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Drug Summary

Alpelisib (BYL719, brand name **Piqray®**) is an orally administered small-molecule inhibitor of phosphatidylinositol-3-kinase alpha (PI3Kα) approved for certain breast cancers [1] [2]. In May 2019, it became the first PI3K inhibitor authorized for **hormone receptor-positive (HR+)/HER2-negative advanced breast cancer** with a **PIK3CA** mutation [1]. Its indication (in both the US and EU) is in combination with fulvestrant for postmenopausal women and men who have HR+/HER2–, **PIK3CA-mutated** advanced or metastatic breast cancer that has progressed on or after endocrine therapy [3] [4]. This precision use targets the ~40% of HR+/HER2– breast cancers that harbor activating PIK3CA mutations [5]. Alpelisib is given orally (300 mg daily with food) and treatment continues until disease progression or unacceptable toxicity [6] [7]. It is marketed by Novartis under the trade name Piqray for oncology, and as **Vijoice®** for non-oncologic PIK3CA-related overgrowth syndrome (PROS) [8] [9], reflecting its PI3Kα-targeted mechanism across different conditions.

Mechanistically, **alpelisib selectively inhibits the p110α catalytic subunit of PI3K** (encoded by *PIK3CA*) [2]. In breast cancers with *PIK3CA* gain-of-function mutations, PI3Kα signaling is hyper-activated, driving downstream AKT/mTOR pathways that promote cell proliferation and survival [10]. By blocking abnormal PI3Kα, alpelisib suppresses these oncogenic signals, leading to reduced tumor cell growth and induced cell-cycle arrest in G_0/G_1 [11] [12]. Its antitumor activity is most pronounced in tumors with *PIK3CA* mutations [13], consistent with clinical trial data showing benefit largely confined to that genomic subgroup [14]. Importantly, in estrogen receptor-positive (ER+) breast cancer cells, PI3Kα inhibition causes a compensatory upregulation of ER-dependent transcription [15]. This feedback loop provides the rationale for combining alpelisib with endocrine therapy (fulvestrant): co-treatment yields synergistic anti-tumor effects and overcomes adaptive ER re-activation [15]. Alpelisib thus exploits a **synthetic lethality** between PI3Kα-pathway dependence and ER signaling in *PIK3CA*-mutant, ER+ breast cancers, improving progression-free survival in this subset when added to hormonal therapy [14]. While its approved use is currently in HR+/HER2– disease, *PIK3CA* mutations also occur (at lower frequency) in HER2-positive (~30%) and triple-negative (~15%) breast cancers [5]. Ongoing research is evaluating PI3K–AKT pathway inhibitors in those subtypes, though alpelisib is not yet standard outside the HR+ context [16] [17].

Identifiers & Synonyms

- **DrugBank ID:** DB12015 [18]
- **ChEMBL ID:** CHEMBL2396661 [19]
- **Synonyms/Code Names:** BYL 719, BYL-719, NVP-BYL719 [20] (development codes used during clinical development)
- **Brand/Trade Names: Piqray®** (for breast cancer indication) and **Vijoice®** (for PIK3CA-related overgrowth syndromes) [9].

Alpelisib may be referred to in literature by its research codes (e.g. NVP-BYL719) or its class description as a "PI3Kα inhibitor." It is classified as a small-molecule targeted anticancer drug (ATC code L01EM03) and is typically formulated as film-coated oral tablets [21].

Mechanism of Action (Breast Cancer Context)

Alpelisib's **mechanism of action** in breast cancer is to potently and selectively inhibit the **PI3K–AKT signaling pathway** at its upstream node, PI3Kα [2] [22]. The catalytic p110α subunit of PI3K (gene *PIK3CA*) is frequently mutated in breast tumors (hotspots in exons 9 and 20, e.g. E545K, H1047R), resulting in constitutive PI3K pathway activation [10]. By binding to the ATP pocket of p110α, alpelisib **blocks the production of PIP₃**, thereby preventing AKT phosphorylation and downstream signaling to mTOR and other effectors [11]. In *PIK3CA*-mutant breast cancer cell lines, alpelisib reduces AKT activation and induces tumor cell death or arrest [11]. In vivo xenograft models of breast cancer, including those with *PIK3CA* mutations, showed significant tumor growth inhibition when treated with alpelisib [23]. This **on-target blockade of PI3K/AKT** signaling halts the proliferative and survival signals that drive tumor progression [10] [13].

In **ER-positive (Luminal) breast cancers**, PI3K and estrogen receptor (ER) pathways exhibit bidirectional crosstalk. Alpelisib-mediated PI3Kα inhibition leads to upregulation of ER signaling at the transcriptional level (a feedback response) [15]. As a result, combining alpelisib with an ER antagonist (fulvestrant) produces enhanced efficacy: alpelisib abrogates PI3K-driven resistance to endocrine therapy, while fulvestrant blocks the compensatory ER activation [15]. This combination yields greater anti-tumor activity than either agent alone in ER+/*PIK3CA* mutant models [15] and in clinical trials (e.g. significantly improved PFS in *PIK3CA*-mutant, HR+ metastatic breast cancer) [14]. Thus, the **mechanism in HR+ breast cancer** is subtype-specific: alpelisib suppresses the PI3K–AKT growth pathway that luminal tumors often become reliant on (especially after endocrine resistance), and fulvestrant concurrently shuts down ER-driven transcription that PI3K inhibition can paradoxically stimulate [15].

In other breast cancer subtypes, the MoA is similarly to inhibit PI3K signaling, though the clinical utility is less established. In **HER2-positive breast cancer**, aberrant PI3K pathway activation (via *PIK3CA* mutation or PTEN loss) can confer resistance to anti-HER2 therapies; accordingly, combining alpelisib with HER2-targeted agents has shown synergistic preclinical activity [24]. In **triple-negative breast cancer (TNBC)**, PI3K pathway alterations (PTEN inactivation or *PIK3CA/AKT1* mutations) occur in ~25% of cases [16] [25]. While alpelisib is not yet standard in TNBC, its mechanism would similarly involve shutting down PI3K–AKT–mTOR signals; trials have instead found that pan-PI3K or AKT inhibitors (e.g. ipatasertib, capivasertib) combined with chemotherapy improve outcomes in pathway-altered TNBC, suggesting the principle of PI3K-pathway blockade is valid in that context [17] [26]. Overall, alpelisib's action is to **selectively target the oncogenic PI3Kα signaling cascade**, leading to growth arrest and apoptosis in breast cancer cells that depend on that pathway – particularly the luminal subtype wherein PI3K and ER pathway co-dependence is exploited for therapeutic benefit [15].

Primary Targets (Human)

PIK3CA (Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha) – Alpelisib's direct target is the p110α isoform of class I PI3K [2]. PI3Kα (gene *PIK3CA*, HGNC:8975) is a lipid kinase that phosphorylates PIP₂ to PIP₃, activating AKT. Alpelisib binds to p110α's ATP-binding site, inhibiting its kinase activity [2] [27]. It has **highest specificity for PI3Kα** over other PI3K isoforms (approximately 50-fold selectivity vs p110β/δ/γ) [28], making *PIK3CA* the primary molecular target.

AKT signaling (indirect) – While not binding AKT directly, alpelisib functionally targets the **AKT/mTOR pathway** by upstream PI3Kα inhibition. This leads to decreased phosphorylation of AKT (gene *AKT1*, HGNC: 391), PRAS40 (*AKT1S1*, HGNC:20384), and downstream effectors. In breast cancer cells, **reduced p-AKT** is a pharmacodynamic marker of alpelisib's target engagement [11]. (AKT is not an **intended** binding target of alpelisib but is a primary downstream **pathway target** affected in humans.)

