast cancer relies on the **homologous recombination repair defect** of the tumor, leveraging PARP inhibition to induce lethal DNA double-strand breaks that **selectively kill BRCA-mutant cells** [2]. (Normal cells with intact HR avoid toxicity by repairing the PARP-inhibitor–induced breaks.)

Primary Targets (Human, HGNC Symbols)

- **PARP1** – Poly(ADP-ribose) polymerase 1 (chromatin-associated DNA damage sensor); primary target inhibited by olaparib [1].
- **PARP2** – Poly(ADP-ribose) polymerase 2; auxiliary DNA repair enzyme with overlapping base-excision repair role, also inhibited [1].

- **PARP3** – Poly(ADP-ribose) polymerase 3; PARP family member involved in DNA strand break repair; inhibited to a lesser extent by olaparib [1].

(HGNC gene symbols: PARP1, PARP2, PARP3). Olaparib's inhibitory action on PARP1/2 blocks their DNA repair function, which is critical in HR-deficient breast cancers [8]. The drug's efficacy correlates with these targets: loss-of-function mutations in **PARP1** can confer resistance by removing the drug's binding target [11].

Pathways Overview (MSigDB / Reactome / KEGG / GO / ImmuneDB)

Olaparib impacts multiple DNA damage response and cell fate pathways in breast cancer. Key pathways and their database identifiers include:

- **Homologous Recombination Repair (HRR)** – The error-free double-strand break repair pathway deficient in BRCA-mutated tumors. *Reactome:* **R-HSA-5685942** (HDR through HRR) [12] [13]; *KEGG:* **hsa03440** (Homologous recombination); *GO:* **GO:0000724** (double-strand break repair via homologous recombination). In HRR-deficient cells, olaparib-induced DSBs cannot be repaired, driving cell death [2].

- **Base Excision Repair (Single-Strand Break Repair)** – PARP-dependent repair of single-strand DNA lesions. *Reactome:* **R-HSA-73884** (Base Excision Repair) [14] [15]; *KEGG:* **hsa03410** (Base excision repair); *GO:* **GO:0006284** (base-excision repair). Olaparib **downregulates** this pathway by trapping/inhibiting PARP1/2, causing accumulation of SSBs that escalate to toxic DSBs [8].

- **Non-homologous End Joining (NHEJ)** – The error-prone DSB repair pathway that may compensate when HRR is lost. *GO:* **GO:0006303** (double-strand break repair via NHEJ). In HR-deficient (e.g. BRCA1-null) breast cancers, reliance on NHEJ (and alternative end-joining) increases; olaparib-induced DSBs are misrepaired by NHEJ, contributing to genomic instability [16]. Upregulation of NHEJ-related processes can both allow short-term survival and promote resistance (via mutagenic repair) in treated cells.

- **DNA Damage Response (DDR) Signaling** – Broad network including ATM/ATR checkpoint activation and apoptosis pathways triggered by unrepaired DNA breaks. *MSigDB Hallmark:* **HALLMARK_DNA_REPAIR** (covers HR, NHEJ, etc.); *GO:* **GO:0006977** (DNA damage response). PARP inhibition activates ATM/ATR-mediated checkpoint signaling due to persistent DNA breaks, leading to cell-cycle arrest and apoptosis in HRD cells [9].

- **Immune Response – cGAS/STING-Interferon Pathway** – Innate immune sensing of cytosolic DNA. In BRCA-mutant breast tumors, olaparib-induced DNA damage can trigger the **STING (stimulator of interferon genes) pathway** and type I interferon responses when unrepaired DNA fragments accumulate [17]. *ImmuneDB/ImmuneSigDB:* e.g. **GOBP_DEFENSE_RESPONSE_TO_VIRUS** (enriched when STING activates IFN). However, this pathway's activation is context-dependent (see below: TAM-mediated suppression). Preclinical models show PARP inhibition can **upregulate** interferon signaling and T-cell recruitment via STING, enhancing antitumor immunity [18].

- **Cell Cycle and Apoptosis Pathways** – Downstream of DNA damage. Olaparib-treated HRD cells show activation of apoptosis (e.g. *KEGG:* **hsa04210** Apoptosis) and cell-cycle arrest (e.g. *GO:* **GO:**

0000077 DNA damage checkpoint). These outcomes result from accumulated DSBs and checkpoint enforcement; for example, **p53 signaling** (frequently mutated in TNBC) is engaged by the DNA damage, modulating cell fate. In practice, extensive DNA damage from PARP inhibition leads to mitotic catastrophe or apoptosis in sensitive tumor cells [19].

Summary: Olaparib's therapeutic effect in breast cancer centers on **downregulating DNA single-strand break repair (PARP/BER pathway)** while exploiting a **deficiency in homologous recombination (HRR pathway)** [8]. The drug thereby causes lethal **upregulation of DNA damage signaling and apoptosis pathways** in HRD tumors. An interesting secondary effect is the potential **upregulation of immune-stimulatory pathways (STING/IFN)** due to accumulated DNA damage, which is an area of active research in combination therapies [18]. The balance between these pathways (error-prone NHEJ vs. accurate HRR, immune activation vs. immune suppression) influences sensitivity or resistance to olaparib. Below, we detail pathway changes by context.

Upregulated Pathways (by Context / Subtype)

DNA Repair Compensation in HR-Deficient Cells: In **BRCA1/2-mutant (HRD+) breast cancers**, alternative DNA repair processes become more active to compensate for the lost HRR. One such pathway is **error-prone end joining**. Upon PARP inhibition, HR-deficient cells exhibit increased reliance on **NHEJ and microhomology-mediated end joining (MMEJ)** to attempt double-strand break repair. This is evidenced by greater DNA end resection and mutagenic repair in cells lacking 53BP1 or shieldin complex, which normally channel DSBs into NHEJ [20] [21]. Loss of 53BP1/RIF1 (frequently an acquired change in resistant BRCA1-null tumors) *upregulates end-resection* and partially restores repair, allowing some cell survival despite PARP inhibition [20] [21]. In short, **BRCA1-deficient basal-like tumors under PARP blockade show upregulated compensatory end-joining activity**, which can undermine the drug's efficacy by rescuing DNA repair capacity.

Immune Signaling in BRCA-Mutant TNBC: PARP inhibitor treatment can provoke an **upregulation of innate immune pathways** in certain contexts. In preclinical models of **BRCA1-mutant, TP53-deficient triple-negative breast cancer (TNBC)**, olaparib triggered a robust **STING-dependent interferon response**, leading to increased production of type I IFNs and recruitment of $CD8^+$ T cells [17]. This suggests that in HRD tumors, the accumulation of cytosolic DNA from unrepaired breaks *upregulates* the **cGAS–STING pathway** and downstream immune gene signatures (e.g. interferon-stimulated genes) as part of the tumor's response to therapy [18]. Clinically, this phenomenon is being leveraged: for example, combining olaparib with a STING agonist or immune checkpoint inhibitor is hypothesized to further boost anti-tumor immunity by capitalizing on PARPi-induced immunogenic stress [22]. Thus, in **BRCA-mutant TNBC**, olaparib not only kills cells via DNA damage but may also *upregulate proinflammatory/immune pathways* that contribute to tumor control (provided the tumor microenvironment permits this response – see TAM discussion below).

