Current Systemic Treatments for the Hereditary Cancer Syndromes: Drug Development in Light of Genomic Defects

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overview

Advances in the genetic basis of different tumors have led to identification of tumor vulnerabilities that can be turn into targeted therapies. In this regard, PARP inhibitors cause synthetic lethality with tumors harboring *BRCA1* or *BRCA2* genetic alterations. On the other hand, tumors with microsatellite instability, either due to germline or sporadic alterations, are candidates for immune checkpoint inhibitors. Finally, patients with von Hippel-Lindau disease who carry a germline alteration in the *VHL* gene may benefit form belzutifan, a hypoxia-inducible factor 2 alpha inhibitor. Overall, research on the underlying pathological mechanisms of these tumors has provided new therapeutic opportunities that might be expanded to other sporadic tumors with similar biology.

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More than a century ago, investigators made clinical observations on the hereditary characteristics of cancer, such as cancers diagnosed in patients at a younger age and in many members of the family.[1,2] Moreover, cancer syndromes began to be recognized as the presentation of multiorgan neoplasms in a single patient or family. In particular, the findings of what later became called von Hippel-Lindau (VHL) syndrome—retinal hemangioblastomas and cerebellar and spinal hemangioblastomas—were reported by Drs. Collins, Hippel, and Lindau at the beginning of the previous century.[3–5] Around that time, Dr. Warthin described the first German immigrant family (named Family G) in Michigan with cancers involving the gastrointestinal tract and uterus,[6,7] later in 1960s further characterized by Dr. Lynch.[8–11] It has been fascinating to see how clinical observations and scientific discoveries have evolved and aided our understanding of the biologic underpinnings of hereditary cancer syndromes over many decades.[12–14] In that line, with the discovery of DNA, in 1950s, the investigators were able to link the concept of heredity to this intracellular genetic material.[15–17] Later in the 1990s, the development of cloning technologies fostered gene discovery and their relationship with hereditary syndromes.[12–14] The gene located at chromosome 3p25-26, *VHL* gene, was found to be associated with VHL syndrome tumors and sporadic renal cell carcinoma.[18–21] Similarly, *BRCA1* gene at chromosome 17q and *BRCA2* gene at chromosome 13q were described as the breast and ovarian cancer susceptibility genes.[22–26] Around the same time, many other laboratories investigating mechanisms of colorectal cancers discovered the ubiquitous mutations in repetitive DNA sequences, microsatellites, and their association with sporadic and hereditary colorectal cancer.[27–32] To close the loop on the systematic investigations on the family "G" with Lynch syndrome, more recently the 929 descendants of Family G were sequenced and confirmed the germline mutation in *MSH2* gene causing microsatellite instability and susceptibility to colorectal cancers.[33]

Based on multigenerational collaboration and commitment leading to foundational discoveries, in recent years, understanding the germline defects and related biologic consequences helped to us develop effective drugs for these syndromes. PARP inhibitors (PARPi) have shown to be effective in patients with breast, ovarian, and prostate cancer with a germline or sporadic *BRCA* mutation.[34–37] Similarly, hypoxia-inducible factor 2α (HIF2α) inhibitors were shown to be effective in VHL syndrome.[38,39] Moreover, advancements in the tumor immunology field and the discovery of immune checkpoint inhibitors led to the development of effective treatment of Lynch syndrome.[40] In this review, we will summarize the mechanism of these drugs and selected clinical trials that led to the U.S. Food and Drug Administration approvals in these neoplastic syndromes (Fig. 1).

DEVELOPMENT OF PARP INHIBITORS IN BREAST AND PANCREAS CANCER

Mechanisms of Action of PARP Inhibitors

Patients with a germline *BRCA1* or *BRCA2* pathogenic variant are likely to have a somatic loss-of-function of the

PRACTICAL APPLICATIONS

- Understanding the biological underpinnings of hereditary neoplastic syndromes is critical to developing therapies not only for the syndromes but also for sporadic cancers with similar pathological mechanisms.
- PARP inhibitors (olaparib, rucaparib, niraparib) are recommended for the treatment of germline or sporadic BRCA mutated, or homologous recombination deficient breast, ovarian, prostate, and pancreas cancer at different specific indications.
- Immune checkpoint inhibitor, pembrolizumab, is recommended for the treatment of patients with germline or sporadic high microsatellite instability/mismatch repair deficient solid tumors. Similarly, nivolumab alone or in combination with ipilimumab is recommended for the treatment of high microsatellite instability/mismatch repair deficient colorectal cancers.
- Hypoxia inducible factor 2α inhibitor, belzutifan, is recommended for the treatment of patients with Von Hippel-Lindau disease who require therapy for renal cell carcinoma, central nervous system hemangioblastoma, or pancreatic neuroendocrine tumors, not requiring immediate surgery.

wild type allele, and therefore have a defective homologous recombination repair pathway for DNA double-strand breaks. PARP is a family of enzymes involved in the repair of single-strand breaks, as well as the repair of collapsed replication forks. PARP inhibitors block the catalytic activity of PARP and lead to trapping of the PARP enzyme in the DNA strand, which consequently leads to an increase of double-strand breaks during cell replication. As a consequence, those tumors lacking a proficient homologous recombination repair pathway (i.e., BRCA-associated) will accumulate DNA damage that will lead to cell death. Following the preclinical proof-of-concept of this synthetic lethality approach, several PARPi have been approved to treat BRCA-associated breast, ovarian, pancreatic, or prostate cancer.[41] Here, we will review and update the current knowledge about the role of PARPi in patients with germline *BRCA* (g*BRCA*) breast cancer and pancreatic cancer. The role of PARPi in ovarian and prostate cancer was reviewed previously in detail.[36,37]

Role of PARPi in Breast Cancer

Clinical development of PARPi in patients with g*BRCA* metastatic breast cancer Four randomized, open-label phase III trials evaluated the use of PARPi in patients with HER2-negative metastatic or locally advanced unresectable breast cancer harboring germline mutations in *BRCA1/2* genes.

OlympiAD, BRAVO, and EMBRACA trial compared olaparib, niraparib, and talazoparib in monotherapy, respectively, with single-agent chemotherapy.[42–44] BROCADE 3 trial randomly assigned patients to receive veliparib or placebo in combination with carboplatin and paclitaxel.[45] All trials allowed until two[43–45] or three prior cytotoxic regimen lines.[42] Crossover was not allowed in any trial, except one.[45] Platinum-based treatment was allowed if there was no progression during treatment or within 6–12 months after last dose in the neo/adjuvant setting.

In all, the primary endpoint was progression-free survival (PFS). Olaparib, talazoparib, and veliparib achieved its primary objective with a significant increase of PFS. The risk of disease progression or death was 42% lower with olaparib than with standard therapy. Talazoparib showed a significantly longer median PFS compared with the standard-therapy group (8.6 months vs. 5.6 months; HR, 0.54; 95% CI, 0.41–0.71). Addition of veliparib to carboplatin-paclitaxel chemotherapy resulted in significant and durable improvement in PFS (HR, 0.71; 95% CI, 0.57–0.88). Niraparib in the BRAVO trial failed in its primary endpoint with no significant differences in PFS between the two study groups (HR, 0.96; 95% CI, 0.65–1.44). A worse baseline prognosis of patients in BRAVO might explain the lower PFS compared with OlympiAD and EMBRACA. In terms of overall survival, a significant improvement was only observed in OlympiAD among patients who did not receive previous chemotherapy for metastatic disease (HR, 0.51; 95% CI, 0.29–0.90).[46] Although the mechanisms of action are similar, variation in the outcome measures between trials can be explained by heterogeneity of study population, assessment, and enrollment criteria per genetic alterations.

The safety profile was similar across the three trials with PARPi in monotherapy, and showed that hematologic toxicity had the most common grade 3–4 events (Table 1). Therefore, close monitoring and management of these toxicities is necessary during the treatment (Table 2). Importantly, a significant delay in the onset of clinically meaningful deterioration according to the global health status quality-of-life scale QLQ-C30 was demonstrated in the OlympiAD and EMBRACA trials.