Estrogen Receptor (ER) – Alpelisib does *not* bind the ER (gene *ESR1*, HGNC:3467) directly, but it **modulates ER activity** via pathway feedback [15]. PI3Kα blockade causes an increase in ER transcriptional output in ER+ breast cancer cells [15]. Because of this, alpelisib's combination with fulvestrant functionally targets the ER signaling axis. In DrugBank, alpelisib is noted as an "ER modulator" in this indirect sense [29]. However, the only **primary biochemical target** of alpelisib in humans is PI3Kα (*PIK3CA*).

Note: Alpelisib's selectivity minimizes off-target interactions; it shows little inhibition of other kinases at therapeutic concentrations. Its **pharmacological target profile** is focused on PI3Kα, which is why it is indicated specifically for tumors driven by *PIK3CA* mutations [1].

Pathways (Overview)

Alpelisib's action in breast cancer intersects several key cellular pathways. Below is an overview of major pathways influenced, with each identified by standard pathway databases and annotated with their relevance (mechanistic link, sensitivity, resistance, or subtype specificity):

- **PI3K–AKT–mTOR Signaling** – *KEGG: hsa04151 (PI3K-Akt signaling pathway)*. **Mechanistically linked:** Alpelisib directly inhibits this pathway's upstream node, PI3Kα, suppressing AKT and mTOR activation [11]. This is the core oncogenic pathway in *PIK3CA*-mutant tumors, and its blockade is the primary driver of alpelisib's anti-tumor effect (pathway downregulated in responders). Inhibition of PI3K–AKT signaling is associated with tumor sensitivity to alpelisib (tumors addicted to this pathway respond best) [10] [13]. Conversely, re-activation of AKT/mTOR signaling (e.g. via alternate PI3K isoforms or loss of PTEN) can mediate drug resistance.

- **Estrogen Receptor Signaling** – *GO:0030520 (estrogen receptor signaling pathway)*. **Mechanistically linked & subtype-specific (HR+):** In ER-positive breast cancers, PI3K and ER pathways are intertwined. Alpelisib's inhibition of PI3Kα triggers a compensatory upregulation of ER-dependent transcription [15]. Thus, ER signaling is an *adaptive pathway* that can limit alpelisib efficacy if unchecked; this underlies the required combination with fulvestrant [15]. ER pathway activity is associated with luminal subtype tumors and is a **sensitivity factor** (presence of functional ER allows effective combination therapy). ER pathway upregulation on PI3K blockade is a unique aspect of HR+ cancers (not observed in ER-negative subtypes), marking this feedback loop as subtype-specific.

- **Receptor Tyrosine Kinase (RTK)/RAS–MAPK Pathway** – *Reactome: R-HSA-1257604 (PI3K cascade with RAS)*. **Resistance-associated:** When PI3K–AKT is inhibited, some tumors compensate via parallel growth pathways like RAS–RAF–MEK–ERK. For instance, relief of feedback inhibition can lead to **MAPK pathway** activation. Preclinical studies suggest that persistent HER2/EGFR or IGF1R–RAS signaling may drive resistance in *PIK3CA*-mutant cancers treated with PI3K inhibitors [30]. Upregulation of RTK/MAPK signaling has been observed in non-responders, indicating this pathway's activation confers relative insensitivity to alpelisib (requiring combination strategies in such cases).

- **Cell Cycle Regulation** – *GO:0045787 (positive regulation of cell cycle)*. **Mechanistically linked (downstream) & sensitivity-associated:** PI3K–AKT signaling promotes cell cycle progression (via Cyclin D–CDK4/6, etc.). Alpelisib's blockade induces G_0/G_1 arrest [12], effectively downregulating proliferation pathways. Sensitive tumors exhibit decreased cell-cycle gene expression and proliferation markers upon PI3Kα inhibition. Conversely, tumors that maintain cell cycle drive (e.g. through cyclin E upregulation or RB loss) may resist alpelisib. This pathway is not unique to a subtype but is a final common effector of PI3K signaling, making it a readout of drug effect (and synthetic lethality target in combination with CDK4/6 inhibitors).

- **Insulin Receptor/Metabolic Signaling** – *Reactome: R-HSA-1643713 (Insulin signaling pathway)*. **Mechanistically linked (on-target metabolic effect):** PI3Kα in normal physiology mediates insulin signaling in liver and muscle. Alpelisib's inhibition of PI3Kα in patients leads to reduced insulin signaling, manifesting as **hyperglycemia** and increased blood insulin levels [31] [32]. While not a cancer pathway per se, this metabolic pathway's disruption is directly related to alpelisib's mechanism and toxicity. It necessitates monitoring and sometimes co-management (e.g. metformin to enhance insulin sensitivity [33]). Tumors with high insulin/IGF1 signaling may also exhibit cross-talk with PI3K; thus, metabolic pathways can indirectly influence tumor sensitivity or resistance (e.g. hyperinsulinemia could drive PI3K-reactivation).

- **Immune Modulation Pathways** – *ImmuneDB: (e.g., PI3K in immune cell activation)*. **Context-dependent:** PI3K signaling in the tumor microenvironment (e.g. in T cells, myeloid cells) can affect anti-tumor immunity. Inhibition of PI3Kα may alter cytokine pathways or immune cell infiltration. While not a primary intended pathway, some studies suggest PI3K inhibitors might modulate **immune pathways** such as IFN-γ signaling or PD-L1 expression (though evidence in human breast cancer is still emerging). Any immune-related pathway changes are under investigation and not yet definitive for alpelisib's clinical use.

Each pathway above is identified by standard databases (KEGG, Reactome, GO) and is annotated with how it relates to alpelisib therapy. Mechanistically, alpelisib's **primary impact** is on the PI3K–AKT–mTOR pathway, and effective treatment leads to its downregulation. Pathways like ER signaling and RTK/MAPK come into play as **feedback or escape routes**, marking sensitivity (ER pathway cooperation) or resistance (alternate pathway activation) mechanisms. Understanding these pathways is crucial for developing combination therapies and biomarkers around alpelisib use.

Upregulated Pathways

Under the pressure of alpelisib therapy or in certain responsive contexts, some pathways become upregulated as compensatory or adaptive changes. All pathway identifiers below correspond to human pathways, and the upregulation is evidenced in responder vs non-responder analyses, drug-exposed models, or subtype-specific settings:

- **Estrogen receptor (ER) signaling (GO:0030520)** – *Upregulated in ER+ tumors upon PI3Kα inhibition.* As noted, blocking PI3K leads to increased ER-driven transcription in breast cancer cells [15]. In responders who are co-treated with fulvestrant, this ER upregulation is pharmacologically countered. However, in the absence of adequate ER blockade, PI3K inhibitor exposure causes a surge in estrogen-responsive gene expression (e.g. *TFF1*, *PGR*), reflecting pathway activation. This is a

feedback upregulation specifically observed in HR+ contexts and necessitates combination therapy [15].

- **HER3/EGFR–RAS–MAPK pathway (Reactome R-HSA-199420)** – *Upregulated in resistant contexts (non-responders).* Preclinical studies show that alpelisib can relieve feedback suppression on receptor tyrosine kinases; as a result, **HER2/HER3 signaling and downstream RAS–ERK** pathway activity may rise in some cells. For instance, increased p-ERK levels have been observed in PI3Kα-inhibited breast cancer models that develop resistance [30]. Clinically, tumors that did not respond to alpelisib sometimes harbor co-activation of MAPK pathway genes, suggesting an **adaptive upregulation**. This pathway up-tick is implicated in **innate or acquired resistance** rather than in those who achieve deep responses (responders usually show sustained suppression of both PI3K and MAPK pathways).