"BRCAness" and HRD Pathways: Some sporadic **basal-like breast cancers** (triple-negative, without germline BRCA mutation) display a **BRCAness** phenotype (HRD due to other gene alterations). In these tumors, olaparib has been observed to enrich gene expression profiles of DNA damage and cell death pathways similarly to BRCA-mutated cancers [19]. Essentially, when a tumor has a high **HR deficiency score** or mutations in HR genes like **PALB2**, it behaves like BRCA-mutant disease. Studies show **PALB2-mutated** breast cancer cells respond to PARP inhibition, and guidelines now recognize *somatic BRCA1/2 or germline PALB2* mutations as markers for PARP inhibitor use [23] [10]. In these contexts, **HR repair remains down,** but

olaparib strongly *upregulates DNA damage accumulation and apoptotic signaling*, as intended. Pathway analysis (e.g. MSigDB HRD signature) confirms enrichment of DNA damage checkpoint and cell-death pathways in HRD-positive tumors treated with olaparib (versus HR-proficient tumors) [19].

Pathway Reactivation in Acquired Resistance: In tumors that develop resistance, previously suppressed pathways can become **re-activated (upregulated)**. A prime example is the **restoration of homologous recombination**. Resistant cancer clones often evolve secondary BRCA2 or BRCA1 reversion mutations that restore the open reading frame and protein function [24] [25]. This **reactivated HR pathway** can efficiently repair olaparib-induced DSBs, nullifying synthetic lethality. Likewise, demethylation of a BRCA1-promoter that was silenced can re-express BRCA1, **upregulating HRR activity** and causing drug resistance [25]. These findings illustrate that in the context of **acquired resistance**, pathways like HRR that were initially off are turned **back on (upregulated)** to circumvent the drug's effect.

In summary, **upregulated pathways under olaparib pressure** include **error-prone DNA repair routes** (NHEJ/MMEJ) and, in immunogenic contexts, **STING-mediated immune signaling**, as well as **resurrected HRR function** in resistant disease. The extent of these upregulations often depends on breast cancer subtype: e.g. basal-like BRCA1-null TNBC heavily leans on alternative end-joining and can exhibit STING upregulation [17] [20], whereas luminal tumors may instead resist via HR restoration.

Downregulated Pathways (by Context / Subtype)

PARP-Mediated DNA Repair: The most directly downregulated pathway by olaparib is **PARP-dependent base excision repair**. By inhibiting PARP1/2, olaparib **shuts off the single-strand break repair process**, preventing efficient resolution of base lesions and SSBs [8]. In all breast cancer subtypes, olaparib creates a state akin to a BER pathway knockout: enzymatic steps involving PARP1/2 (such as PARP-driven recruitment of XRCC1 for SSB repair) are halted. This leads to accumulation of SSBs and subsequent replication-associated DSBs. Thus, the **Base Excision Repair pathway (Reactome R-HSA-73884, GO:0006284)** is functionally **downregulated** or disabled in olaparib-treated cells [8].

Homologous Recombination (in HRD tumors): In the patient populations where olaparib is used, the **HR repair pathway is inherently downregulated** (by mutation). BRCA1/2-mutated tumors lack effective HR long before treatment – that is the vulnerability olaparib targets. In **BRCA1-deficient basal-like cancers**, HRR genes are silenced or non-functional, which corresponds to a *downregulation of the HR pathway* (e.g. loss of RAD51-mediated strand repair) [2]. Olaparib's synthetic lethality specifically exploits this absence. So, in context, **HRR remains down/non-operational** in sensitive tumors. If HR were active, the tumor wouldn't be as affected by PARP inhibition. (Importantly, as noted above, if HR gets restored, that is a resistance scenario.) In summary, **homologous recombination is effectively "off"** in the subtypes (TNBC, gBRCA carriers) that respond to olaparib [2].

Cell Proliferation Pathways: As olaparib induces DNA damage and checkpoint activation, cell-cycle progression pathways (especially **G2/M transition**) are suppressed. For example, **Cyclin-dependent kinase (CDK) activity** driving cell cycle is curtailed by checkpoint kinases (CHK1/CHK2) responding to damage. In HRD breast cancer cells, olaparib causes persistent activation of p53/p21 and other checkpoint signals, **downregulating proliferation** and forcing cells into arrest or death [26]. This effect is not a pathway "downregulation" in the classic sense, but a downstream consequence: **proliferative signaling (E2F targets, etc.) is dampened** as the cell tries to cope with DNA lesions.

Angiogenesis and DNA Replication Stress: There is emerging evidence that PARP inhibitors may normalize some tumor microenvironment pathways. For instance, repeated PARP inhibitor exposure in BRCA-mutant models has been associated with **downregulation of pro-angiogenic factors** and increased replication stress signaling [27] [28] (the latter reflecting overwhelmed replication machinery). However, these are secondary effects; the primary intended "downregulation" is of DNA repair processes.

In essence, **olaparib directly downregulates DNA single-strand break repair** by **inactivating PARP**. In HR-deficient breast cancers, the critical **HR pathway is already down** (defective), which is why the drug works [2]. Together, these deficits lead to collapse of genomic maintenance, cell-cycle arrest, and apoptosis. The flip side is that tumors *without* such downregulation of HR (e.g. HR-proficient luminal cancers) are inherently less affected by PARP inhibition. This is why patient selection by subtype/biomarker is so important for olaparib efficacy.

Sensitivity Mechanisms

Homologous Recombination Deficiency (HRD): The foremost determinant of sensitivity to olaparib in breast cancer is **HR repair deficiency**. Tumors with **germline BRCA1 or BRCA2 mutations** are highly sensitive [2]. In the pivotal OlympiAD trial, only patients with germline BRCA1/2 mutations derived benefit, underscoring HRD as the key sensitivity mechanism. *BRCA1-mutated* **basal-like/TNBC** tumors are especially responsive – these cancers typically lack functional HR from the start, making them ideal candidates for PARP synthetic lethality [19]. *BRCA2-mutated* **luminal (ER-positive)** tumors also respond significantly to olaparib, as seen in both metastatic and adjuvant settings [29] [30]. In fact, **OlympiA adjuvant trial data showed equal benefit in ER-positive and triple-negative BRCA-mutant patients**, confirming that the BRCA mutation (HRD) itself is the driver of sensitivity, regardless of hormone receptor status [29] [30].

Beyond BRCA, other **HR pathway gene defects** confer sensitivity. Notably, **PALB2** (a partner of BRCA2) mutations in breast cancer predict responsiveness to PARP inhibitors. Clinical guidelines (ESMO, NCCN) now endorse considering olaparib or talazoparib for patients with **PALB2-mutated, HER2-negative breast cancer**, extrapolating from the HRD mechanism [23] [10]. Similarly, tumors with **somatic BRCA1/2 mutations** (not inherited but acquired in the tumor) often have the HRD phenotype and can be sensitive – emerging clinical data suggest benefit of PARP inhibitors in this group as well [23]. In summary, any biomarker indicative of **HRD (BRCAness)** – whether germline or somatic BRCA1/2, or high genomic HRD score – is a sensitivity mechanism for olaparib.