A relevant issue is the lack of platinum in the control arms of the above trials, whose expected overall response rate in this population is 68% and very similar to PARPi in monotherapy.[47] This leads to the question of the

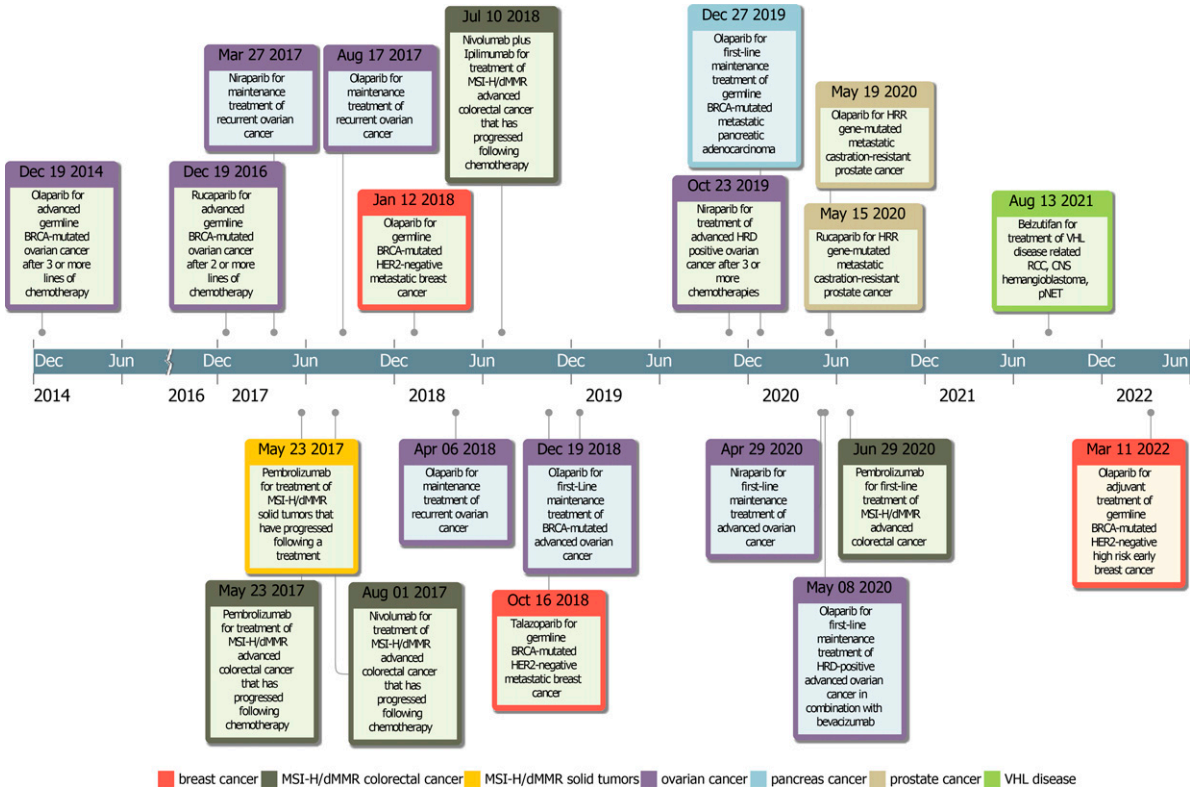

FIGURE 1. U.S. Food and Drug Administration Approval Timeline of PARP Inhibitors for Germline and Sporadic *BRCA*-Mutated Cancers, MSI-H/dMMR Solid Tumors, and VHL Syndrome

Abbreviations: MSI-H/dMMR, high microsatellite instability/mismatch repair deficient; VHL, von Hippel-Lindau disease.

appropriateness of sequencing these treatments. Interestingly, the ABRAZO phase II trial aimed to answer this question and observed that talazoparib's efficacy after platinum was correlated with longer platinum-free interval.[48] Similarly, in the BROCADE 3 trial, a subset of patients assigned to the control group received veliparib monotherapy as first subsequent therapy after disease progression. Among them, a platinum-free interval longer than 180 days was correlated with greater veliparib activity.[49]

Regarding combination with immunotherapy, the TOPACIO phase II trial explored the safety and efficacy of niraparib in combination with pembrolizumab in patients with metastatic triple negative breast cancer (TNBC) including a cohort of patients with tumor *BRCA1/2* mutation.[50] Among 15 patients with a tumor *BRCA1/2* mutation, the objective response rate (ORR) was 47% and the median PFS was 8.3 months (95% CI, 2.1–not estimable). Therefore, with a similar ORR to monotherapy with olaparib or talazoparib in patients with TNBC and mutated *BRCA1/2,* but a 3-month longer median PFS. The MEDIOLA phase I/II basket trial evaluated the safety, tolerability, and 12-week disease control rate with the combination of durvalumab and olaparib in solid tumors.[51] Overall, 34 patients with metastatic HER2− breast cancer with g*BRCA1/2* mutation were included. At 12 weeks, 80% achieved disease control and 63% an ORR. The safety profile of the combination was similar to that previously described for olaparib and durvalumab in monotherapy.

Clinical development of PARPi in the adjuvant setting for patients with g*BRCA* breast cancer After the improved outcome and quality of life observed in the metastatic setting with both olaparib and talazoparib versus chemotherapy,[42,43] testing PARPi at an earlier phase of the disease was expected.

In the phase III randomized OlympiA trial,[52] patients with HER2-negative high-risk breast cancer harboring a pathogenic g*BRCA1/2* mutation were randomly assigned 1:1 to receive olaparib versus placebo for 1 year after completion of neoadjuvant or adjuvant treatment, with invasive disease-free survival as the primary endpoint. A total of 1,836 patients were included; 82.2% with TNBC, 72.3% presenting a g*BRCA1*, and 27.2% a g*BRCA2* mutation; 93.7% had received neoadjuvant/adjuvant chemotherapy with an anthracycline and a taxane, and a platinum agent was used in 26.5% of the patients. At 3 years of follow-up, invasive disease-free survival was significantly longer in the olaparib arm:

TABLE 1. Common Adverse Events of Recently Approved Agents in Selected Clinical Trials*

	Niraparib		Rucaparib		Olaparib		Talazoparib		Pembrolizumab		Belzutifan	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Any adverse event	99	71	100	54	98	39	99	26	97	56	100	33
Blood and Lymphatic System Disorders												
Thrombocytopenia	66	39	28	5	11	1	27	15	—	—	—	—
Anemia	64	31	37	18	38	21	53	39	18	5	90	7
Neutropenia	42	21	18	7	17	6	35	21	2	0	—	—
Leukopenia	28	5	44	3	13	3	17	7	1	0	11	0
Gastrointestinal Disorders												
Nausea	57	1	75	4	77	1	49	0	31	3	31	0
Constipation	40	1	37	2	28	0	22	<1	17	0	20	0
Vomiting	22	1	37	4	40	0	25	2	22	1	—	—
Diarrhea	19	1	32	1	37	3	22	1	44	6	13	2
Abdominal pain	22	1	30	2	45	2	19	—	24	5	13	0
Abdominal distension	7	0	11	0	—	—	—	—	—	—	—	—
Dyspepsia	—	—	15	<1	17	0	10	—	6	0	23	2
Stomatitis	—	—			11	0	8	—	7	0		
General Disorders and Administration Site Conditions												
Fatigue	51	3	69	7	67	4	50	2	38	4	64	5
Investigations												
AST/ALT elevation	14	3	34	10	—	—	36	2	16	3	20	0
Metabolism and Nutrition Disorders												
Decreased appetite	19	1	23	1	20	0	21	<1	24	0		
Weight increased	—	—	—	—	—	—	—	—	—	—	13	2
Musculoskeletal and Connective Tissue Disorders												
Musculoskeletal pain	39	1	15	1	25	0	21	2	18	1	20	0
Nervous System Disorders												
Headache	26	0.4	18	<1	23	<1	33	2	14	0	39	0
Dizziness	19	0	15	0	20	0	17	—	16	0	38	0
Dysgeusia	—	—	40	0	26	0	10	—	—	—	—	—

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TABLE 1. Common Adverse Events of Recently Approved Agents in Selected Clinical Trials* (Continued)