- **SRC–STAT3 Inflammatory Pathway (KEGG: hsa04630 for JAK/STAT)** – *Upregulated in certain drug-exposed resistant models.* In cell lines with acquired resistance to alpelisib (particularly those with PTEN loss), **SRC kinase and STAT1/STAT3 signaling** were found hyperactivated [34]. Transcriptomic profiling of resistant tumors revealed enrichment of inflammatory and adhesion pathways (e.g. β1-integrin/FAK signaling, which converges on SRC/STAT3) [35]. This suggests an upregulation of pro-survival inflammatory pathways in the context of PI3Kα inhibitor exposure. These changes are associated with **non-responder phenotypes**, where despite PI3K blockade, cells survive via alternate signals (e.g. cytokine/JAK-STAT pathways).

- **mTORC2/AKT re-activation (Reactome R-HSA-198203)** – *Upregulated as a bypass in some tumors.* Though alpelisib inhibits p110α, some resistant tumors upregulate the PI3K pathway downstream or via alternate isoforms. For example, **AKT phosphorylation (S473 via mTORC2)** can eventually return in resistant cells. Additionally, if PI3Kβ (PIK3CB) compensates (especially in PTEN-null settings), the PI3K–AKT pathway may be reactivated despite drug. This would appear as an **upregulation of AKT activity** after an initial suppression. Clinically, **PTEN loss** (which shifts PI3K signaling to the β-isoform) has been correlated with lack of maintained PI3Kα inhibition, effectively an upregulated alternate PI3K signaling route in resistant tumors [36].

- **Glycolysis/Glucose metabolism (Hallmark: Glycolysis)** – *Upregulated systemically in patients (as an effect of hyperglycemia) and potentially in tumors.* Alpelisib-induced insulin feedback can increase systemic insulin and glucose levels [31]. High insulin can activate insulin receptor pathways in tumors, potentially upregulating **glucose uptake and glycolytic pathways** in cancer cells. Some patients on alpelisib exhibit metabolic gene signature changes (though this is more of a systemic effect). This pathway's upregulation is managed by interventions like metformin, which are being tested to curb the metabolic side effects [33]. While not a direct mediator of response, changes in metabolic pathways reflect the on-target action of alpelisib and can influence tumor cell energetics.

It's noteworthy that **desired upregulation** (like pro-apoptotic pathways) is part of response too. For instance, in responders, **intrinsic apoptosis pathways** (GO:0008625) may be upregulated as cells undergo cell death. However, such changes are harder to measure clinically. The listed pathways above focus on known adaptive responses. Each pathway is identified by a standard ID and is documented to rise in activity either in laboratory models or clinically, highlighting the complex cellular adjustments during alpelisib therapy. Monitoring or co-targeting these upregulated pathways (e.g. adding an RTK inhibitor to block MAPK upsurge, or using ER blockade for ER upsurge) is a strategy to improve outcomes.

Downregulated Pathways

Alpelisib's therapeutic effect is evidenced by the downregulation of key signaling and cellular processes in responsive tumors. Below are pathways (with human identifiers) that are suppressed in responders, drug-exposed models, or certain subtype contexts as a result of PI3Kα inhibition:

- **PI3K–AKT–mTOR Pathway (KEGG: hsa04151)** – *Robustly downregulated in responders.* This is the primary target pathway, and effective alpelisib treatment leads to a marked decrease in **AKT phosphorylation and mTOR activity** [11]. In tumors that respond, gene expression of PI3K downstream targets (e.g. ribosomal protein S6, 4EBP1 signaling) is reduced, and pathway activity assays confirm suppression. Clinically, responders show reduced **phospho-AKT** in tumor biopsies on-treatment, indicating pathway shutdown. Non-responders, in contrast, often fail to fully suppress this cascade (due to parallel inputs). Thus, PI3K–AKT pathway downregulation is a **pharmacodynamic hallmark of sensitivity**.

- **Cell Proliferation/Cell Cycle (Reactome R-HSA-1640170: Cell cycle checkpoints)** – *Downregulated in treated tumors.* Alpelisib causes G_1 cell cycle arrest and decreased proliferation indices (Ki-67) in breast cancer models [12]. In responders, transcriptional programs driving the cell cycle (E2F targets, G₁-S transition genes) are downregulated, reflecting a halt in cell division. For example, Cyclin D/CDK4 activity is diminished (some patients on alpelisib show tumor shrinkage associated with lowered Ki-67). This **cell-cycle pathway suppression** correlates with clinical benefit. In contrast, tumors that continue to progress may sustain cell cycle gene expression despite PI3K inhibition (sometimes via cyclin E upregulation or loss of RB feedback).

- **Survival/Anti-apoptotic Pathways (Hallmark: Apoptosis – *negative regulation*)** – *Effectively, pro-survival signaling is down.* PI3K signaling upholds anti-apoptotic proteins (like BCL-2, MCL-1). Alpelisib's action tilts the balance toward apoptosis in sensitive cells. Though "apoptosis" is an outcome, we consider the **downregulation of survival pathways** such as NF-κB signaling (GO: 0043124) or BCL-2 pathway. In responders, pro-survival gene expression is reduced, caspase activation occurs, and cells undergo programmed death. While not always measured as a "pathway" in clinical settings, molecular studies show **reduced PI3K-dependent survival signals** in tumors responding to alpelisib, leading to increased cell death.

- **Protein Synthesis (Reactome R-HSA-165159: mTOR signaling)** – *Downregulated via mTORC1 inhibition.* PI3K–AKT drives mTORC1, which in turn drives cap-dependent translation. Alpelisib's inhibition of this axis leads to decreased phosphorylation of S6 ribosomal protein and 4EBP1 [11], effectively dampening global protein synthesis. This is a downstream metabolic pathway whose suppression is part of the anti-proliferative effect. In responders' tumors, one can detect reduced activity of mTOR-regulated translation machinery. This **translational downregulation** contributes to growth arrest and is a mechanistic consequence of PI3Kα blockade.

- **DNA Repair Pathways (GO:0006281)** – *Potentially downregulated in some settings.* There is evidence that PI3K signaling interfaces with DNA damage repair (via AKT's effects on ATM/ATR). Some studies suggest that PI3K inhibition can reduce the expression of BRCA1/2 or homologous recombination genes, making cells more prone to DNA damage (or exploiting a synthetic lethal interaction with PARP inhibitors). While not a primary, universal effect, certain gene sets related to DNA repair were

found downregulated in PI3K-inhibited cells, especially when combined with other therapies [37]. This implies that, in some contexts, **DNA repair pathways** may be suppressed (or at least, cells are less able to mount repair), contributing to cell death. This is being explored by combining alpelisib with DNA-damaging agents.

- **PI3K Feedback Regulators (ImmuneDB or GO terms for negative regulation of PI3K)** – *Enhanced negative feedback leads to pathway downregulation.* Upon chronic PI3Kα inhibition, cells sometimes upregulate negative regulators like PTEN or INPP4B (in an attempt to restore equilibrium). While this is an adaptive mechanism by the cell, from a pathway perspective it means further dampening of PI3K output. Thus, **enhanced expression of PI3K pathway suppressors** can be observed, which is essentially the pathway self-downregulating. This has been noted in some prolonged treatment contexts as tumors undergo metabolic rewiring.

In summary, effective alpelisib therapy in breast cancer is characterized by the **downregulation** of the PI3K–AKT–mTOR growth pathway and its downstream processes (proliferation, protein synthesis, survival signaling). The pathway IDs above correspond to these processes that are turned **off or diminished** in responders. By contrast, tumors that fail to downregulate these pathways (due to alternative route activations) are those that show resistance. Monitoring these pathway activities in clinical trials (e.g. pAKT levels, Ki-67) has corroborated that their suppression correlates with better outcomes [14].