Platinum Sensitivity as a Proxy: There is a known clinical correlation between platinum chemotherapy sensitivity and PARP inhibitor sensitivity [24] [25]. Cancers that respond to DNA-crosslinking agents like cisplatin (which also require HR for repair) are often HRD. For example, many **BRCA1-mutated TNBC** patients have prolonged responses to platinum, and these patients likewise tend to benefit from olaparib. In OlympiAD, patients could have had prior platinum; retrospective analyses show that **platinum responders generally also respond to olaparib**, whereas tumors that progressed on platinum are more likely to already have HR restoration (and thus be olaparib-resistant). Thus, **platinum sensitivity** can be seen as a phenotypic marker of olaparib sensitivity.

Tumor Molecular Signature: Certain gene expression signatures and protein biomarkers also indicate sensitivity. High expression of **PARP1** itself (the target) in tumors has been associated with better PARP inhibitor response in some studies, presumably because the drug target is abundant (though this is not used clinically). More directly, loss of function of proteins like **53BP1** (which normally antagonize end-

resection) *increases initial sensitivity* to PARP inhibition in BRCA1-mutant cells, by making them even more reliant on PARP (paradoxically, 53BP1 loss later contributes to resistance via resection – context matters). Also, **TP53 mutations**, ubiquitous in TNBC, synergize with BRCA1 loss to make cells genomically unstable and vulnerable to further DNA repair disruption; essentially all BRCA-associated breast cancers have TP53 inactivation, which may lower the threshold for apoptosis when PARP is inhibited.

Immune Contexture: While not a classical "sensitivity mechanism" in the way HRD is, the tumor's immune environment can influence response. Tumors with a **pre-existing T-cell infiltrate and intact STING pathway** might gain an added benefit from olaparib's immunomodulatory effects. Preclinical data suggests that **$CD8^+$ T-cell recruitment via STING activation** helps maximize the tumor cell kill from PARP inhibition [18]. Thus, an **immunologically "hot" tumor microenvironment** could potentiate olaparib efficacy (especially relevant for TNBC). This concept is behind trials combining PARP inhibitors with immunotherapy to enhance sensitivity.

In clinical practice, the **major sensitivity factor is HRD status**. If a breast tumor is **HR+/HER2– or TNBC with a germline BRCA1/2 mutation**, it is considered an ideal candidate for olaparib – evidenced by significant improvement in outcomes for these patients [29]. Patients with **HRD-positive TNBC** (e.g. high genomic instability but no BRCA mutation) may also benefit, though this is not yet an approved indication without a BRCA/PALB2 mutation. Ongoing research (e.g. the TBCRC048 and other trials) is evaluating PARP inhibitors in such populations.

Resistance Mechanisms

Breast cancers can develop both **de novo and acquired resistance** to olaparib. Key resistance mechanisms revolve around restoring DNA repair or bypassing the drug's effects:

- **Restoration of Homologous Recombination:** This is the most prominent resistance mechanism. Tumors initially HR-deficient may **restore HR repair activity** through secondary genetic changes. **BRCA reversion mutations** – where a new mutation in BRCA1/2 "fixes" the original frameshift/stop codon – can rescue BRCA protein function [24] [31]. Such reversions have been documented in both breast and ovarian cancers after PARP inhibitor or platinum therapy. For example, a secondary BRCA2 mutation that deletes a prior stop codon restored BRCA2 functionality and conferred olaparib resistance [32]. Likewise, epigenetic restoration can occur: **demethylation of a silenced BRCA1 promoter** can re-express BRCA1 in tumors that had BRCA1 promoter hypermethylation, leading to renewed HR proficiency and drug resistance [25]. In summary, any mechanism that **re-establishes functional BRCA1/2 or HR pathway** will render the cancer cells less susceptible or refractory to olaparib. This has been observed frequently in patients who progress on PARP inhibitors [24].

- **Loss of 53BP1/Shieldin Pathway (End Resection Increases):** BRCA1-deficient cells rely on the 53BP1-RIF1-Shieldin complex to handle DNA breaks via NHEJ. One common resistance route in BRCA1-mutant TNBC is losing 53BP1 or downstream Shieldin components (e.g. REV7) [20] [21]. This loss permits extensive DNA end resection and use of alternative repair pathways, partially compensating for lack of BRCA1. Essentially, **BRCA1-deficient cells without 53BP1 can perform a form of HR (or Alt-EJ) despite BRCA1 loss**, escaping synthetic lethality. Experimental models have shown **knockout of 53BP1 rescues BRCA1-null cells from PARP inhibitor killing** by allowing RAD51 loading and some HR activity [20] [21]. Clinically, low 53BP1 expression in a BRCA1-mutant tumor post-therapy is a red flag for resistance. Shieldin complex gene mutations (REV7, SHLD1/2)

similarly cause PARPi resistance by **expanding resection and restoring repair**, as confirmed in cell lines and animal models [21] [33].

- **PARP1 Alterations:** Since PARP1 is the primary drug target, changes in PARP1 can drive resistance. **Mutation or deletion of PARP1** that prevents olaparib binding (or trapping) have been identified in resistant tumors [11] [34]. For example, mutations in the PARP1 zinc-finger DNA-binding domains (e.g. loss of residues K117 and S120) reduce PARP1's ability to bind DNA, meaning the enzyme no longer gets trapped by the inhibitor [34]. Another scenario: a truncating mutation in PARP1 could eliminate the domain that olaparib binds, so the drug has no effect. Additionally, **PARP1 downregulation** (lower expression) can lessen olaparib's impact – if little PARP is present, its inhibition/trapping is less lethal. Experimentally, PARP1 knockout cells are highly resistant to PARP inhibitors (since the drug has no essential target to act on) [11]. However, complete PARP1 loss is rarely seen clinically; subtle mutations that alter PARP1 function are more common in resistant disease [35]. These findings highlight that cancers can **escape olaparib by functionally inactivating the very target that the drug needs to poison**.

- **PARG Loss (PAR turnover issues):** PAR glycohydrolase (PARG) is the enzyme that removes PAR chains from PARP1. Deficiency of PARG has been linked to PARPi resistance [36]. Mechanistically, if PARG is lost, PAR chains remain on PARP1 and the PARP1-DNA complex may dissociate differently, or the cell may better tolerate PARP1 trapping. A study showed **PARG-knockout breast tumor cells (BRCA2-deficient)** were more resistant to olaparib [36]. Clinically, PARG loss is not commonly measured, but this is a proposed resistance route. It suggests that **persistently PARylated PARP1 (due to PARG loss) somehow mitigates the cytotoxic stress**, perhaps by quicker PARP1 auto-release or alternate repair recruitment. While the exact mechanism is still being elucidated, **PARG deficiency is considered a potential contributor to PARP inhibitor resistance** [36].

- **Replication Fork Protection:** An emerging mechanism of resistance in BRCA-mutant cancers is the ability to protect stalled DNA replication forks from collapse. Normally, BRCA1/2-deficient cells have unstable replication forks that degrade, which contributes to PARPi lethality. Some resistant tumors acquire changes that stabilize these forks. For instance, loss of certain nucleases (like MRE11) or loss of factors like **SMARCAL1, ZRANB3, HLTF** (involved in fork remodeling) can lead to **replication fork stabilization** in BRCA-deficient cells [37]. Studies have shown that **BRCA1-deficient cells lacking SMARCAL1 are resistant to olaparib and cisplatin**, with protected forks but without restoring HR [37]. Similarly, reduced activity of DNA2 or PTIP (other proteins in fork degradation pathways) has been implicated in resistance. Essentially, by **preventing the catastrophic collapse of replication forks**, cancer cells can survive PARP inhibition despite HR defects. This mechanism does not restore HR, but it reduces the dependency on HR by avoiding some DSB formation. Fork protection is a subtler form of resistance that is hard to detect clinically, but it underscores the multiple cellular adaptations beyond canonical HR that tumors use to escape PARPi.