	Niraparib		Rucaparib		Olaparib		Talazoparib		Pembrolizumab		Belzutifan	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Psychiatric Disorders												
Insomnia	25	1	14	0	—	—	—	—	—	—	—	—
Respiratory, Thoracic, and Mediastinal Disorders												
Dyspnea	22	0.4	13	0	15	0	18	2	14	1	20	2
Cough	18	0	15	0	16	0	—	—	17	0		
Upper respiratory tract infection	10	0	11	0	28	0	—	—	10	0	21	0
Skin and Subcutaneous Tissue Disorders												
Rash	—	—	12	<1	—	—	4	<1	13	1	—	—
Pruritus	—	—	13	0	—	—	—	—	16	0	—	—
Vascular Disorders												
Hypertension	18	6	—	—	—	—	—	—	12	7	13	3
Inflammatory disorders												
Hypothyroidism	—	—	—	—	—	—	—	—	12	0	—	—
Colitis	—	—	—	—	—	—	—	—	7	0	—	—
Pneumonitis	—	—	—	—	—	—	—	—	4	0	—	—
Adrenal insufficiency	—	—	—	—	—	—	—	—	3	1	—	—
Hepatitis	—	—	—	—	—	—	—	—	3	3	—	—
Eye Disorders												
Vision blurred	—	—	—	—	—	—	—	—	—	—	16	0

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase.
* Table summarizing the adverse events reported in individual trials (PRIMA for niraparib, ARIEL3 for rucaparib, SOLO-1 for olaparib, EMBRACA for talazoparib, Keynote-177 for pembrolizumab, Study 004 for belzutifan) and described in the U.S. Food and Drug Administration drug label or primary publication. "—" stands for no data available.

TABLE 2. Management of Common Adverse Events Related to PARP Inhibitors, Pembrolizumab, and Belzutifan*

Drug Name	Adverse Reaction	Severity	Dosage Modification
Belzutifan	Anemia	Hb < 9 g/dL or transfusion indicated	Withhold until Hb ≥ 9 g/dL. Resume at reduced dose or discontinue depending on the severity of anemia.
		Life-threatening or urgent intervention indicated	Withhold until Hb ≥ 9 g/dL. Resume at a reduced dose or permanently discontinue.
	Hypoxia	Decreased oxygen saturation with exercise (e.g., pulse oximeter < 88%)	Consider withholding until resolved. Resume at the same dose or at a reduced dose depending on the severity of hypoxia.
		Decreased oxygen saturation at rest (e.g., pulse oximeter < 88% or PaO_2 ≤ 55 mmHg) or urgent intervention indicated	Withhold until resolved. Resume at reduced dose or discontinue depending on the severity of hypoxia.
		Life-threatening or recurrent symptomatic hypoxia	Permanently discontinue.
	Other adverse reactions	Grade 3	Withhold dosing until resolved to ≤ grade 2. Consider resuming at a reduced dose (reduce by 40 mg). Permanently discontinue upon recurrence of grade 3.
		Grade 4	Permanently discontinue.
Pembrolizumab	Pneumonitis	Grade 2	Withhold pembrolizumab and initiate corticosteroid**
		Grade 3 or 4	Permanently discontinue pembrolizumab, initiate corticosteroid, and other immunosuppressive agents as indicated
	Colitis	Grade 2 or 3	Withhold pembrolizumab and initiate corticosteroid**
		Grade 4	Permanently discontinue pembrolizumab, initiate corticosteroid, and other immunosuppressive agents as indicated
	Hepatitis with no tumor involvement of the liver	AST or ALT increases to more than three and up to eight times ULN or Total bilirubin increases to more than 1.5 and up to three times ULN	Withhold pembrolizumab and initiate corticosteroid**
		AST or ALT increases to more than eight times ULN or Total bilirubin increases to more than three times ULN	Permanently discontinue pembrolizumab, initiate corticosteroid, and other immunosuppressive agents as indicated
	Hepatitis with tumor involvement of the liver	Baseline AST or ALT is more than one and up to three times ULN and increases to more than five and up to 10 times ULN or Baseline AST or ALT is more than three and up to five times ULN and increases to more than eight and up to 10 times ULN	Withhold pembrolizumab and initiate corticosteroid**
		ALT or AST increases to more than 10 times ULN or Total bilirubin increases to more than three times ULN	Permanently discontinue pembrolizumab, initiate corticosteroid, and other immunosuppressive agents as indicated
	Endocrinopathies	Grade 3 or 4	Withhold until clinically stable or permanently discontinue depending on severity

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TABLE 2. Management of Common Adverse Events Related to PARP Inhibitors, Pembrolizumab, and Belzutifan* (Continued)

Drug Name	Adverse Reaction	Severity	Dosage Modification
	Nephritis with renal dysfunction	Grade 2 or 3 increased blood creatinine	Withhold pembrolizumab and initiate corticosteroid**
		Grade 4 increased blood creatinine	Permanently discontinue pembrolizumab, initiate corticosteroid, and other immunosuppressive agents as indicated
	Exfoliative dermatologic conditions	Suspected SJS, TEN, or DRESS	Withhold pembrolizumab and initiate corticosteroid**
		Confirmed SJS, TEN, or DRESS	Permanently discontinue pembrolizumab, initiate corticosteroid, and other immunosuppressive agents as indicated
	Myocarditis	Grade 2, 3, or 4	Permanently discontinue pembrolizumab and initiate corticosteroid
	Neurologic toxicities	Grade 2	Withhold pembrolizumab and initiate corticosteroid**
		Grade 3 or 4	Permanently discontinue pembrolizumab, initiate corticosteroid, and other immunosuppressive agents as indicated
	Hematologic toxicity in patients with cHL or PMBCL	Grade 4	Withhold pembrolizumab until resolution to grades 0 or 1
	Infusion-related reactions	Grade 1 or 2	Interrupt or slow the rate of infusion
		Grade 3 or 4	Permanently discontinue pembrolizumab
PARPi	Anemia	Hb < 8 g/dL	Withhold and monitor weekly until Hb returns to ≥ 9 g/dL, resume at reduced dose
		Hb < 7 g/dL, or higher levels if the patient is symptomatic or has significant comorbidities	Transfusion should be considered
	Thrombocytopenia	Platelet count $< 100{,}000/\mu$L	Withhold and monitor weekly until platelet count returns to $\geq 100{,}000/\mu$L; resume at reduced dose if platelet count is $< 75{,}000/\mu$L
		Platelet count $\leq 10{,}000/\mu$L	Transfusion should be considered
	Neutropenia	Neutrophil $< 1{,}000/\mu$L	Withhold and monitor weekly until neutrophil counts return to $< 1{,}000/\mu$L, resume at reduced dose†
	Nausea	Common class adverse event. It is an early event. Severe nausea/vomiting is infrequent. The use of metoclopramide, prochlorperazine, or promethazine 30 minutes prior to the PARPi is a good option. The administration of food 30–60 minutes before the PARPi may also help. The neurokinin-1 receptor antagonist, such as aprepitant, should be avoided with olaparib due to drug interactions.	
	Fatigue	Nearly universal toxicity for all PARPi and seems to be a class effect. Nonpharmacological treatments are recommended, such as exercise. However, caution in determining level of activity is warranted specifically if there is concurrent treatment-related anemia or thrombocytopenia. Massage therapy and psychosocial interventions are also recommended. Optimizing treatment of sleep dysfunction and nutritional deficit/imbalance may also be helpful.	

Abbreviations: Hb, hemoglobin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ULN, upper limit of normal; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis; DRESS, drug reaction with eosinophilia and systemic symptoms; cHL, classical Hodgkin lymphoma; PMBCL, primary mediastinal large B-cell lymphoma; PARPi, PARP inhibitor.

* Recommendations and approach summarized based on the information provided in U.S. Food and Drug Administration drug label. Please review individual drug labels for more specific and detailed guidance.

** Resume in patients with complete or partial resolution (grades 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to 10 mg per day or less (or equivalent) within 12 weeks of initiating steroids.

† Myelodysplastic syndrome/acute myeloid leukemia is a serious rare adverse event (1% of patients). If unexplained or prolonged pancytopenia, patients should be referred to a hematologist for consideration for bone marrow aspiration. If myelodysplastic syndrome/acute myeloid leukemia is diagnosed, treatment with PARPi should be permanently discontinued.