Sensitivity Mechanisms

Several molecular and pathway-based factors in human breast cancers have been linked to **heightened sensitivity** to alpelisib. These markers indicate contexts in which tumors are more likely to respond (often in a subtype-specific manner). Key sensitivity mechanisms include:

- **Activating *PIK3CA* Mutations:** The presence of a *PIK3CA* mutation is the fundamental predictive biomarker for alpelisib sensitivity [3]. Tumors harboring hotspot mutations in *PIK3CA* (e.g. E545K, H1047R) exhibit dependence on PI3Kα signaling, so inhibiting that target yields significant anti-tumor effects [10] [13]. Clinically, the benefit of alpelisib + fulvestrant was confined to patients with *PIK3CA*-mutant cancers (no PFS advantage in *PIK3CA* wild-type cohort) [14]. Thus, **PIK3CA mutation (especially in exons 9 or 20)** is a requisite for sensitivity and is mandated in patient selection [3]. It reflects oncogene addiction to PI3Kα.

- **HR+ (Luminal) Subtype with ER Dependence:** Within *PIK3CA*-mutant cases, **ER-positive/HER2-negative** tumors are particularly sensitive because of the dual dependency on PI3K and estrogen signaling. Alpelisib exploits this by synergizing with endocrine therapy [15]. Hormone receptor positivity is required for the approved indication and is a context where alpelisib's impact is maximized (due to the combination strategy). Tumors that are strongly ER-driven (high ER expression, wild-type ESR1 prior to therapy) respond well, as they rely on PI3K for resistance to hormonal therapy and can be resensitized by adding alpelisib [14]. In contrast, ER-negative *PIK3CA*-mutant tumors (e.g. some TNBC) have shown more modest responses in trials, highlighting luminal context as a sensitivity mechanism.

- **Lack of Redundant PI3K Pathway Activations:** Tumors that do *not* have aberrations in parallel growth pathways tend to be more sensitive. For example, **absence of RAS/RAF mutations** or

activated HER2 signaling correlates with better PI3K inhibitor efficacy, because the PI3K–AKT pathway can be singularly targeted. If a tumor has an active RAS-MAPK pathway or multiple driver pathways, it might be less dependent on PI3K alone. Similarly, tumors with **intact PTEN** (and thus full reliance on mutant PI3Kα rather than alternative PI3Kβ activity) should be more sensitive. In HR+ breast cancers, concurrent **AKT1 E17K mutations** are rare but if present may also predict some sensitivity to PI3K or AKT inhibitors (as they further activate the pathway) – though data are limited, NCCN notes testing for AKT1/PTEN in absence of *PIK3CA* [38].

- **Synthetic Lethality with Cell Cycle Dependence:** Preclinical studies indicate that *PIK3CA*-mutant cells have a particular vulnerability to CDK4/6 inhibition and vice versa. The success of combining alpelisib with fulvestrant after CDK4/6 inhibitor progression suggests that tumors which initially responded to CDK4/6 inhibitors and then progressed via PI3K upregulation are sensitive to PI3K inhibition (a form of adaptive sensitivity) [39]. Thus a "CDK4/6i-resistant, *PIK3CA*-mutant" state defines a population sensitized to alpelisib (since the tumor may have become more PI3K-addicted as an escape from CDK4/6 blockade). This is more of a clinical scenario than a static biomarker, but it underlies guideline recommendations to use alpelisib after CDK4/6 inhibitor failure in *PIK3CA*-mutant HR+ disease [40].

- **Dependence on Insulin/IGF Signaling:** Tumors that are metabolically reliant on the insulin-like growth factor receptor (IGF1R)–PI3K axis could be especially sensitive to PI3Kα inhibition. While difficult to measure clinically, laboratory models show that cells with overactive IGF1R signaling (feeding into PI3Kα) undergo apoptosis with PI3Kα inhibitor treatment. Conversely, if a tumor uses alternate glucose metabolism pathways, it might be less sensitive. The metabolic effects of alpelisib (hyperglycemia) underscore how tightly linked PI3Kα is to insulin/IGF signaling [41] [31]; thus, cancers heavily utilizing that axis (like some luminal cancers with obesity/insulinemia factors) might respond well – though this remains an area of investigation.

- **Co-existing Genomic Context:** Preliminary data suggest some co-mutations can modulate sensitivity. For example, **MAP3K1 mutations** (found in some ER+ cancers) correlate with less aggressive, highly endocrine-dependent tumors, which might remain more PI3K-dependent (thus sensitive). Also, tumors without TP53 mutations (often more genomically stable, luminal A type) might have better responses, as observed in some correlative analyses. These correlations are not fully validated, but point to the idea that a tumor's overall genomic profile (luminal A vs B, presence of *ESR1* mutation, etc.) can influence the degree of sensitivity to alpelisib.

In summary, **the clearest sensitivity mechanism is the presence of a PIK3CA mutation in an ER-positive breast cancer** [3]. That scenario defines the approved population, with clinical data showing a significant PFS gain [14]. Within that group, factors like intact PTEN, absence of parallel oncogenes, and prior CDK4/6 inhibitor exposure (which primes tumors to be more PI3K-dependent) further refine who benefits most. These mechanisms are all **human clinical or translational findings** underpinning therapy selection: e.g., *PIK3CA* genotyping is now standard of care per guidelines [39] to identify the sensitive subset for alpelisib.

Resistance Mechanisms

Despite initial responses, many breast tumors develop **resistance** to alpelisib. Research (in patients and models) has elucidated several mechanisms of resistance in human cancers, including both acquired genomic alterations and adaptive pathway reprogramming. Key proven resistance mechanisms are:

- **Loss of PTEN Function:** Inactivating alterations in the tumor suppressor *PTEN* (phosphatase that negatively regulates PI3K) are a **recurrent mechanism of resistance to PI3Kα inhibition** [36]. Clinical sequencing of patients who progressed on alpelisib has shown emergent PTEN mutations or deletions in ~25% of resistant cases [36]. PTEN loss causes hyperactivation of the PI3K pathway via the *PIK3CB* (PI3Kβ) isoform, which alpelisib does not effectively inhibit [30]. Essentially, tumors bypass the drug's isoform specificity by routing PI3K signaling through p110β when PTEN is absent. This can restore AKT signaling despite continued alpelisib, leading to treatment failure. PTEN loss can be pre-existing or selected by therapy; it has been associated with **both primary and acquired resistance** in HR+ breast cancer [36]. Clinically, PTEN-null/*PIK3CA*-mutant cancers derive less benefit from alpelisib, and concurrent PTEN mutation was a common feature in non-responders. This mechanism is subtype-agnostic (it can occur in luminal or TNBC) but is especially relevant in PI3Kα-selective inhibitor therapy due to isoform compensation.

- **ESR1 Mutations (Estrogen Receptor Alpha)**: *ESR1* ligand-binding domain mutations (e.g. Y537S, D538G) often emerge in ER+ metastatic breast cancers after endocrine therapy and were also observed to **expand under alpelisib–fulvestrant treatment** [42]. These mutations confer constitutive ER activity and partial resistance to ER downregulators. In the context of alpelisib, an ESR1 mutant clone can drive tumor growth even if PI3K is inhibited, reducing dependence on the PI3K pathway. Razavi *et al.* (2020) showed *ESR1* mutations increased in allele frequency during progression on alpelisib + aromatase inhibitor therapy [42]. This suggests that tumors circumvent the need for PI3K-driven estrogen receptor crosstalk by activating ER through mutation. As a result, even with fulvestrant present, ER signaling may persist at a level sufficient to support tumor survival, rendering the combination less effective. Thus, **ESR1 mutation is a known resistance mechanism**, particularly in luminal cancers, indicating that effective ER blockade is compromised. Patients with pre-existing ESR1 mutations have shorter benefit from alpelisib–endocrine therapy, and those mutations often increase upon progression [36]. This is subtype-specific (only ER+ cancers) and highlights the need to consider next-line therapies (like SERDs or AKT inhibitors) when ESR1-mediated resistance occurs.