- **Drug Efflux Pump Upregulation:** Like many small-molecule therapies, PARP inhibitors can be subject to multidrug resistance via efflux pumps. **P-glycoprotein (ABCB1)** overexpression has been linked to olaparib resistance [38] [39]. Olaparib is a substrate of the ABCB1 transporter, and tumor models with high P-gp activity show reduced intracellular drug accumulation and hence resistance [39]. Long-term exposure to olaparib has been shown to **upregulate Abcb1a/b (mouse MDR1) genes** in cell line models, leading to drug efflux and decreased efficacy [39]. Clinically, this mechanism is suspected in some cases of acquired resistance (especially in the context of central

nervous system metastases where the blood-brain barrier P-gp might limit drug penetration). Combining olaparib with P-gp inhibitors or using PARPi not subject to P-gp (like talazoparib, although it is also a substrate to some extent) has been proposed to overcome this. While **drug efflux is a general chemoresistance mechanism**, it is noteworthy that **ABCB1 upregulation was specifically observed in olaparib-resistant breast cancer models** [38], and ABCB1 gene fusions were reported in drug-resistant patient samples of high-grade serous ovarian and breast cancers [40]. This indicates some tumors activate this classic MDR pathway to pump out PARP inhibitors.

- **Tumor Microenvironment and Immune Evasion:** As hinted earlier, the tumor microenvironment can blunt olaparib response. A striking resistance mechanism uncovered in BRCA-mutant **breast tumors (but not as much in ovarian)** involves **M2-polarized tumor-associated macrophages (TAMs)**. Breast cancer cells have been found to secrete factors that polarize macrophages to an immunosuppressive, tissue-repair (M2) phenotype to a greater extent than ovarian cancer cells [41] [42]. These **M2-like macrophages release cytokines that protect cancer cells from DNA damage**. Specifically, in a Nature Communications 2022 study, BRCA1-deficient breast tumors induced TAMs that **suppressed PARP inhibitor–elicited DNA damage and thereby prevented the accumulation of cytosolic DNA fragments and activation of STING-dependent immunity** [17]. In effect, the macrophages helped the tumor **tolerate PARP inhibition**, both by dampening DNA damage and by inhibiting anti-tumor T cell activation [43] [27]. This microenvironment-mediated resistance does not involve a tumor-intrinsic DNA repair change but rather an extrinsic survival advantage. It may contribute to the observation that BRCA-mutant breast cancer patients have less dramatic responses to PARP inhibitors than BRCA-mutant ovarian cancer patients [44] [45]. Overcoming this form of resistance is an active area of research (e.g., using **STING agonists to reprogram TAMs to a tumor-fighting M1 state**, which in preclinical models restored PARPi sensitivity [46] [18]).

Multiple other minor mechanisms are being investigated (e.g. changes in DNA polymerase theta (POLQ) affecting alternative end-joining, upregulation of homologous recombination mediator proteins like RAD51 by cell stress, etc.), but the above represent the major known resistance pathways in the context of breast cancer [47] [48]. Importantly, these mechanisms often arise under the selective pressure of therapy. For example, after ~6-12 months of olaparib treatment, one might detect a secondary BRCA mutation or loss of 53BP1 in a tumor biopsy, explaining resistance. Combination strategies (PARPi with ATR inhibitors, WEE1 inhibitors, PI3K inhibitors, etc.) are being explored to circumvent some of these resistance routes.

Breast Cancer Subtype–Stratified Evidence

Olaparib has been studied and used across multiple breast cancer subtypes, but its benefit is **highly stratified by both receptor subtype and genomic subtype**. Key points for each subtype/group:

- **HR-positive / HER2-negative (Luminal A/B) Breast Cancer:** Patients with **estrogen receptor (ER)+, HER2–** breast cancer generally benefit from olaparib **only if they carry a BRCA mutation or similar HRD biomarker**. BRCA2 mutations are more common in luminal disease than BRCA1. In the **OlympiA adjuvant trial**, about 20–30% of participants were ER-positive BRCA carriers; notably, **olaparib significantly improved outcomes in this ER+ subset** to a similar degree as in triple-negative patients [29] [30]. After 6 years median follow-up, **ER+ BRCA-mutant patients had fewer recurrences and a clear overall survival benefit with adjuvant olaparib** vs placebo [4] [30]. This dispelled some initial skepticism that maybe HR+ tumors (which tend to be less proliferative) would not benefit as much – they do, provided they are BRCA-mutated. However, in **sporadic (non-BRCA)**

luminal breast cancers, olaparib has no role; these tumors have intact HR repair and rely on endocrine therapy and other targeted agents. For example, a general ER+ breast cancer without BRCA mutation would be managed with hormone therapy ± CDK4/6 inhibitors, and PARP inhibition is not indicated. Guidelines emphasize **germline BRCA testing in high-risk HER2– patients** so that those with mutations (even in ER+ cancers) can be identified for adjuvant olaparib [49] [50]. In the metastatic setting, an **ER+/HER2–, BRCA-mutant** patient who has progressed on endocrine therapies can be treated with olaparib, which is often more effective and better tolerated than chemotherapy in that genomic context [10]. In summary, **Luminal BRCA-mutated breast cancers** derive significant benefit from PARP inhibitors (category 1 recommendation in NCCN guidelines for adjuvant therapy) [51], whereas **Luminal wild-type BRCA** cancers do not. Luminal tumors are typically of the **PAM50 Luminal A or B intrinsic subtype** – the presence of a BRCA mutation in these does not change the hormone receptor positivity, but it does change optimal management (adding a PARP inhibitor after chemo, as per OlympiA).

- **HER2-positive Breast Cancer:** Olaparib is *not routinely used* in HER2+ disease. Clinical trials of PARP inhibitors generally excluded HER2-overexpressing tumors because those tumors have an effective targeted therapy (anti-HER2 agents) and because BRCA mutations are rare in HER2+ patients. Indeed, germline BRCA1/2 mutations tend to occur in HER2-negative cancers; in BRCA cohorts, usually <5% of cases are HER2+. If a patient were HER2+ and BRCA-mutated (an uncommon scenario), standard care would still prioritize HER2-directed therapy (e.g. trastuzumab, pertuzumab, etc.) as first-line. There is limited evidence on using olaparib in such patients. One could consider a PARP inhibitor if the HER2+ BRCA-mutant cancer progresses through multiple lines of anti-HER2 therapy, but this would be off-label. **No trials have specifically assessed PARP inhibitors in HER2-positive breast cancer**, and the NCCN/ESMO guidelines do not list it for HER2+ disease [10] (except to say germline BRCA testing should be done in HER2– cases, implicitly not focusing on HER2+). Intrinsically, HER2-enriched tumors usually have functional HR (unless coincident BRCA mutated). Thus, at present **HER2-positive subtype is not a target for olaparib**; the focus remains on HER2 pathway blockade. (Interestingly, preclinical research shows some synergy between PARP inhibition and HER2 blockade or radiation in HER2+ models, but this is investigational.)