86% and 77% for olaparib versus placebo, respectively (HR, 0.58; 95% CI, 0.41–0.82; p < .001). Distant disease-free survival was also clinically improved with 88% in the olaparib group and 80% in the placebo group (HR, 0.57; 95% CI, 0.39–0.83; p < .001), leading to the U.S. Food and Drug Administration approval of olaparib in the adjuvant setting. More importantly, the benefit of invasive disease-free survival was observed in all prespecified subgroups irrespective of *BRCA* mutation, estrogen receptor status, or previous chemotherapy (neoadjuvant vs. adjuvant). No new safety signals were identified, with only 10% of patients having to discontinue olaparib due to toxicity (vs. 4% in the placebo arm). No statistically significant benefit in overall survival was observed at an interim-analysis, and final analysis are awaited.

Integrating these results with the CREATE-X[53] and the last update from Keynote-522[54] studies are challenging. The CREATE-X trial evaluated the benefit of adjuvant capecitabine (vs. no capecitabine) for patients with HER2-negative breast cancer who had residual disease after neoadjuvant chemotherapy. At 5 years, a significant impact on overall survival was mostly observed in those with TNBC, with 78.8% versus 70.3% in the capecitabine versus control arm, respectively (HR, 0.52; 95% CI, 0.30–0.90). In the Keynote-522, pembrolizumab (vs. placebo) in addition to neoadjuvant chemotherapy followed by nine cycles of adjuvant pembrolizumab was tested in TNBC, yielding an absolute benefit of 13.6% in pathologic complete response and 7.7% in event-free survival (HR, 0.63; 95% CI, 0.48–0.82), becoming the new standard of care for unselected early stage TNBC. Importantly, none of the trials have specifically examined the benefit of adjuvant capecitabine or pembrolizumab in the g*BRCA* population. Furthermore, olaparib has proven to be more effective than capecitabine in the advanced setting in the OlympiAD trial.[43] A research question is whether combining olaparib and pembrolizumab might be a future option for patients with TNBC harboring a g*BRCA* mutation who do not achieve a pathologic complete response. In view of these results, we conclude that g*BRCA* testing at an early phase of the disease plays a key role to select the best treatment strategy.

The role of PARPi in the neoadjuvant setting for patients with g*BRCA* breast cancer One of the multiple lessons learned with the clinical development of PARPi in the metastatic setting was the appearance of resistant mechanisms mostly due to recovery of homologous recombination function. One of the biologic reasons for homologous recombination recovery is the predominance of cancer cell clones that carry *BRCA* reversion mutations that restore the reading frame and translate a functional protein. These cancer cell clones seem to arise from Darwinian selection under selective therapeutic pressure, which is expected to be less frequent in treatment-naïve patients with *BRCA*-associated breast cancer. Together with the favorable safety profile of PARPi, an increased interest in assessing the clinical efficacy of PARPi in the neoadjuvant setting arose. Following this rationale, NeoTALA[55] is a phase II trial assessing the efficacy of neoadjuvant talazoparib in patients with g*BRCA1/2*-mutated, HER2-negative early breast cancer. Overall, 61 patients, all with TNBC, were enrolled to receive 1 mg/day of talazoparib during 24 weeks. The pathologic complete response was 49%, comparable with that observed with combination of anthracycline and taxane-based chemotherapy, and without unexpected safety findings. So far, results are encouraging to continue with clinical development in this setting. Additionally, two clinical trials have reported their results of combining a PARPi with chemotherapy in the neoadjuvant setting. BrighTNess assessed the efficacy of adding carboplatin, with or without veliparib, to standard paclitaxel and anthracycline-based regimen in patients with TNBC, stratified by g*BRCA1/2* genetic status.[56] In the overall population, the study showed the efficacy of adding carboplatin, but not veliparib, in terms of pathologic complete response and event-free survival.[57] Of note, a recent matched cohort study of g*BRCA* mutation carriers within this trial showed that the addition of carboplatin, regardless of veliparib, to neoadjuvant paclitaxel and anthracycline-based chemotherapy, was associated with increased pathologic complete response in patients with non-g*BRCA*, but not in g*BRCA* carriers.[58] Another trial is GeparOLA, which assessed the rate of pathologic complete response of paclitaxel with olaparib compared with paclitaxel with carboplatin, followed by anthracycline-based chemotherapy in patients with HER2-negative breast cancer and homologous recombination deficiency, which includes patients with germline or tumor *BRCA1/2* mutation.[59] No differences in pathologic complete response were observed between olaparib and carboplatin combinations in patients with tumor or *gBRCA1/2* pathogenic variants (60%). However, patients who were hormone receptor–positive and patients younger than age 40 benefited from olaparib compared with carboplatin (53% vs. 20%, and 76% vs. 45%, respectively). These results deserve further investigations.

Ongoing clinical trials and future directions with PARPi in patients with g*BRCA* breast cancer There are multiple ongoing trials of the commercially available PARPi, as well as a new generation of selective PARP1 inhibitors, like AZD5305,[60] intended to reduce hematologic toxicity driven by PARP2 trapping. In Table 3, the main ongoing clinical trials with PARPi in patients with g*BRCA* breast cancer are summarized.

PARP inhibitors have shown to be a targeted therapeutic option for patients with breast cancer and a g*BRCA* mutation in the metastatic and adjuvant setting with an optimal safety profile. Ongoing research is focused on expanding their use beyond patients with g*BRCA* alterations, and to define whether combination with immunotherapy or other DNA damage-repair agents are more effective. Within a

TABLE 3. Ongoing Clinical Trials With PARPi Enrolling Patients With Breast Cancer and *BRCA1/2* Mutations

Trial	Type of Study	Setting	Treatment and Comparator	Primary Endpoint
NCT04296370	Phase III, randomized	HER2 negative metastatic breast cancer g*BRCA*mut	Arm I: Fluzoparib + apatinib Arm II: Fluzoparib Arm III: Physician's choice chemotherapy: capecitabine or vinorelbine	DLT, RP2D, PFS
NCT01009788	Phase II, single-arm	Locally advanced or metastatic breast cancer *BRCA*mut (not recruiting)	ABT-888 + temozolomide	ORR, safety, efficacy
NCT03641755	Phase Ib/II, single-arm	Unresectable or metastatic breast cancer *BRCA*mut (not recruiting)	Olaparib + sapacitabine	MTD, RP2D, ORR
NCT04556292	Phase II, single-arm	Locally advanced or metastatic breast cancer g*BRCA*mut	SC10914	ORR
NCT03685331	Phase I–II, single-arm	HR+/HER2− locally advanced or metastatic breast cancer *BRCA*mut	Olaparib + fulvestrant + palbociclib (DLT phase I)	PFS
NCT03911973	Phase II, single-arm	Advanced TNBC or *BRCA1/2*mut HER2− breast cancer	Talazoparib + gedatolisib	MTD, ORR
NCT04584255	Phase II, randomized	ER+/HER2− or TNBC candidates for neoadjuvant strategy with g*BRCA*mut or *PALB2*mut	Arm I (TNBC): Niraparib continuous + dostarlimab/3 weeks since week 1, day 1 Arm II (TNBC): 3-week lead-in of niraparib monotherapy followed by niraparib continuous + dostarlimab since week 4 Arm III (ER+/HER2−): Niraparib every day continuous + dostarlimab/3 weeks since week 1, day 1	Tumor infiltrating lymphocytes, pCR
NCT03931551	Phase II, single-arm	HER2+ g*BRCA*mut advanced breast cancer	Olaparib + trastuzumab	Efficacy*
NCT02401347	Phase II, single- arm	Advanced TNBC with HRD and *BRCA1/2*wt or advanced HER2− solid tumors with deleterious mutation implicated in the HR pathway ‡ excluding *BRCA1/2*	Cohort A: TNBC with HRD based on the myriad HRD assay: talazoparib tosylate Cohort B: HER2− solid tumor with deleterious mutation in the HR pathway excluding *BRCA1/2***: talazoparib tosylate	ORR
NCT03025035	Phase II, single-arm	Advanced breast cancer with HRD or *BRCA*mut	Pembrolizumab + olaparib	ORR
NCT04090567	Phase II, randomized	HER2− metastatic breast cancer g*BRCA*mut	Arm I: Olaparib + cediranib Arm II: Olaparib + ceralasertib	ORR
NCT02595905	Phase II, randomized	HER2− recurrent or metastatic TNBC g*BRCA*mut with or without brain metastasis (not recruiting)	Arm I: Cisplatin + placebo Arm II: Cisplatin + veliparib	PFS
NCT04673448	Phase Ib, single-arm	Unresectable or metastatic breast, pancreas, ovary, fallopian tube, or primary peritoneal cancer t/ g*BRCA*mut	Niraparib + dostarlimab	Best objective response