- **Activating Mutations in PI3K Pathway Nodes (Secondary Mutations):** Tumors can acquire **secondary mutations in PIK3CA** or downstream kinases that render alpelisib ineffective. For example, a mutation in *PIK3CA*'s drug-binding site (analogous to gatekeeper mutations in other kinases) could prevent alpelisib from binding – though none have yet been conclusively identified in patients, it remains a theoretical possibility. More commonly, mutations in *AKT1* (like AKT1 E17K) or upregulation of *PIK3CG* (PI3Kγ) in the microenvironment could sustain PI3K signaling independently of p110α. In other cancers, resistance to PI3K inhibitors has been linked to PIK3CA amplification or RAS mutations; in breast cancer, one study noted a case of acquired KRAS mutation in an alpelisib-resistant tumor [43]. Generally, any mutation reactivating the PI3K–AKT pathway downstream of the drug's target could confer resistance.

- **Upregulation of Compensatory Pathways (Network Rewiring):** A major mode of resistance is **adaptive rewiring of signaling networks**. Tumors exposed to alpelisib may upregulate other survival pathways, diminishing reliance on PI3K. Notably:

- **MAPK/MEK Pathway Activation:** As PI3K–AKT and RAS–MAPK pathways often exhibit cross-talk, suppression of one can lead to increased signaling through the other. Resistant biopsies have shown heightened phospho-ERK and MAPK pathway gene signatures, suggesting a shift to RAS–RAF–MEK–ERK drive [30]. Clinically, combination of PI3K + MEK inhibitors was explored to overcome this.
- **HER2/HER3 and IGF1R Feedback:** Alpelisib can relieve feedback inhibition on receptor tyrosine kinases. Many resistant tumors show **increased HER3 (ERBB3) or IGF1R expression** and activation. This reactivates downstream PI3K (through p110β or other isoforms) and MAPK, bypassing the need for p110α. For instance, HER2+ cells might respond transiently then use HER3 to reactivate PI3K. Similarly, **insulin feedback** due to hyperglycemia can activate InsR/IGF1R on tumor cells, potentially mitigating PI3Kα blockade – a unique clinical consideration wherein a side-effect (high insulin) may paradoxically feed the tumor.

- **Cell Cycle and Cyclin Dependencies:** Some tumors upregulate cyclin-CDK activity to overcome growth arrest. Activation of CDK2/cyclin E or loss of RB1 can confer resistance, as cells proliferate without reliance on PI3K signaling. In the SOLAR-1 study, prior CDK4/6 inhibitor exposure (which selects for cyclin E or RB alterations in some cases) was associated with shorter benefit from alpelisib in certain cohorts [44]. This suggests **cell-cycle alterations** can mediate resistance to the cytostatic effects of PI3K inhibition.

- **Phenotypic Shift and Tumor Heterogeneity:** Resistance can also emerge via changes in tumor cell identity:

- **Epithelial–Mesenchymal Transition (EMT):** Chronic PI3K inhibition pressure can select for cells with a more mesenchymal, stem-like phenotype which rely less on PI3K signaling. A study indicated alpelisib could inhibit breast cancer stemness and EMT traits [45]; the corollary is that if subclones undergo EMT, they may activate alternative pathways (like FGFR or SRC) and become drug-resistant.

- **Clonal Selection:** Most metastatic breast cancers are heterogeneous. Under therapy, clones with pre-existing resistance features (like a co-occurring *PIK3CA* wild-type clone or a KRAS mutant subclone) may outgrow. For example, if only a subset of tumor cells had *PIK3CA* mutation and others did not, the latter will be less affected by alpelisib and could dominate the tumor population on treatment, appearing as resistance.

- **Pharmacologic Resistance (ADME-related):** Though not tumor-intrinsic, issues like poor drug absorption (perhaps due to patient factors or interactions) or suboptimal dosing due to toxicity can lead to "clinical resistance." If a patient cannot tolerate full-dose alpelisib and requires dose reductions, drug exposure may be insufficient to suppress PI3K signaling fully, and the cancer progresses – effectively a resistance due to inadequate drug levels. This is mitigated by managing side effects (e.g. hyperglycemia, rash) proactively.

Proven clinical mechanisms include PTEN loss and ESR1 mutation, evidenced by patient samples [36]. These are particularly important in HR+ disease: PTEN loss tends to occur in more aggressive, often ER-low tumors, whereas ESR1 mutations occur in strongly ER-driven tumors as a late resistance. Both were observed in patients progressing on alpelisib. Understanding these resistance mechanisms guides the

development of next-line therapies: for example, trials of combined PI3Kα + PI3Kβ inhibition for PTEN-null tumors, or adding novel SERDs or degraders for ESR1-mutant progression. Additionally, the approval of AKT inhibitors (like capivasertib) provides an alternate strategy for some resistant tumors (since capivasertib can target the pathway downstream and has shown efficacy even in some *PIK3CA*-wild, PTEN-null cases).

In practice, **molecular profiling at progression** is recommended. If an ESR1 mutation arises, switching to an ER pathway modulator that can tackle that mutation (or to chemotherapy) may be indicated. If no clear new mutation is found, one assumes adaptive pathway activation and might consider clinical trials of combinations (e.g. adding an mTOR inhibitor or a MAPK inhibitor). Importantly, these resistance mechanisms underscore that single-agent PI3Kα inhibition is not curative – combination approaches and sequential therapies are needed to address the evolving tumor biology.

Contraindications and Safety

Contraindications: Alpelisib is contraindicated in patients with a history of severe hypersensitivity to it or any of its formulation components [46]. This includes any prior anaphylaxis or severe cutaneous reactions attributed to alpelisib. There are no other absolute contraindications listed in the FDA and EMA labels besides hypersensitivity [46]. However, due to its mechanism, **pregnancy** is effectively a contraindication: based on animal studies and mechanism of action, alpelisib can cause fetal harm, so it should **not be used in pregnant women** (and pregnancy status must be verified before initiation) [47]. Breastfeeding is also advised against during and for 1 week after alpelisib treatment, as the risk to infants is unknown [48] [49].

Population Restrictions: Alpelisib is approved for adults (in breast cancer). Its safety and efficacy in pediatric cancer patients have not been established (the pediatric approval for PROS is a separate context). It should be used only in patients with the biomarker-defined indication (*PIK3CA*-mutant, HR+ breast cancer) [3] – other patients would not be expected to benefit and hence it is "contraindicated" from a precision medicine standpoint if the tumor is *PIK3CA* wild-type. There are no specific race or renal function contraindications, but caution is noted in certain groups: - **Diabetic patients:** Since alpelisib causes hyperglycemia, patients with uncontrolled diabetes mellitus are at high risk for serious glucose elevations. While not an absolute contraindication, these patients require careful optimization of blood sugar and monitoring; severe uncontrolled diabetes could be considered a **relative contraindication** until improved, due to risk of diabetic ketoacidosis on alpelisib [50]. - **Severe hepatic impairment:** There is limited data in patients with Child-Pugh C liver impairment. The EMA label likely advises caution or avoidance in severe hepatic impairment (since metabolism could be affected), although no formal contraindication is declared. - **History of severe cutaneous reactions:** Patients who have experienced Stevens-Johnson syndrome (SJS), erythema multiforme, or drug reaction with eosinophilia and systemic symptoms (DRESS) on any PI3K inhibitor may not be candidates for alpelisib. The product information carries strong warnings about rare cases of SJS (0.4%) and DRESS reported with alpelisib [51]. If a patient had such a reaction, rechallenge is contraindicated.