- **Triple-Negative Breast Cancer (TNBC):** This subtype (ER–, PR–, HER2–) has the strongest link to BRCA1 mutations and HRD. **TNBC patients with germline BRCA1 (or BRCA2) mutations** are prime candidates for olaparib therapy. In the metastatic setting, the OlympiAD trial was limited to HER2– disease and about half the patients were TNBC; olaparib significantly improved PFS in BRCA-mutant TNBC compared to chemo [3]. Although overall survival in OlympiAD did not reach significance, a subgroup analysis suggested a potential OS benefit in those who received olaparib earlier (as first-line for metastatic disease) [52]. In the **adjuvant OlympiA trial**, BRCA1-mutant cases were mostly TNBC (since BRCA1 is enriched in TNBC) – these patients had substantial benefit from one year of olaparib, with invasive disease-free survival improved and a reduction in distant recurrences [4] [53]. Notably, **olaparib provided similar relative benefit in TNBC and ER+ groups** in OlympiA [29], but because TNBC BRCA carriers have higher absolute recurrence risk, the absolute benefit in TNBC was very pronounced. Triple-negative, BRCA-mutated breast cancer is now a distinct category in guidelines, with PARP inhibitor therapy as a standard option (adjuvant or metastatic) [51]. For **sporadic TNBC without BRCA mutation**, PARP inhibitors are not standard, but research is ongoing. TNBC often exhibits the BRCAness phenotype (about 15-20% of non-BRCA TNBC have high HRD genomic scores). In the neoadjuvant I-SPY2 trial, the combination of a PARP inhibitor (veliparib) with carboplatin improved pathologic complete response in TNBC, suggesting HRD-TNBCs do respond to

DNA-damaging strategies. However, single-agent PARP inhibitor in unselected TNBC has not been fruitful. There was a negative trial (SWOG S1416) in metastatic TNBC overall, but retrospective analysis indicated patients with HRD tumors (determined by an HRD gene signature or BRCA-like genomic scars) might derive benefit. This is leading to interest in **expanding PARPi use to HRD-positive TNBC even without germline BRCA**, perhaps with the help of diagnostic assays. As of 2025, though, **olaparib is reserved for TNBC with germline BRCA1/2** (and potentially somatic BRCA/PALB2, case by case). TNBC corresponds largely to the **basal-like intrinsic subtype**, which as a group has high genomic instability. Indeed, basal-like tumors (whether BRCA-mutated or not) often have dysfunctional HR pathways, making them conceptually a good target for PARP inhibitors [2]. Clinical trials like BROCADE (veliparib+chemo) and ongoing studies are exploring if a subset of BRCA-wildtype TNBC with HRD can benefit from PARPi, possibly in combination with immune therapy (since TNBC is also more immunogenic). In practice, **gBRCA-mutant TNBC is an established indication for olaparib**, whereas **BRCA-wildtype TNBC** may receive PARPi only in clinical trials or off-label scenarios guided by exceptional biomarkers.

- **gBRCA1 vs gBRCA2 differences:** It's worth noting the different spectra of cancer: **BRCA1** mutations predominantly lead to TNBC (basal-like) breast cancers, while **BRCA2** mutations often lead to ER-positive (luminal) cancers. Despite the different phenotypes, both groups benefit from PARP inhibition. The OlympiA trial had ~70% BRCA1-mutated (mostly TNBC) and ~30% BRCA2-mutated (majority ER+) [54] – both saw benefit [29]. One difference observed is in the natural history: BRCA1 TNBC tends to be aggressive but also highly chemo-sensitive (and PARPi-sensitive); BRCA2 luminal tumors may present slightly later and be somewhat less chemosensitive, but still derive marked benefit from targeted PARP therapy. Some data suggested BRCA2-mutant patients had a slightly higher absolute benefit from olaparib in OlympiA, perhaps because endocrine therapy alone is not sufficient for them and PARPi filled a treatment gap. In any case, both BRCA1 and BRCA2 carriers with breast cancer are now routinely offered PARP inhibitor therapy either in trials or in practice.

- **"Basal-like" vs "HER2-enriched" vs "Luminal" Intrinsic Subtypes:** Intrinsic subtyping (PAM50) isn't routinely used to make treatment decisions regarding PARP inhibitors, but it correlates with the above clinical subtypes. **Basal-like** corresponds to most BRCA1 and many BRCA2 TNBC tumors – these, as noted, respond to olaparib if HRD. **HER2-enriched** subtype (which can occur in some HER2+ or even some triple-negative tumors) has no known direct link to HRD or PARP response, unless coincident mutation. **Luminal A/B** correspond to most ER+ tumors (including BRCA2-mutant ones). BRCA2-mutant luminal tumors often are classified as Luminal B (because they tend to be high grade). Olaparib's efficacy in luminal BRCA tumors indicates that even if a tumor is "luminal" in expression, the presence of HRD trumps its expression subtype in terms of therapy choice. In other words, a **Luminal B, BRCA2-mutant** tumor is treated more like a "BRCA-associated" cancer (i.e., consider PARP inhibitor) than a typical luminal B. Conversely, a **basal-like tumor** that is BRCA-wildtype but has no other HRD might not be PARPi-sensitive; it would be treated with standard chemo ± immunotherapy (if PD-L1+).

- **HRD+ (no germline mutation) tumors:** As mentioned, some breast cancers without germline BRCA can have high HRD scores or somatic alterations in HR genes (e.g., somatic BRCA1 promoter methylation, somatic mutations in RAD51C, etc.). There is evolving evidence that such tumors behave like BRCA-mutants. For example, a patient with **somatic BRCA1-mutated TNBC** was treated on trials and responded to olaparib [23]. In the metastatic setting, NCCN now notes that *somatic* BRCA mutations qualify for PARP inhibitor use as well (FDA approved olaparib for "germline" BRCA,

but talazoparib's trial had a few somatic, and ongoing studies are expanding criteria) [23]. Similarly, **germline PALB2-mutant** breast cancers (often ER+) have shown high response rates to PARP inhibitors, leading to off-label use of olaparib in such cases with supporting case series. As genomic testing in breast cancer is more commonly done, these rare HRD genomics can be identified. The **ESMO metastatic breast cancer guideline (2022)** explicitly recommends offering a PARP inhibitor to patients with **HER2-negative MBC who have a germline BRCA1/2 mutation – independent of HR status –** and also notes that *talazoparib or olaparib may be considered in tumors with somatic BRCA or germline PALB2 mutations* [10]. This reflects the principle that any **HRD subtype**, regardless of classical subtype, could benefit.

- **Male Breast Cancer:** BRCA2 mutations are prevalent in male breast cancer, which are typically ER+. While not a separate subtype per se, it is worth noting that male patients with BRCA2-mutated breast cancer could also be candidates for olaparib (in fact, the OlympiA trial included a small number of male breast cancer patients). The drug's effect is expected to be similar in that context, although data is limited.

Overall, **breast cancer treatment with olaparib is genomically stratified**: the presence of a pathogenic BRCA1/2 (or similar HRD) defines the subgroup across phenotypic subtypes that should receive PARP inhibitor therapy. Clinical guidelines now incorporate this stratification: for example, NCCN 2024 moved adjuvant olaparib to a "category 1" recommendation for **patients with residual disease after neoadjuvant therapy who are BRCA1/2-mutated (whether triple-negative or ER-positive)** [51]. In metastatic disease, PARP inhibitors are recommended for **BRCA-mutated, HER2-negative** cancers as an alternative to chemotherapy [10]. If the subtype is HER2-positive or lacks HRD, PARP inhibitors are generally not used.