(Continued on following page)

TABLE 3. Ongoing Clinical Trials With PARPi Enrolling Patients With Breast Cancer and *BRCA1/2* Mutations (Continued)

Trial	Type of Study	Setting	Treatment and Comparator	Primary Endpoint
NCT04053322	Phase II, single-arm	ER+/HER2− locally advanced or metastatic breast cancer with g*BRCA*mut or alterations of genes involved in HR or MSI status	Durvalumab + olaparib + fulvestrant	PFS rate at 24 weeks
NCT04240106	Phase II, single-arm	ER+/HER2− locally recurrent or metastatic breast cancer g*BRCA*mut or with HRD	Niraparib + aromatase inhibitors	Clinical benefit rate†
NCT03150576	Phase II/III, randomized	TNBC and/or g*BRCA*mut candidates for neoadjuvant strategy	Arm I: Paclitaxel and carboplatin Arm II: Paclitaxel and carboplatin + olaparib	Safety, pCR
NCT03330847	Phase II, randomized	Metastatic TNBC with presence or absence of any somatic HRR mutation (not recruiting)	Arm I: Olaparib Arm II: Olaparib + ceralasertib Arm III: Olaparib + adavosertib	PFS
NCT04915755	Phase III, randomized	t*BRCA*mut HER2− breast cancer or t*BRCA*wt TNBC with molecular disease based on circulating tumor DNA following surgery or completion of adjuvant therapy	Cohort 1: t*BRCA*mut HER2− breast cancer: niraparib or placebo Cohort 2: t*BRCA*wt TNBC: niraparib or placebo	Disease-free survival
NCT02849496	Phase II, randomized	HER2− *BRCA*mut locally advanced or metastatic breast cancer	Arm I: Olaparib Arm II: Olaparib + atezolizumab	PFS
NCT01149083	Phase II, randomized	Locally advanced or metastatic breast cancer *BRCA*mut (not recruiting)	Arm I: Veliparib Arm II: Veliparib + carboplatin	Response rate
NCT05033756	Phase II, single-arm	Unresectable or metastatic HER2− breast cancer and a deleterious germline mutation or a HRD	Pembrolizumab + olaparib	ORR
NCT03167619	Phase II, randomized	Platinum sensitive metastatic TNBC	Arm I: Olaparib Arm II: Olaparib + durvalumab	PFS
NCT03565991	Phase II, single-arm	Metastatic solid tumors with *BRCA*mut or ATM defect	Talazoparib + avelumab	ORR
NCT04644068	Phase I/IIa	Unresectable or metastatic breast, pancreas, ovary, fallopian tube, t*BRCA*mut, *PALB2, RAD51C/D*	AZD5305 AZD5305 + paclitaxel AZD5305 + carboplatin +/− paclitaxel AZD5305 + Dato-DXd AZD5305 + T-Dxd	Safety, DLT

Abbreviations: PARPi, PARP inhibitor; g*BRCA*mut, germline *BRCA* mutation; DLT, dose-limiting toxicity; RP2D, recommended phase II dose; PFS, progression-free survival; *BRCA*mut, *BRCA* mutated; ORR, objective response rate; MTD, maximum tolerated dose; TNBC, triple-negative breast cancer; ER, estrogen receptor; *PALB2*mut, *PALB2* mutated; pCR, pathologic complete response; HRD, homologous recombination deficiency; *BRCA1/2*wt, *BRCA* wild type; HR, homologous recombination pathway; t/g*BRCA*mut, tumoral or germline *BRCA* mutation; MSI, microsatellite instability; HRR, homologous recombinant repair; wt, wild type; Dato-DXd, datopotamab deruxtecan; T-Dxd, trastuzumab/deruxtecan.

* Efficacy as determined by the clinical benefit rate response divided by the number of patients in the analysis set—in patients with germinal *BRCA*-mutated (cohort A) based on local investigator's assessment according to RECIST criteria guidelines v.1.1.

** *PTEN, PALB2, CHEK2, ATM, NBN, BARD1, BRIP1, RAD50, RAD51C, RAD51D, MRE11, ATR*, Fanconi anemia complementation group of genes.

† The clinical benefit rate as best response, defined as the percentage of patients who experience a complete response, partial response, or stable disease for at least 24 weeks and assessed by modified RECIST v1.1 criteria.

‡ *ATM, ATR, BARD1, BRIP1 (FANCJ), CHEK2, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCM, MRE11A, NBN, PALB2, RAD50, RAD51C, RAD51D*, plus other homologous recombination pathway-related genes.

selected population in the neoadjuvant setting, research will determine whether PARPi might help to delineate a chemotherapy-based de-escalation strategy.

Role of PARPi in Pancreatic Ductal Adenocarcinoma

Defects in the DNA damage-repair pathway are known to occur in the oncogenesis of pancreatic ductal adenocarcinoma. While many of these errors are somatic, some reflect underlying germline mutations in DNA damage-repair mechanisms. Up to 9% of patients with pancreatic ductal adenocarcinoma harbor a g*BRCA* mutation,[61] which causes homologous recombination defects and synthetic lethality with PARPi.[62]

The POLO trial sought to establish the first targeted therapy in g*BRCA*-mutant pancreatic ductal adenocarcinoma.[63] Positioning a PARPi as postchemotherapy maintenance, POLO was a randomized, double-blind, phase III design that assigned patients in a 3:2 ratio to olaparib 300-mg tablets twice daily versus placebo control. Of the 3,315 patients who underwent screening, 154 underwent randomization and were assigned to a trial intervention (92 to receive olaparib vs. 62 on placebo). Regarding the primary endpoint, the median PFS was significantly longer on olaparib versus placebo (7.4 months vs. 3.8 months; HR for disease progression or death, 0.53; 95% CI, 0.35–0.82; p = .004). Based on the POLO-demonstrated PFS benefit, the U.S. Food and Drug Administration approved olaparib's use in this g*BRCA* pancreatic ductal adenocarcinoma maintenance treatment setting in December 2019.[64] However, when overall survival data matured (with primary analysis performed after 108 deaths), overall survival was similar for olaparib versus placebo (median 19.0 and 19.2 months, respectively; HR, 0.83; 95% CI, 0.56–1.22; p = .3487).[65] In addition to the lack of overall survival benefit, concerns have been raised with the design of the study including placebo instead of 5-FU monotherapy.[66] Moreover, olaparib associated health care costs with lack of overall survival benefit is further concerning.

Nonetheless, the POLO trial heightened awareness of pancreatic ductal adenocarcinoma as a sentinel feature of germline cancer predisposition syndromes. Correspondence written to the *New England Journal of Medicine* following the seminal publication objected "the authors do not mention the crucial implications related to the broadening population of patients who are going to be tested for and counseled about germline *BRCA* mutations," noting that "the recognition of hereditary syndromes is important in order to set up dedicated follow-up to reduce the incidence of second tumors among survivors and to reduce mortality among their relatives."[67]

POLO-prompted identification of this "tip-of-the-iceberg" phenomenon may ultimately have a more substantial impact on survival than olaparib itself. It is within such cascades that genomically driven oncology can become a matter of public health concern. Because large-scale germline exome sequencing efforts have surfaced a "highly polygenic genomic architecture, the 'genetic economics' of frequency penetrance clearly indicates that focused identification of carriers of mutations like *BRCA* is most impactful for cancer control."[68]

DEVELOPMENT OF PEMBROLIZUMAB FOR THE TREATMENT OF HIGH MICROSATELLITE INSTABILITY COLORECTAL CANCER

Microsatellite instability and mismatch repair deficiency are closely interrelated phenomena that confer potential susceptibility to immune checkpoint inhibitors like pembrolizumab, a PD-1 blocker. The KEYNOTE-177[69] study was a phase III open-label trial of pembrolizumab versus chemotherapy (5-FU-based therapy with or without bevacizumab or cetuximab) in which 307 treatment-naive patients with metastatic high microsatellite instability/mismatch repair deficient colorectal cancer were randomly assigned 1:1. At the second interim analysis, pembrolizumab was superior to chemotherapy with respect to the coprimary endpoint of PFS (median, 16.5 vs. 8.2 months; HR, 0.60; 95% CI, 0.45–0.80; p = .0002).