Safety Profile and Precautions: The main safety concerns with alpelisib are related to on-target effects on metabolic pathways and immune-related skin effects: - **Hyperglycemia:** High blood sugar is the dose-limiting toxicity. In SOLAR-1, 79% of patients on alpelisib experienced hyperglycemia (Grade $\geq$3 in 36–39%) versus hyperglycemia in ~1% on placebo [52]. This stems from PI3Kα's role in insulin signaling, causing insulin resistance and increased hepatic gluconeogenesis [31]. Patients often require anti-hyperglycemic medications (metformin, insulin, etc.), and in some cases hyperglycemia can progress to ketoacidosis.

Contraindication-wise, there's no absolute rule against treating a diabetic patient, but the presence of uncontrolled diabetes would delay therapy initiation until control is achieved. Guidelines (e.g. by FDA/EMA) recommend not starting alpelisib if baseline fasting glucose is excessively high (>250–300 mg/dL) until improved [50]. Blood glucose must be monitored frequently, and if Grade 3 hyperglycemia occurs, hold drug until improved and consider dose reduction [50]. Co-administration of medications like metformin at therapy start has been used to mitigate this risk [33]. - **Dermatologic toxicity (Rash):** Rash (generally maculopapular or acneiform) is very common (~**52%** of patients, with ~20% Grade 3) [53]. Severe cutaneous reactions including SJS/TEN have been reported rarely [51]. Patients should be counseled on rash, and prophylactic antihistamines can be given to reduce incidence/severity [54]. Any sign of severe mucocutaneous reaction mandates permanent discontinuation (this is one of the few instances requiring stopping drug, hence effectively a contraindication to continue if SJS/TEN is confirmed) [51]. - **GI toxicity:** Diarrhea, nausea, vomiting, and mucositis are common (diarrhea in ~58%, with ~7–9% Grade 3) [55]. Severe diarrhea can cause dehydration and acute kidney injury [50]. Patients should proactively manage diarrhea (antidiarrheals, hydration). If Grade ≥3 diarrhea occurs, interrupt alpelisib until recovery and dose-reduce. There is no outright contraindication for patients with mild GI issues, but those with inflammatory bowel disease might be at higher risk for severe diarrhea (so caution is advised). - **Other notable risks:** - **Pancreatic enzyme elevations and rare pancreatitis:** In trials, ~7% had Grade 3 hypertriglyceridemia and some had elevated lipase [55]. A small number of pancreatitis cases occurred. Use in patients with active pancreatitis is contraindicated until resolved. - **Hepatotoxicity:** Elevated liver enzymes occurred (ALT/AST Grade ≥3 ~5–6%). Liver function should be monitored. Active hepatic disease is a caution. - **Renal:** Elevations in creatinine (~67% any grade) were seen [56], likely due to dehydration or hyperglycemia effects. Acute kidney injury can result from severe hyperglycemia or diarrhea – thus, ensure adequate hydration. Severe renal impairment (CrCl <30) – no specific contraindication, but since only ~2% is renally excreted unchanged [57], dosing is not changed; still, the patient's overall condition (e.g. if on dialysis) should be considered. - **Infections:** As a class effect, PI3K inhibitors (especially isoform-nonspecific ones) have immune suppression risk. Alpelisib in combination with fulvestrant did not show a large infection signal, but some neutropenia and lymphopenia occurred (lymphocytes decreased in ~52%, mostly mild) [55]. There is no formal contraindication, but patients with active serious infections should probably defer therapy until resolved. - **Drug Interactions:** Alpelisib is metabolized partly by CYP3A4 and can be affected by CYP3A4 inducers/inhibitors [58]. Strong CYP3A4 **inducers** (e.g. rifampin, phenytoin) may significantly reduce alpelisib levels and should be avoided [58] – if a patient requires such drugs, use of alpelisib may be impractical (alternatives should be sought). BCRP transporter inhibitors (e.g. cyclosporine) can raise alpelisib concentrations and risk toxicity [59]. On the flip side, alpelisib can reduce plasma concentrations of CYP2C9 substrates like warfarin (by inducing metabolism) [60], so caution with co-administered narrow-index drugs. While not "contraindicated" per se, these interactions warrant close monitoring or avoiding certain combinations. For instance, patients on warfarin should either be switched to a non-CYP2C9 anticoagulant or have frequent INR checks [60]. - **Concurrent therapy restrictions:** Since alpelisib is given with fulvestrant, ensure no contraindication to fulvestrant (pregnancy, bleeding disorders, etc.). Combination with other targeted therapies is being studied but not standard; outside trials, adding other potent drugs could increase toxicity.

Guideline & Regulatory Safety Notes: The FDA label carries a **black box warning for severe hyperglycemia** (for some class PI3K inhibitors, though Piqray's label highlights warnings rather than a formal boxed warning). EMA labels similarly emphasize monitoring blood glucose and rash. Both FDA and EMA documentation instruct to permanently discontinue alpelisib for Grade 4 hyperglycemia, any grade 4 rash, evidence of SJS/TEN, or Grade 3 pneumonitis [61]. There is no indication that alpelisib prolongs QT

(studies did not show a large QTc effect) [62], which is one less concern compared to some other oncology drugs.

In summary, **contraindications** are limited (hypersensitivity, pregnancy), but **precautions are extensive**. Patients must be carefully selected and managed: those with a history of severe reactions or uncontrolled comorbidities need optimization or may not be candidates. Regulatory agencies (FDA, EMA, PMDA) and NCCN/ESMO guidelines all underscore the need for metabolic monitoring and rash prophylaxis [63] [54]. Education on early toxicity signs (excess thirst/urination for hyperglycemia, skin lesions for rash, etc.) is critical for safe use. With appropriate safety measures, alpelisib's side effects are manageable for most patients and the drug can be administered long-term, but clinicians must be vigilant to adhere to dose modification guidance for toxicities [61].

Trial and Guideline Context

Clinical Trials: The pivotal trial establishing alpelisib's role is the Phase III **SOLAR-1** study (NCT02437318). SOLAR-1 enrolled 572 patients with HR+/HER2– advanced breast cancer after prior endocrine therapy; 341 had tumors with *PIK3CA* mutations [64]. In that *PIK3CA*-mutant cohort, adding alpelisib to fulvestrant significantly improved **progression-free survival (PFS)**: median PFS 11.0 months vs 5.7 months with placebo + fulvestrant (HR 0.65, p<0.001) [14]. This translated to a 35% reduction in risk of progression [14]. Objective response rates roughly doubled (26.6% vs 12.8%) [14]. Importantly, in the *PIK3CA wild-type* cohort, there was no PFS benefit (median ~7.4 vs 5.6 months, HR ~0.85, not significant) [65]. These results, published by André *et al.* (2019, *NEJM*), led to regulatory approvals in 2019 [66]. Final overall survival (OS) analysis did not show a statistically significant OS prolongation in the overall mutant cohort, though a numerical 7.9-month OS increase was noted [67]. Subgroup analysis suggested OS benefit in patients who had prior CDK4/6 inhibitor exposure was limited, emphasizing line-of-therapy context.

Following SOLAR-1, the single-arm Phase II **BYLieve** trial (NCT03056755) was conducted to evaluate alpelisib in more pragmatic settings – specifically in patients who had progressed on a CDK4/6 inhibitor plus endocrine therapy. BYLieve had three cohorts; Cohort A (whose disease progressed on a CDK4/6 inhibitor + aromatase inhibitor) is particularly relevant. BYLieve met its primary endpoint: >30% of patients were alive without progression at 6 months (actual 50.4%, 6-month PFS ~5.7 months) [68], demonstrating that **alpelisib + fulvestrant retains clinical activity after CDK4/6 inhibitor failure**. This supported sequencing alpelisib after CDK4/6-based regimens, an approach later reflected in guidelines. BYLieve also reinforced the safety profile in a post-CDK4/6 population and suggested no new signals. Another noteworthy trial is the Phase Ib **FERGI** and **SANDPIPER** trials (with taselisib, another PI3K inhibitor) which, despite showing PFS gains, had toxicity issues. Alpelisib's favorable risk-benefit in SOLAR-1 made it the agent to enter practice.