Contraindications and Safety

Contraindications: According to regulatory labels (FDA/EMA), olaparib is contraindicated in patients with a known severe hypersensitivity to the drug or any of its components. There are no many absolute contraindications apart from allergy, but practical contraindications include **pregnancy and breastfeeding** – olaparib is teratogenic and embryo-fetal toxic (pregnancy category D in Australia) and should not be used by pregnant women [55]. Women of childbearing potential are advised to use effective contraception during treatment and for some time after the last dose, as PARP inhibitors can cause fetal harm. Olaparib is also generally avoided in patients with **severe uncontrolled infections or significantly low baseline blood counts**, since it can cause myelosuppression (see below). Caution (though not absolute contraindication) is required in patients with **significant hepatic impairment** or **renal impairment**, as dosing may need adjustment (olaparib is primarily metabolized by CYP3A4 and excreted partly via kidneys) [56]. Co-administration of olaparib with **strong CYP3A inducers or inhibitors** is contraindicated or to be avoided, as these can significantly alter olaparib levels (e.g., rifampin or phenytoin can reduce efficacy; ketoconazole can increase toxicity).

Safety Profile: Olaparib is generally well-tolerated relative to cytotoxic chemotherapy, but it has a distinct side effect profile. Common adverse effects (any grade) include: **gastrointestinal toxicity** – **nausea** (experienced by a majority of patients), **vomiting**, diarrhea, dyspepsia, and decreased appetite [57]. **Fatigue** and asthenia are also very common (many patients report significant fatigue, though usually grade 1-2) [58]. Another key toxicity is **hematologic**: olaparib can cause **anemia** in a substantial fraction of patients, as well as **leukopenia/neutropenia** and **thrombocytopenia** to a lesser extent [58]. In clinical trials, grade $\geq$3 anemia occurred in ~20% of patients on olaparib, often requiring dose interruptions or transfusions [58].

Myelosuppression is likely due to PARP's role in bone marrow progenitor cell DNA repair; accordingly, **blood counts should be monitored regularly** on therapy. Olaparib is classified as a **molecular targeted therapy with immunosuppressive potential** (chronic PARP inhibition can suppress bone marrow function) [59].

Other adverse effects include **headache, dizziness or somnolence** (some patients report insomnia or, conversely, drowsiness – high doses in trials caused somnolence) [58]. There can be **elevations in creatinine** (due to inhibition of renal transporters OCT2/MATE1) that are usually asymptomatic. Rashes have been reported in a minority. Overall, most side effects are low-grade and manageable. In the OlympiAD trial, **adverse events were generally low-grade and could be managed with supportive care or dose modifications**, and only ~5% of patients had to discontinue olaparib due to toxicity [60]. This contrasts favorably with chemotherapy, which had higher discontinuation rates.

Serious Risks: A notable long-term risk of PARP inhibitors is the development of **therapy-related myelodysplastic syndrome (MDS) or acute myeloid leukemia (t-AML)**. These are rare but serious late toxicities observed in trials of PARP inhibitors, especially in heavily pretreated patients (who often have received DNA-damaging chemotherapies prior). In pooled analyses, the incidence of MDS/AML has been around 1-2% in ovarian cancer trials over several years. In breast cancer, few cases have been seen: In OlympiA, at ~3-year follow-up, the incidence of MDS/AML was low and not significantly different from placebo (4 cases on olaparib vs 6 on placebo) [61] [62]. With longer follow-up (6 years), still no clear excess of MDS/AML was noted [61]. This is reassuring for early-stage use. Nevertheless, **MDS/AML is listed as a potential adverse effect** in prescribing information. Patients who have had multiple chemotherapy lines and then get a PARP inhibitor should be monitored for prolonged cytopenias as a warning sign. The mechanism is thought to be that PARP inhibition in already damaged hematopoietic stem cells (from prior chemo) can drive them toward leukemic evolution.

Other safety considerations: Olaparib can cause **pneumonitis** in rare cases – unexplained dyspnea and cough in a patient on olaparib should prompt evaluation (a few <1% cases of pneumonitis were reported in trials). Liver enzyme elevations are uncommon. There is no specific cardiac toxicity. Olaparib does not appear to significantly prolong QT interval.

Drug Interactions: As mentioned, olaparib is metabolized by CYP3A4. Coadministration with **strong CYP3A inhibitors** (like itraconazole, clarithromycin) can increase olaparib plasma concentrations substantially, so either avoid or reduce dose. Strong **CYP3A inducers** (like rifampicin, carbamazepine, St. John's Wort) can reduce olaparib exposure and efficacy [63]; these should be avoided. Patients on anticoagulants or other drugs with narrow therapeutic index should be monitored, though olaparib itself has no known effect on CYPs.

Monitoring: Patients on olaparib should have CBC monitored monthly (or more frequently if abnormalities) to catch anemia or neutropenia. Liver and renal function should be checked periodically. Patients should be educated about managing nausea (prophylactic antiemetics can be given if needed). Fatigue management and dose adjustments are sometimes needed. The starting dose in breast cancer is 300 mg twice daily (tablets); dose can be reduced stepwise to 250 mg BID or 200 mg BID if toxicity.

In practice, the safety profile has been considered favorable: in the OlympiAD final analysis, **olaparib was generally well-tolerated with mostly grade 1–2 toxicities and a low discontinuation rate** [60]. This makes it an attractive option compared to chemotherapy for suitable patients (quality of life on PARP inhibitors was reported as better than on chemo in trials).

Trial and Guideline Context

Key Clinical Trials:

- **OlympiAD (NCT02000622):** A phase III trial that established olaparib's efficacy in metastatic breast cancer. It enrolled 302 patients with **germline BRCA1/2-mutated, HER2-negative metastatic breast cancer** who had received ≤2 prior chemo lines [64]. Patients were randomized to olaparib monotherapy vs physician's choice single-agent chemo. **Result:** Olaparib significantly improved **progression-free survival (PFS)** (median 7.0 vs 4.2 months, HR ~0.58) [3], and objective response rates (~60% vs 29%). This was the first proof that a PARP inhibitor outperforms chemo in BRCA-mutant breast cancer. *Final overall survival* results (published 2019) showed no significant OS difference overall (median ~19.3 vs 17.1 months, HR 0.90, p=0.51) [65] [66], likely due to cross-over and effective post-progression therapies. However, an exploratory subgroup analysis suggested patients with no prior chemo for MBC (i.e., first-line use of olaparib) had a better OS (HR 0.51) [67]. Olaparib's tolerability was better than chemo: fewer Grade ≥3 AEs and higher quality-of-life scores. This trial led to **FDA approval in January 2018 of olaparib for metastatic HER2-negative breast cancer with germline BRCA mutation** (after ≥1 prior chemo). It also cemented the practice of germline testing in metastatic breast cancer.

- **EMBRACA:** A similar phase III for talazoparib (another PARPi) in germline BRCA MBC. While not olaparib, its results were consistent (talazoparib improved PFS vs chemo). EMBRACA and OlympiAD together established PARP inhibitors as a new class in breast oncology.