The U.S. Food and Drug Administration approval of pembrolizumab for this indication in June 2020 was predicated on the PFS benefit,[70] and the editorial accompanying the landmark *New England Journal of Medicine* publication heralded a new standard of care for high microsatellite instability colorectal cancer, citing the durability of response (among those with an overall response, 83% of the pembrolizumab group had ongoing responses at 24 months), better safety profile, and improved quality of life as reasons to prefer immunotherapy over chemotherapy.[71]

Though it had long been known that somatic mutations had the potential to encode "nonself" immunogenic antigens that increased tumor identification to the host and, in turn, susceptibility to PD-1 blockade,[72,73] KEYNOTE-177 also immediately changed the standard of care for patients with germline mismatch repair deficiency and its hallmark microsatellite instability who developed advanced or metastatic colorectal cancer.

In patients with Lynch syndrome, there had previously been dual concerns about the lessened efficacy of fluoropyrimidines (at least as monotherapy[74]) and thus the need for intensified exposure to partner drugs like platinums,[75] which then incurred the very real threat of irreversible toxicities like chemotherapy-induced peripheral neuropathy in patients with a > 80% lifetime risk of developing colorectal cancer.[76] Whereas the prior U.S. Food and Drug Administration approval of pembrolizumab in high microsatellite instability metastatic colorectal cancer in 2017 had required "progress[ion] following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan," with the advent of

KEYNOTE-177 in 2020, patients with Lynch syndrome could finally be treated with a truly chemotherapy-free approach, mitigating their greatest risk of cancer-related death while better preserving quality of life.[77]

ROLE OF HIF2α INHIBITOR BELZUTIFAN IN THE TREATMENT OF VHL SYNDROME

Von Hippel-Lindau Disease and Biology

Von Hippel-Lindau disease is a hereditary autosomal dominant syndrome caused by a germline mutation and/or deletion of the *VHL* gene.[38] The disease is characterized by an abnormal accumulation of HIFs transcription factors that lead to the transcription of proangiogenic and metabolic genes resulting in the development of tumors and cysts in multiple organs, including the brain, kidney, pancreas, and adrenal glands, among others. It has been shown that the small molecule HIF2α inhibitor belzutifan (MK6482) has significant efficacy in renal cell carcinomas, hemangioblastomas, and pancreatic neuroendocrine tumors that are associated with VHL syndrome, while also exhibiting an acceptable safety profile.[78] In this section, we briefly describe the biologic rationale and studies that led to the development of belzutifan for patients with VHL, which has been discussed in detail in our previous review.[38]

The *VHL* gene resides on chromosome 3p25-26,[20] and deletion or inactivation of both alleles is necessary for tumor development.[79] The most well-studied function of the pVHL is its function as E3 ubiquitin ligase as part of the VCB complex with partners including elongin B, elongin C, cullin 2, and RBX1.[80–82] Hypoxia inducible factors are the first of the many targets of the VCB complex that have been identified.[14,83,84] The interaction of VHL and HIFs is dependent on the hydroxylation of proline residues on HIFs' oxygen-dependent degradation domain.[85–87] During the normoxic conditions, prolyl hydroxylases (PHD1, PHD2, and PHD3) hydroxylate proline residues on HIFs that allow for pVHL recognition, followed by ubiquitination and proteasomal degradation.[30,88–90] Physiologically, when cells lack oxygen in a hypoxic environment, PHDs are unable to hydroxylate proline residues and therefore, pVHL is unable to recognize HIFs essential for ubiquitination. Similarly, in VHL syndrome or sporadic clear cell renal cell carcinoma, lack of functional pVHL causes buildup of HIFs in the cytoplasm.[85,86,91–93] Accumulated HIFs form a heterodimer with aryl hydrocarbon receptor nuclear translocator, which then translocates to the nucleus to promote angiogenic, metabolic gene expression (i.e., VEGF, GLUT1, GLUT3, hexokinase 2, etc.) necessary for cell survival in a hypoxic environment.[94–97] Due to the lack of functional pVHL, the unnecessary overproduction of these genes in nonhypoxic environment contributes to the tumorigenesis in VHL syndrome and sporadic clear cell renal cell carcinoma. With this pathogenic mechanism, tyrosine kinase inhibitors targeting vascular endothelial growth factor receptors have been extensively studied and approved for the treatment of clear cell renal cell carcinoma.[98,99]

Development of HIF2α Inhibitor Belzutifan for VHL Disease Treatment

In VHL disease, sunitinib, pazopanib, and dovitinib were tested in clinical trials. A pilot study of sunitinib on 15 patients with VHL demonstrated the drug is safe and achieved 33% partial response in evaluated kidney tumors, but no response in other VHL-related lesions.[100] Dovitinib was tested in another pilot study and after the enrollment of six patients, the study was stopped per toxicity stopping rules. The best response was stable disease.[101] In a phase II study of pazopanib, 31 patients with VHL were treated and had 52% ORR in renal cell carcinoma, 4% ORR in hemangioblastoma, and 53% ORR in pancreatic neuroendocrine tumor lesions.[102] In all these studies, diarrhea, fatigue, hypertension, and nausea were the most common tyrosine kinase inhibitor-related side effects. Additionally, in pazopanib study, 67% of the patients had elevated transaminases requiring dose reduction. Given the paucity of clinical efficacy tyrosine kinase inhibitors and adverse event profiles, there was a need for the development of better systemic therapy agents with higher efficacy and more tolerable side effects. Although for many years, it was known that HIF2α is the tumor oncogene that contributes most to the renal cell carcinoma, pheochromocytoma, and paraganglioma,[91,103,104] it was considered to be nondruggable until the identification of 290-Å^3 internal cavity within the HIF2α PAS-B domain required for the interaction with aryl hydrocarbon receptor nuclear translocator.[105–107] Subsequent studies led to the discovery of first-generation HIF2α inhibitors.[108–114] The first HIF2α inhibitor, PT2385, was tested in a phase I study had limited efficacy (14% ORR) given the extensive glucuronidation of the drug in the enterocytes with the UGT2B17 enzyme. Therefore, investigators modified the germinal difluoro group of PT2385 to the vicinal difluoro group, which resulted in decreased glucuronidation and improved pharmacokinetics.[115] The new compound PT2977 (MK-6482, belzutifan) had higher potency and was tested in further studies.

Based on the phase I dose-escalation study in 34 patients with advanced solid tumors, 120-mg daily was defined as the recommended phase II dose.[115] In a multinational, phase II, single-arm, open-label study, 61 patients with VHL disease and clear cell renal cell carcinoma were treated with belzutifan 120-mg daily.[78] The primary endpoint of the study was to determine the ORR in clear cell renal cell carcinoma. At the median 21.8 months follow-up, 49.2% of the patients had partial response in clear cell renal cell carcinoma and 98.4% of the patients had disease control. Secondary endpoints of the study were safety, duration of response, time to response, PFS, and the efficacy of belzutifan in retinal and central nervous system

hemangioblastoma, pancreatic lesions. The median time to response was 8.2 months (range, 2.7–19.1). The median duration of response was not reached at the time of evaluation. The PFS rate at 24 months was 96% (95% CI, 87–99). Among 61 patients with pancreatic lesions, 77% had ORR, including 10% with complete response. Among 50 patients with central nervous system hemangioblastoma, 30% had ORR. There were 12 patients in the study with retinal hemangioblastoma, and all had improvement at the time of the data cutoff. Regarding safety, the drug was overall well-tolerated with manageable side effects, including the most common adverse events such as anemia, fatigue, headache, and dizziness (Table 1). The majority of the adverse events were at grade 1 and 2 levels, and only 15% of the patients required dose reduction due to adverse events (Table 2). Based on these study results, on August 13, 2021, the U.S. Food and Drug Administration approved belzutifan for adult patients with VHL syndrome who require therapy for associated renal cell carcinoma, central nervous system hemangioblastoma, or pancreatic neuroendocrine tumors, not requiring immediate surgery.[39]