In HER2-positive breast cancer, trials like **PIK3CA-mutated HER2+** (e.g., NCT04208178) are investigating alpelisib added to HER2 blockade for patients with *PIK3CA* mutations, given preclinical synergy. For **triple-negative** disease, as mentioned, PI3K inhibitors have been less successful; instead AKT inhibitors (LOTUS trial with ipatasertib, and CAPItello-290 with capivasertib) showed improved PFS in metastatic TNBC with pathway mutations [17]. Alpelisib is being tested in subsets of TNBC (e.g., in combination with nab-paclitaxel for *PIK3CA*-altered TNBC in a sub-study of NCT03368760), but no practice-changing data yet.

Guideline Placement: International guidelines have rapidly incorporated alpelisib for HR+ advanced breast cancer: - The U.S. **NCCN Guidelines** (National Comprehensive Cancer Network) for Breast Cancer include

alpelisib + fulvestrant as a category 1 recommendation for **second-line therapy** in postmenopausal HR+/HER2– metastatic breast cancer that harbors a *PIK3CA* mutation (typically determined via genomic testing of tumor or circulating DNA) [39]. NCCN recommends *PIK3CA* mutation testing as part of initial metastatic workup, or at least at time of progression on first-line endocrine therapy [69]. In 2019, after FDA approval, NCCN placed alpelisib as an option after progression on an AI ± CDK4/6 inhibitor (the most common first-line for HR+ MBC) [70]. If a patient has a known *PIK3CA* mutation and progresses on endocrine therapy (especially if a CDK4/6 inhibitor was used), NCCN endorses using alpelisib + fulvestrant in the next line of treatment [38]. The NCCN Patient Guidelines explicitly note alpelisib (Piqray) as a targeted therapy for tumors with *PIK3CA* mutations, alongside mentioning the newer AKT inhibitor capivasertib for AKT1 or PTEN mutations in trials [38]. NCCN also provides management guidelines for hyperglycemia and rash when using alpelisib.

- The European **ESMO Clinical Practice Guidelines** and ABC (Advanced Breast Cancer) Consensus also recommend alpelisib + fulvestrant for *PIK3CA*-mutated, ER+ advanced breast cancer after prior endocrine therapy. The ESO-ESMO 5th International Consensus (ABC5, 2020) stated that if available, patients should be tested for *PIK3CA* mutations (in tumor tissue or ctDNA) and, if mutant, offered alpelisib with endocrine therapy after progression [71]. The ESMO guidelines assign an "ESCAT I-A" level of evidence to *PIK3CA* as a target and note a modest ESMO-MCBS (Magnitude of Clinical Benefit) score (a score of 3 or 4 out of 5) for alpelisib–fulvestrant, reflecting a meaningful PFS benefit [72]. In 2023, with new data, ESMO's Living Guidelines reiterated that **fulvestrant + alpelisib is an option after CDK4/6 inhibitor failure** in *PIK3CA*-mutant cases [73]. They also discuss emerging alternatives like capivasertib + fulvestrant (from CAPItello-291 trial) which showed PFS benefit even in *PIK3CA* wild-type, but until approval, alpelisib remains the standard for *PIK3CA*-mutant patients.

- **ASCO Guidelines:** ASCO's 2021 guideline on endocrine therapy for metastatic HR+ breast cancer recommends offering a PI3K inhibitor (alpelisib) + fulvestrant to postmenopausal patients with *PIK3CA*-mutated, HR+/HER2– breast cancer who have progressed on an AI (with or without CDK4/6 inhibitor) [39]. This is based on SOLAR-1. ASCO notes the need for FDA-approved companion diagnostic testing for *PIK3CA*. They also mention managing toxicities aggressively and that patient selection is key.

- **Regional Guidelines:** In the UK, **NICE** (National Institute for Health and Care Excellence) initially did not recommend alpelisib due to cost-effectiveness concerns, but subsequently, after a commercial arrangement, NICE **TA816 (Aug 2022)** approved alpelisib + fulvestrant for **PIK3CA-mutated, HR+/HER2– advanced breast cancer after ≥1 line of endocrine therapy including a CDK4/6 inhibitor** [74]. NICE specifically restricts use to those whose disease progressed after an aromatase inhibitor plus a CDK4/6 inhibitor (reflecting BYLieve population) [74]. This narrower positioning was due to cost and to avoid overlap with first-line CDK4/6 inhibitor usage. NICE acknowledged it as a life-extending therapy at end-of-life criteria [75]. Similarly, Canada (pCODR) and Australia (PBS) have approved it in this niche. The **ABC (Advanced Breast Cancer) international consensus** also endorses its use in second line for *PIK3CA*-mutants, and recommends molecular testing to find those patients [71].

- **Special Cases:** For premenopausal women, all trials were in postmenopausal or ovarian-suppressed patients. Guidelines stipulate that premenopausal women should be rendered functionally postmenopausal (with ovarian suppression) before using alpelisib + fulvestrant [76]. Men with breast cancer were included in trials and guidelines equally recommend alpelisib for men with *PIK3CA*-

mutated HR+ disease (with concurrent suppression of testicular estrogen via GnRH analog if using fulvestrant, by analogy).

- **Sequencing:** The general consensus sequence in HR+ MBC is: first-line – AI + CDK4/6 inhibitor; second-line – if *PIK3CA* mutated, switch to fulvestrant + alpelisib [39] (if not mutated, other options like everolimus-exemestane or chemo are used); third-line – consider other trials or chemo. With the advent of capivasertib (an AKT inhibitor that in the CAPItello-291 trial improved PFS broadly, but especially in *PIK3CA/AKT1/PTEN*-altered tumors), guidelines will likely incorporate that as well once approved (ESMO has given capivasertib + fulvestrant an ESCAT I-A for *PIK3CA* mutant and also some benefit in wild-type). As of 2024, alpelisib remains the only approved targeted option for this mutation.

- **Other Trials:** It's worth noting ongoing trials like **NCT04304434 (phase III EPIK-B5)** evaluating alpelisib in the early breast cancer setting (adjuvant therapy for *PIK3CA*-mutated HR+ high-risk patients) – results pending. If positive, guidelines might expand alpelisib use to earlier stages in a subset. Also, combination trials (alpelisib with PARP inhibitors for BRCA-mutant/*PIK3CA*-mutant cancers, or alpelisib with immunotherapy) are being explored.

In conclusion, **current guidelines uniformly endorse testing for PIK3CA mutations** in advanced HR+ breast cancer and using alpelisib + fulvestrant in mutation-positive cases after initial endocrine therapy [39]. The positioning is typically **second-line post-CDK4/6 inhibitor** (or first-line if CDK4/6 inhibitors were not used and patient already progressed on endocrine therapy) [74]. This integration into care represents a paradigm of precision oncology, and multidisciplinary teams (medical oncology, endocrinology for glucose management, dermatology for rash if needed) often collaborate to implement this therapy safely.

Additional Relevant Mechanistic/Clinical Notes

- **Biomarkers and Patient Selection:** Accurate detection of *PIK3CA* mutations is critical. Both tissue and plasma (circulating tumor DNA) testing are used. The FDA approved the therascreen® PIK3CA PCR kit concurrently with Piqray [77]. Notably, some patients have *PIK3CA* mutations only detectable in plasma (due to tumor heterogeneity). If plasma testing is negative, guidelines advise testing the tumor tissue as well [78]. Approximately 28% of *PIK3CA* mutations in advanced HR+ breast cancer might only be found via more comprehensive sequencing beyond the PCR hotspot test [5] (e.g., mutations like N345K not on the kit) [79] [80]. Ongoing studies evaluate if non-hotspot *PIK3CA* mutations also predict benefit (likely yes, if activating). Some real-world data suggest that even rare activating mutations respond to alpelisib.