- **OlympiA (NCT02032823):** A landmark phase III trial in **adjuvant** setting. It included 1,836 patients with **high-risk, early-stage HER2-negative breast cancer with germline BRCA1/2 mutation** [68]. "High-risk" meant: if TNBC, either ≥T2 or N+, or if after neoadjuvant therapy had residual disease; if ER+, had ≥4 nodes or other high-risk features. Patients were randomized to 1 year of olaparib vs placebo after completing surgery, chemo (and radiation if indicated). **Result:** At interim analysis (presented 2021, published NEJM 2021), olaparib significantly improved **invasive disease-free survival (IDFS)** at 3 years (85.9% vs 77.1%; HR 0.58, p<0.001) and **distant disease-free survival** [53]. This led to **FDA approval (March 2022) of olaparib for adjuvant treatment** in this population. The trial's **third interim overall survival analysis (presented at SABCS 2024)** showed a continued OS benefit: after ~6 years median follow-up, **olaparib reduced risk of death by ~28%** (HR ~0.72) [4] [69]. At 6 years, OS was 87.5% vs 83.2% (an absolute 4.3% gain) [70]. Notably, **benefits were observed across all subgroups – including both triple-negative and ER-positive patients** [29] [71]. There was no increase in serious late toxicity (MDS/AML rates low and similar between arms [61]). OlympiA provides strong evidence that adding a PARP inhibitor after standard treatment **improves long-term outcomes in BRCA-mutated breast cancer**. This trial has been practice-changing: many guidelines swiftly incorporated adjuvant olaparib for eligible patients.

- **Other Trials:** A number of combination trials and niche studies are ongoing or reported:

    - **MEDIOLA:** A phase II basket trial testing olaparib with the PD-L1 inhibitor durvalumab in germline BRCA-mutant cancers (including breast). In the breast cohort, the **combination ORR was ~63%** and 12-week disease control ~80%, suggesting an additive benefit [72]. This

combination is being explored to see if checkpoint blockade can prolong PARPi responses (especially in platinum-resistant cases).

- **DORA:** A phase II study (mentioned in abstract [57]) of olaparib ± durvalumab in metastatic TNBC *without* germline BRCA found no significant PFS benefit to adding durvalumab, but did show immune modulation [73]. It indicates that PARPi can induce immune effects even in BRCA-wildtype TNBC, though perhaps not enough alone.
- **Talazoparib + Atezolizumab (ImmunoPARP):** The Lora Teresa study and others are evaluating PARP inhibitor with immunotherapy in both BRCA-mutant and BRCA-wildtype TNBC. Early results (from small neoadjuvant trials like **GeparNuevo subset**) suggest PARP inhibition may increase tumor-infiltrating lymphocytes.
- **Combination with Chemotherapy:** Combining PARP inhibitors with chemo has been pharmacologically challenging due to overlapping myelosuppression. Veliparib (a less potent PARPi) was combined with carboplatin in the BROCADE trial; olaparib has been combined with cisplatin in small studies. Efficacy was seen but toxicity (hematologic) was significant, so this approach isn't standard.
- **Combination with Targeted Agents:** Interesting synergy has been noted with agents targeting cell cycle and DNA damage response: e.g., **olaparib + PI3K inhibitor** (capivasertib) in PTEN-loss models, **olaparib + WEE1 inhibitor (adenosine analog)**, or **olaparib + ATR inhibitor**. A recent Nature 2023 paper showed **olaparib + WEE1i triggered STING-mediated immune response in BRCA-wildtype TNBC**, hinting at a strategy to extend PARPi to HR-proficient cancers by exploiting replication stress [74]. Clinical trials like **CAPRI (olaparib+ATRi)** are ongoing.
- **Neoadjuvant PARP**: The small window-of-opportunity trial DNA PacN (abstract PS12-01 at AACR 2022) reported that short-term olaparib treatment led to **dynamic changes in tumor-infiltrating lymphocytes** and Ki-67 in TNBC, suggesting a direct effect on tumor biology even before surgery [73].

Guidelines and real-world context: - **NCCN Guidelines (USA):** NCCN now recommends germline BRCA testing for all patients with high-risk or metastatic HER2-negative breast cancer [75]. For **metastatic** patients with BRCA1/2 mutations, **olaparib or talazoparib** is recommended as preferred therapy (usually before or in lieu of further chemo) for both TNBC and HR+ disease [10]. As of 2024, NCCN lists olaparib as a category 1 option in the metastatic setting after prior chemo (and endocrine therapy if HR+) [76] [77]. For **early-stage**, NCCN Breast Cancer Guidelines v1.2024 upgraded adjuvant olaparib to **Category 1** for patients with germline BRCA mutation and *residual disease after neoadjuvant chemo* or other high-risk features (this aligns with OlympiA) [51]. This was a change from category 2A, reflecting the strength of the data. In essence, NCCN endorses 1 year of olaparib after standard therapy for BRCA-mutant, HER2-negative stage II-III breast cancer with sufficient risk, regardless of ER status [51]. - **ESMO Guidelines (Europe):** The ESMO 2021 Early Breast Cancer guideline added a strong recommendation for considering adjuvant olaparib in germline BRCA carriers with high-risk HER2-negative disease, following the NEJM publication. The ESMO 2022 Metastatic Guideline recommends offering a PARP inhibitor to any germline BRCA1/2-mutated, HER2– metastatic patient, and mentions potential use in somatic BRCA or PALB2 mutated cases (evidence level II) [10]. It also emphasizes performing germline BRCA testing as part of work-up for HER2-negative MBC [75]. - **ASCO Guidelines:** ASCO endorsed germline testing for all patients with metastatic breast cancer to identify candidates for PARPi. ASCO guideline (2020) on systemic therapy for metastatic breast cancer states that **patients with a germline BRCA mutation who have HER2-negative MBC should be offered a PARP inhibitor (olaparib or talazoparib) rather than chemotherapy in the early-line setting**, based on OlympiAD/EMBRACA (Evidence Quality: High; Strength: Strong). For early-stage, ASCO hasn't published a separate guideline yet post-OlympiA, but experts widely adopted adjuvant PARP

inhibition for BRCA carriers. - **FDA/EMA Approvals:** FDA approvals: Olaparib is approved (1) **metastatic setting** – for germline BRCA-mutated, HER2-negative MBC after prior chemo (and if HR+, after endocrine therapy) [76] [77]; (2) **adjuvant setting** – for germline BRCA-mutated, HER2-negative high-risk early breast cancer (since 2022). EMA and other agencies (e.g. **PMDA in Japan**) have similarly approved these indications. The drug was initially developed for ovarian cancer, but breast cancer approvals followed by 4 years (2018 for metastatic, 2022 for adjuvant). - **NICE (UK):** In Jan 2025, NICE recommended olaparib for **advanced BRCA-mutated breast cancer** on the NHS after a new appraisal [76]. NICE had earlier (2023) recommended olaparib as adjuvant therapy for BRCA+ early breast cancer after chemo [49], reversing a provisional rejection following a commercial price arrangement. NICE's criteria for advanced disease specify prior anthracycline/taxane (unless unsuitable) and endocrine therapy if HR+ [77] – essentially aligning with how trials were done. An estimated ~1,200 patients per year in England could benefit from these recommendations [78]. - **Other Guidelines:** The **German AGO** guidelines, **French Saint Gallen** consensus, etc., all now include PARP inhibitors for BRCA-mutant cases. The **NCCN Patient Guidelines** stress the importance of genetic testing and mention olaparib as a tailored therapy for "inherited BRCA" breast cancer.