Belzutifan for the Treatment of Sporadic Renal Cell Carcinoma

In the dose-escalation phase of the phase I study (NCT02974738), 43 patients with advanced solid tumors were treated.[116] At doses up to 160 mg daily, no dose-limiting toxicities were observed, and the maximum tolerated dose was not reached. The recommended phase II dose was decided as 120-mg once daily. In the dose-expansion cohort, 55 patients with sporadic clear cell renal cell carcinoma were treated. Sixty-two percent of patients had more than three lines of prior therapy, and 80% of patients progressed on immune checkpoint inhibitors. Despite the heavy previous treatment history of the study population, the ORR with belzutifan was 25%. Additionally, 54% of the patients had stable disease. The ORR was comparable across different IMDC groups, with 31% in the favorable risk group and 24% in the intermediate/poor risk group. The median duration of response was not reached at the time of data cutoff. The median PFS was 14.5 months. Regarding the safety profile, the most common adverse events were anemia (76%), fatigue (71%), dyspnea (49%), nausea (36%), cough (31%), and hypoxia (31%). Sixty-seven percent of the patients with anemia received exogenous erythropoietin, and 36% underwent blood transfusions. Hypoxia was usually managed with supplemental oxygen. In severe cases of hypoxia, two patients required dose reduction and discontinuation of the treatment. No treatment-related grade 4 or 5 events occurred. In this study, belzutifan demonstrating antitumor activity in heavily pretreated patients with sporadic clear cell renal cell carcinoma encouraged more studies in different settings and combinations. Belzutifan is currently being tested for adjuvant, metastatic first-line, and after progression on immune checkpoint inhibitors (Table 4). Different regimens are also under investigation, including combinations with pembrolizumab, pembrolizumab + lenvatinib, cabozantinib, and abemaciclib.

CONCLUSIONS

Here we described the landmark studies that led to the approval of HIF2α inhibitors in VHL syndrome, anti-PD-1 pembrolizumab in high microsatellite instability/mismatch repair deficient colorectal cancer and solid tumors, and

TABLE 4. Ongoing Clinical Trials With Belzutifan in Sporadic Renal Cell Carcinoma

Trial	Type of Study	Setting	Treatment and Comparator	Primary Endpoint
NCT05239728	Phase III, randomized	Post nephrectomy (adjuvant)	Arm 1: Belzutifan + pembrolizumab Arm 2: Placebo + pembrolizumab	DFS
NCT03634540	Phase II	Advanced or metastatic	Belzutifan + cabozantinib	ORR
NCT04195750	Phase III, randomized	Advanced or metastatic, previously treated with TKI and ICB	Arm 1: Belzutifan Arm 2: Everolimus	PFS, OS
NCT04736706	Phase III, randomized	Advanced or metastatic, first line	Arm 1: Belzutifan + pembrolizumab + lenvatinib Arm 2: Pembrolizumab/quavonlimab + lenvatinib Arm 3: Pembrolizumab + lenvatinib	PFS, OS
NCT04586231	Phase III, randomized	Advanced or metastatic, previously treated with ICB	Arm 1: Belzutifan + lenvatinib Arm 2: Cabozantinib	PFS, OS
NCT04627064	Phase I	Advanced or metastatic, previously treated with TKI and ICB	Arm 1: Abemaciclib Arm 2: Abemaciclib + belzutifan	ORR of arm 1 and arm 2, MTD or arm 2

Abbreviations: DFS, disease-free survival; ORR, overall response rate; TKI, tyrosine kinase inhibitor; ICB, immune checkpoint blocker; PFS, progression-free survival; OS, overall survival; MTD, maximum tolerated dose.

PARPi in breast and pancreatic cancer. Developing these drugs for the hereditary cancer syndromes is the product of more than 100 years of cumulative efforts of physicians and scientists who have contributed for the establishing clinical diagnosis, discovering the biologic mechanisms of disease that led to these novel drug developments in recent years. It is necessary to note that, although these hereditary cancer syndromes include less than 5% of all malignancies, in light of the biologic and clinical knowledge gained from developing these drugs for the neoplastic syndromes, the investigation and application of these gents has expanded in sporadic cancers with similar mechanisms. HIF2α inhibitor, belzutifan, is under investigation for sporadic renal cell carcinoma.[38] PARP inhibitors have been approved for prostate cancer with sporadic *BRCA* alterations or other DNA damage gene defects.[64,117,118] Immune checkpoint inhibitors have been approved as for the treatment of colorectal cancer with sporadic high microsatellite instability or mismatch repair deficient tumors.[119,120] These studies serve as a model for and encourage further clinical and biologic research on other rare cancer syndromes that may benefit both those patients and other sporadic cancers with similar underlying pathologic mechanisms.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

1. Banks W. The Lettsomian Lectures being Practical Observations on Cancer of the Breast: Delivered before the Medical Society of London, March 19th, 1900. BMJ. 1900;1:685-690.
2. Richardson MH. Cancer of the breast. J Am Med Assoc. 1909;52:1553-1557.
3. Collins ET. Intra-ocular growths (two cases, brother and sister, with peculiar vascular new growth, probably retinal, affecting both eyes). Trans Ophthalmol Soc U K. 1894;14:141-149.
4. Hippel E. Über eine sehr seltene Erkrankung der Netzhaut. Graefes Arch Clin Exp Ophthalmol. 1904;59:83-106.
5. Lindau A. Zur Frage der Angiomatosis retinae und ihrer Hirnkomplikationen. Acta Ophthalmol. 1926;4:193-226.
6. Warthin AS. Heredity with reference to carcinoma: as shown by the study of the cases examined in the pathological laboratory of the University of Michigan, 1895–1913. Arch Intern Med. 1913;12:546-555.
7. Warthin AS. The further study of a cancer family. J Cancer Res. 1925;9:279-286.
8. Lynch HT, Shaw MW, Magnuson CW, et al. Hereditary factors in cancer. Study of two large midwestern kindreds. Arch Intern Med. 1966;117:206-212.
9. Lynch HT, Krush AJ. Heredity and adenocarcinoma of the colon. Gastroenterology. 1967;53:517-527.
10. Lynch HT, Krush AJ, Larsen AL. Heredity and multiple primary malignant neoplasms: six cancer families. Am J Med Sci. 1967;254:322-329.
11. Lynch HT, Krush AJ. Cancer family "G" revisited: 1895–1970. Cancer. 1971;27:1505-1511.
12. Narod SA, Foulkes WD. BRCA1 and BRCA2: 1994 and beyond. Nat Rev Cancer. 2004;4:665-676.
13. Boland CR, Lynch HT. The history of Lynch syndrome. Fam Cancer. 2013;12:145-157.
14. Gossage L, Eisen T, Maher ER. VHL, the story of a tumour suppressor gene. Nat Rev Cancer. 2015;15:55-64.
15. Hershey AD, Chase M. Independent functions of viral protein and nucleic acid in growth of bacteriophage. J Gen Physiol. 1952;36:39-56.
16. Watson JD, Crick FH. The structure of DNA. Cold Spring Harb Symp Quant Biol. 1953;18:123-131.
17. Portin P. The birth and development of the DNA theory of inheritance: sixty years since the discovery of the structure of DNA. J Genet. 2014;93:293-302.
18. Zbar B, Brauch H, Talmadge C, et al. Loss of alleles of loci on the short arm of chromosome 3 in renal cell carcinoma. Nature. 1987;327:721-724.
19. Tory K, Brauch H, Linehan M, et al. Specific genetic change in tumors associated with von Hippel-Lindau disease. J Natl Cancer Inst. 1989;81:1097-1101.
20. Latif F, Tory K, Gnarra J, et al. Identification of the von Hippel-Lindau disease tumor suppressor gene. Science. 1993;260:1317-1320.
21. Iliopoulos O, Kibel A, Gray S, et al. Tumour suppression by the human von Hippel-Lindau gene product. Nat Med. 1995;1:822-826.
22. Hall JM, Lee MK, Newman B, et al. Linkage of early-onset familial breast cancer to chromosome 17q21. Science. 1990;250:1684-1689.
23. Margaritte P, Bonaiti-Pellie C, King MC, et al. Linkage of familial breast cancer to chromosome 17q21 may not be restricted to early-onset disease. Am J Hum Genet. 1992;50:1231-1234.