- **Pharmacodynamics and Dosing Nuances:** Alpelisib is taken with food to improve absorption (a high-fat meal increases AUC by ~73%) [81]. The drug reaches steady state in ~3 days [82]. The half-life is relatively short (~8–9 hours) [83], but daily dosing maintains exposure. There is ongoing exploration of alternate dosing (to mitigate toxicities, e.g. twice daily lower dose for those who cannot tolerate once daily 300 mg [84], or intermitted dosing schedules), but standard remains daily.

- **Hyperglycemia Management:** Given the frequency of hyperglycemia, oncologists often co-manage patients with endocrinologists. Metformin prophylaxis (e.g., start 500 mg daily and uptitrate) has been studied in the METALLICA trial, which showed it can significantly reduce the incidence of Grade

≥3 hyperglycemia [33]. The trial (Lancet, 2023) provided evidence that **metformin** can blunt the blood sugar rise, presumably by improving insulin sensitivity and reducing hepatic glucose output. Some centers have adopted starting metformin alongside alpelisib in patients without contraindications. Additionally, dietary counseling (low-carb diet) and home glucose monitoring are recommended to patients. For high-risk patients (e.g. HbA1c in prediabetes range), starting an SGLT2 inhibitor or other anti-diabetic agent prophylactically is being considered, though metformin remains the most common first measure.

- **Rash Prophylaxis:** As mentioned, prophylactic non-sedating antihistamines (like cetirizine) starting with treatment has been shown to roughly halve the incidence of rash (as in a subgroup analysis of SOLAR-1: 27% rash with prophylaxis vs 54% without) [54]. The mechanism is thought to be mast-cell mediated; PI3Kα inhibition in the skin may cause apoptosis of keratinocytes that release neoantigens triggering immune reactions. Antihistamines mitigate the inflammatory component. If rash occurs, prompt intervention with topical corticosteroids and a brief oral steroid course can prevent progression. These supportive measures are now part of standard practice when initiating alpelisib.

- **Combination Therapies in Development:** To tackle known resistance routes, combinations are being tried:

- **Alpelisib + PARP Inhibitors:** Preclinical data suggests *PIK3CA* mutant cancers (especially if co-existing BRCA mutation or HRD) could be vulnerable to combined PI3K + PARP inhibition, due to PI3K's role in DNA damage repair. A small trial of alpelisib with olaparib in triple-negative, BRCA-mutated cancers showed some activity.
- **Alpelisib + CDK4/6 Inhibitors:** There is interest in triplet therapy (endocrine + CDK4/6i + alpelisib) upfront for *PIK3CA*-mutant cases. However, toxicity has been a concern (the FELINE trial tested letrozole + ribociclib + alpelisib in the neoadjuvant setting; while it showed greater Ki-67 suppression, toxicity was high). Ongoing studies aim to fine-tune dosing or sequence (staggered start) to enable such combos safely.
- **Next-generation PI3K inhibitors:** Newer agents (like inavolisib, also known as GDC-0077) aim to improve potency or isoform specificity and possibly better tolerability (e.g., a smaller effect on glucose by sparing PI3Kβ). Early-phase trials of inavolisib plus endocrine therapy show promising efficacy with perhaps less rash and hyperglycemia [85] [86]. These could eventually either supplement or replace alpelisib in this setting if proven superior.
- **Alpelisib + AKT or mTOR inhibitors:** To overcome pathway reactivation via AKT or downstream, combinations like alpelisib + everolimus (mTOR inhibitor) or alpelisib + capivasertib (pan-AKT inhibitor) are being explored in trials. These are heavy on side effects, but there is rationale in tumors with multiple aberrations (e.g., concurrent *PIK3CA* and *PTEN* loss – maybe dual PI3K/mTOR blockade could help).

- **Immunotherapy:** While HR+ breast cancer is not very immunogenic, some trials test alpelisib with checkpoint inhibitors (e.g., to see if modulating PI3K affects tumor immune microenvironment). Moreover, in TNBC, combining PI3K pathway inhibitors with anti-PD-1 is hypothesized to potentially augment response by altering immune suppressive myeloid cells.

- **Real-world usage and data:** Early real-world analyses indicate many patients required dose reductions (to 250 mg or 200 mg daily) due to toxicities, but those who can continue therapy derive similar benefit to trial populations [51] [50]. Adherence to blood sugar monitoring is crucial; there

have been reports of cases of hyperglycemic hyperosmolar coma when monitoring was not strict. Education around this has improved outcomes. There are ongoing post-marketing studies as required by FDA/EMA to further assess long-term safety (given theoretical risk of PI3K inhibitors on immune function and potential secondary malignancies, though none clearly seen so far in alpelisib data up to now) [87].

- **Special approval (PROS indication):** In a notable extension, the FDA in 2022 approved alpelisib (as Vijoice) for PIK3CA-Related Overgrowth Spectrum, a non-malignant condition caused by mosaic *PIK3CA* mutations [88]. This highlights the precise targeting of PI3Kα – even in benign overgrowth, the drug can induce tissue shrinkage by inhibiting the PI3K-driven proliferation. The dose used for PROS (50 mg daily to start) is much lower, reflecting a chronic therapy mindset. While not directly related to breast cancer, it exemplifies alpelisib's mechanism in *human pathophysiology* and underscores the importance of PI3Kα across diseases.

- **Patient quality of life considerations:** Given the side effects, there is a trade-off between PFS benefit and QoL. Many patients on alpelisib experience some decrease in QoL initially due to GI effects and rash, though these often plateau or improve with supportive care. The PFS gain is meaningful (5–6 months median), and some patients have prolonged disease control beyond a year. In making decisions, clinicians discuss the toxicity profile openly. Some patients who are elderly or have significant comorbidities might opt for another line of endocrine therapy or chemotherapy instead, to avoid the intensive monitoring alpelisib requires. However, for many, especially younger or fit patients, the chance to continue an endocrine-based (chemotherapy-sparing) regimen with alpelisib is very valuable.

- **Future Directions:** As the field evolves, *PIK3CA* mutation will remain a critical predictive biomarker. Other drugs targeting the pathway, like **capivasertib** (AKT inhibitor) and **everolimus** (mTOR inhibitor), are/will be available, raising questions of sequencing: e.g., if a patient is *PIK3CA*-mutant, should one use alpelisib or capivasertib? Current evidence suggests alpelisib for *PIK3CA* (since capivasertib benefited both mutant and wild-type, but had its strongest effect in pathway-mutant, and may be used if *PIK3CA* is mutant but patient cannot tolerate alpelisib). It's conceivable that in the near future, combination approaches (like triplet with CDK4/6 earlier, or dual blockade in resistant cases) will refine how we use alpelisib. Additionally, translational studies are examining if certain *PIK3CA* mutations (helical domain vs kinase domain) differ in response – SOLAR-1 didn't show a difference [65], but subtle differences in specific co-mutation contexts might exist.

In summary, alpelisib's introduction is a milestone in breast cancer targeted therapy, offering a new line of tailored treatment. It requires multidisciplinary management of side effects, careful patient selection via biomarkers, and awareness of emerging resistance mechanisms to plan subsequent therapy. The knowledge gained from its use is informing the development of next-gen PI3K pathway inhibitors and optimal care strategies for patients with *PIK3CA*-mutant breast cancer.

Sources: Regulatory labels and approvals [3] [1]; DrugBank and mechanistic references [2] [15]; pivotal trial data from SOLAR-1 [14] and BYLieve; NCCN, ESMO, ABC5 guidelines [39] [74]; Razavi *et al.* 2020 on resistance (PTEN, ESR1) [36]; FDA safety warnings [51] [50]; and others as cited above. All evidence is up to date as of 2024, reflecting the evolving landscape of PI3K-targeted therapy in breast cancer.

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