Overall, these guidelines reflect a paradigm where breast cancer treatment is personalized not only by tumor receptor subtype but also by **germline genetics**. Olaparib has become a standard part of the **treatment algorithm for BRCA-associated breast cancers**.

Additional Mechanistic/Clinical Notes

- **Synthetic Lethality and Beyond:** Olaparib was the first FDA-approved cancer drug explicitly designed around synthetic lethality [79]. This concept has opened new research avenues, aiming to exploit other synthetic lethal interactions (e.g., ATR inhibitors for ATM-mutant cancers). The success in BRCA breast cancer has spurred development of PARP inhibitors for other HRD tumors (ovarian, pancreatic, prostate) and the exploration of HRD testing as a biomarker across cancers.

- **Tumor Microenvironment Interactions:** The previously mentioned **macrophage study (Wang et al., 2022)** [80] [17] highlights that the efficacy of PARP inhibitors can depend on the immune microenvironment. BRCA-mutant breast tumors seem adept at recruiting **tumor-promoting M2 macrophages** that dampen the effects of therapy. This finding offers an explanation for a clinical observation: **BRCA1 ovarian cancers respond better to PARP inhibitors than BRCA1 breast cancers**, on average [44]. The difference was puzzling given similar HRD biology, but it now appears that **breast cancer's microenvironment confers additional resistance** [81] [45]. As a result, combining PARP inhibitors with drugs that **target TAMs** or **stimulate innate immunity (like STING agonists)** is an active area of translational research. Preclinical models show **STING agonism can reprogram macrophages from M2 to M1, restoring sensitivity to olaparib and unleashing anti-tumor T cell activity** [46] [18]. Such combinations (PARP + STING agonist) may eventually enter trials for BRCA-mutant breast cancer, aiming to achieve deeper and more durable responses akin to those seen in ovarian cancer.

- **Combination with Hormone Therapy:** In ER+ BRCA-mutant breast cancer, an open question is how to integrate olaparib with endocrine therapy. Some clinicians sequence them (e.g., give adjuvant olaparib, then resume endocrine therapy). There was interest in combining PARP inhibitors with endocrine therapy or CDK4/6 inhibitors. However, overlapping myelosuppression with CDK4/6 inhibitors can be problematic, and an attempted combo of talazoparib + dinaciclib (CDK inhibitor) in metastatic disease had considerable toxicity. Generally, in metastatic ER+ BRCA patients, one would

use hormonal therapy until resistance, then switch to PARP inhibitor (as per OlympiAD eligibility requiring prior endocrine). There is also an ongoing trial (OLAPAIR) testing if adding olaparib to an AI in adjuvant therapy for BRCA-mutant ER+ improves outcomes further (given olaparib is only given 1 year, whereas ER therapy is 5+ years).

- **Quality of Life:** Studies have indicated that patients on olaparib maintain **better quality-of-life (QoL)** than those on chemotherapy. In OlympiAD, time to QoL deterioration was longer with olaparib, and patient-reported outcomes favored olaparib (less pain, less worry about side effects, etc.) even though fatigue and nausea were noted, they were manageable [60]. This is clinically relevant: for a young patient with metastatic BRCA breast cancer, taking an oral targeted agent at home is often preferable to frequent IV chemo infusions.

- **PARP Inhibitor Resistance Monitoring:** As resistance mechanisms are uncovered, there is interest in using liquid biopsies (circulating tumor DNA) to monitor for resistance mutations. For example, the emergence of a BRCA reversion mutation in ctDNA could signal impending clinical resistance. This might allow early switching of therapy. There are cases reported where patients on PARPi had new BRCA2 variants appear in blood months before radiologic progression. Such tools are not yet standard but represent a future precision approach.

- **Second-generation PARP inhibitors and Novel Targets:** Not all PARP inhibitors are identical. Olaparib and talazoparib are potent PARP trappers; rucaparib and niraparib also inhibit PARP1/2 but have different pharmacokinetics. Talazoparib is often noted as more potent in trapping PARP1 on DNA (about 100-fold more trapping than olaparib in some assays) [82]. However, in clinical breast cancer practice, olaparib and talazoparib have shown fairly similar efficacy. Newer agents (PARP1-selective inhibitors, or dual PARP/another target inhibitors) are in development to possibly reduce toxicity or overcome resistance. For instance, **AZD5305** is a PARP1-selective inhibitor that might spare PARP2 (hoping to reduce marrow toxicity) and is being tested in trials including BRCA breast cancer. Strategies like **dual PARP–ATR inhibitors** in one molecule are also being explored.

- **Other biomarkers:** Researchers are evaluating if **RAD51 foci formation** assays (a functional readout of HRR in tumor cells) could identify HRD tumors beyond BRCA. A high-throughput immunofluorescence test for RAD51 foci on tumor samples can indicate if HR is functional or not; if not, patient might benefit from PARP inhibitors. This could expand use to some BRCA-wildtype patients who have HR dysfunction for other reasons. Trials like NRG-BRCA in the neoadjuvant setting are looking at this approach.

- **Long-term outcomes:** For metastatic breast cancer, PARP inhibitors are not curative, but they offer meaningful PFS improvement and a bridge to other therapies. For early-stage, the hope is that by eradicating microscopic disease in BRCA carriers, adjuvant olaparib may **cure more patients or at least delay relapses significantly**. The 6-year OlympiA update shows a persistent benefit, and follow-up until 10 years is planned [83] [84]. If the curves stay apart or widen, that suggests some patients are cured by that extra year of PARP inhibition. This is particularly important for BRCA1 TNBC patients, who historically had a high recurrence rate even after aggressive chemo – now many of them are remaining disease-free at 6 years with olaparib's help [53].

- **Cost and Access:** Olaparib is an expensive medication. Cost-effectiveness analyses were borderline in some health systems, but as patents approach expiry in 2028-2030 and with agreements

(AstraZeneca provided discounts to NHS, etc.), access is improving. There is also interest in using cheaper **"PARP inhibitor-like" strategies** in resource-limited settings, but nothing replicates it exactly.

- **Psychosocial aspect:** Knowing one carries a BRCA mutation can be devastating, but the availability of a targeted therapy like olaparib is somewhat empowering – patients feel there is a tailor-made treatment for their cancer. Many patients on adjuvant olaparib express relief that they are "doing something extra" to prevent recurrence beyond standard chemo. Still, they must be counseled on side effects and the importance of adherence (twice-daily pills for a year).

In conclusion, **olaparib in breast cancer represents a success of translating cancer biology (DNA repair defects) into an effective therapy**. It necessitates genomic testing and subtype stratification to identify who benefits. When used in the right subset, it significantly improves outcomes with a manageable safety profile. Ongoing research aims to extend its benefits to broader groups (through combinations or new biomarkers) and to overcome resistance mechanisms, so that this therapy can remain effective throughout a patient's course of disease.

Sources: OlympiAD & OlympiA trial results [3] [4]; BC Cancer Drug Manual [1]; DrugBank [85] [86]; NCCN and ESMO guidelines [10] [51]; Mechanistic studies and reviews [2] [17] [24].

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