24. Miki Y, Swensen J, Shattuck-Eidens D, et al. A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science. 1994;266:66-71.
25. Wooster R, Neuhausen SL, Mangion J, et al. Localization of a breast cancer susceptibility gene, BRCA2, to chromosome 13q12-13. Science. 1994;265:2088-2090.
26. Wooster R, Bignell G, Lancaster J, et al. Identification of the breast cancer susceptibility gene BRCA2. Nature. 1995;378:789-792.
27. Peinado MA, Malkhosyan S, Velazquez A, et al. Isolation and characterization of allelic losses and gains in colorectal tumors by arbitrarily primed polymerase chain reaction. Proc Natl Acad Sci USA. 1992;89:10065-10069.
28. Aaltonen LA, Peltomäki P, Leach FS, et al. Clues to the pathogenesis of familial colorectal cancer. Science. 1993;260:812-816.
29. Fishel R, Lescoe MK, Rao MR, et al. The human mutator gene homolog MSH2 and its association with hereditary nonpolyposis colon cancer. Cell. 1993;75:1027-1038.
30. Ionov Y, Peinado MA, Malkhosyan S, et al. Ubiquitous somatic mutations in simple repeated sequences reveal a new mechanism for colonic carcinogenesis. Nature. 1993;363:558-561.
31. Peltomäki P, Aaltonen LA, Sistonen P, et al. Genetic mapping of a locus predisposing to human colorectal cancer. Science. 1993;260:810-812.
32. Thibodeau SN, Bren G, Schaid D. Microsatellite instability in cancer of the proximal colon. Science. 1993;260:816-819.
33. Douglas JA, Gruber SB, Meister KA, et al. History and molecular genetics of Lynch syndrome in family G: a century later. JAMA. 2005;294:2195-2202.
34. Chan CY, Tan KV, Cornelissen B. PARP inhibitors in cancer diagnosis and therapy. Clin Cancer Res. 2021;27:1585-1594.
35. Cortesi L, Rugo HS, Jackisch C. An overview of PARP inhibitors for the treatment of breast cancer. Target Oncol. 2021;16:255-282.
36. Foo T, George A, Banerjee S. PARP inhibitors in ovarian cancer: an overview of the practice-changing trials. Genes Chromosomes Cancer. 2021;60:385-397.
37. Teyssonneau D, Margot H, Cabart M, et al. Prostate cancer and PARP inhibitors: progress and challenges. J Hematol Oncol. 2021;14:51.
38. Hasanov E, Jonasch E. MK-6482 as a potential treatment for von Hippel-Lindau disease-associated clear cell renal cell carcinoma. Expert Opin Investig Drugs. 2021;30:495-504.
39. Merck & Co. Inc. Welireg (belzutifan) [package insert]. U.S. Food and Drug Administration website. Updated August 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/215383s000lbl.pdf. Accessed March 13, 2022.
40. Therkildsen C, Jensen LH, Rasmussen M, et al. An update on immune checkpoint therapy for the treatment of Lynch syndrome. Clin Exp Gastroenterol. 2021;14:181-197.
41. Ashworth A, Lord CJ. Synthetic lethal therapies for cancer: what's next after PARP inhibitors? Nat Rev Clin Oncol. 2018;15:564-576.
42. Litton JK, Rugo HS, Ettl J, et al. Talazoparib in patients with advanced breast cancer and a germline BRCA mutation. N Engl J Med. 2018;379:753-763.
43. Robson M, Im SA, Senkus E, et al. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. N Engl J Med. 2017;377:523-533.
44. Turner NC, Balmaña J, Poncet C, et al; BRAVO Steering Committee and the BRAVO investigators. Niraparib for advanced breast cancer with germline *BRCA1* and *BRCA2* mutations: the EORTC 1307-BCG/BIG5-13/TESARO PR-30-50-10-C BRAVO study. Clin Cancer Res. 2021;27:5482-5491.
45. Diéras V, Han HS, Kaufman B, et al. Veliparib with carboplatin and paclitaxel in BRCA-mutated advanced breast cancer (BROCADE3): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2020;21:1269-1282.
46. Robson ME, Tung N, Conte P, et al. OlympiAD final overall survival and tolerability results: olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer. Ann Oncol. 2019;30:558-566.
47. Tutt A, Tovey H, Cheang MCU, et al. Carboplatin in BRCA1/2-mutated and triple-negative breast cancer BRCAness subgroups: the TNT trial. Nat Med. 2018;24:628-637.
48. Turner NC, Telli ML, Rugo HS, et al; ABRAZO Study Group. A phase II study of talazoparib after platinum or cytotoxic nonplatinum regimens in patients with advanced breast cancer and germline *BRCA1/2* mutations (ABRAZO). Clin Cancer Res. 2019;25:2717-2724.
49. Puhalla SL, Diéras V, Arun BK, et al. Relevance of platinum-free interval and *BRCA* reversion mutations for veliparib monotherapy after progression on carboplatin/paclitaxel for g*BRCA* advanced breast cancer (BROCADE3 Crossover). Clin Cancer Res. 2021;27:4983-4993.
50. Vinayak S, Tolaney SM, Schwartzberg L, et al. Open-label clinical trial of niraparib combined with pembrolizumab for treatment of advanced or metastatic triple-negative breast cancer. JAMA Oncol. 2019;5:1132-1140.
51. Domchek SM, Postel-Vinay S, Im SA, et al. Olaparib and durvalumab in patients with germline BRCA-mutated metastatic breast cancer (MEDIOLA): an open-label, multicentre, phase 1/2, basket study. Lancet Oncol. 2020;21:1155-1164.
52. Tutt ANJ, Garber JE, Kaufman B, et al; OlympiA Clinical Trial Steering Committee and Investigators. Adjuvant olaparib for patients with *BRCA1*- or *BRCA2*-mutated breast cancer. N Engl J Med. 2021;384:2394-2405.
53. Masuda N, Lee SJ, Ohtani S, et al. Adjuvant capecitabine for breast cancer after preoperative chemotherapy. N Engl J Med. 2017;376:2147-2159.
54. Schmid P, Cortes J, Dent R, et al; KEYNOTE-522 Investigators. Event-free survival with pembrolizumab in early triple-negative breast cancer. N Engl J Med. 2022;386:556-567.
55. Litton JK, Scoggins ME, Hess KR, et al. Neoadjuvant talazoparib for patients with operable breast cancer with a germline *BRCA* pathogenic variant. J Clin Oncol. 2020;38:388-394.
56. Loibl S, O'Shaughnessy J, Untch M, et al. Addition of the PARP inhibitor veliparib plus carboplatin or carboplatin alone to standard neoadjuvant chemotherapy in triple-negative breast cancer (BrighTNess): a randomised, phase 3 trial. Lancet Oncol. 2018;19:497-509.

57. Geyer CE, Sikov WM, Huober J, et al. Long-term efficacy and safety of addition of carboplatin with or without veliparib to standard neoadjuvant chemotherapy in triple-negative breast cancer: 4-year follow-up data from BrighTNess, a randomized phase III trial. Ann Oncol. 2022;33:384-394.
58. Metzger-Filho O, Collier K, Asad S, et al. Matched cohort study of germline BRCA mutation carriers with triple negative breast cancer in brightness. NPJ Breast Cancer. 2021;7:142.
59. Fasching PA, Link T, Hauke J, et al; German Breast Group and Arbeitsgemeinschaft Gynäkologische Onkologie Breast. Neoadjuvant paclitaxel/olaparib in comparison to paclitaxel/carboplatinum in patients with HER2-negative breast cancer and homologous recombination deficiency (GeparOLA study). Ann Oncol. 2021;32:49-57.
60. Johannes JW, Balazs A, Barratt D, et al. Discovery of 5-{4-[(7-Ethyl-6-oxo-5,6-dihydro-1,5-naphthyridin-3-yl)methyl]piperazin-1-yl}-N-methylpyridine-2-carboxamide (AZD5305): a PARP1-DNA trapper with high selectivity for PARP1 over PARP2 and other PARPs. J Med Chem. 2021;64:14498-14512.
61. Lee MS, Pant S. Personalizing medicine with germline and somatic sequencing in advanced pancreatic cancer: current treatments and novel opportunities. Am Soc Clin Oncol Educ Book. 2021;41:1-13.
62. Rose M, Burgess JT, O'Byrne K, et al. PARP inhibitors: clinical relevance, mechanisms of action and tumor resistance. Front Cell Dev Biol. 2020;8:564601.
63. Golan T, Hammel P, Reni M, et al. Maintenance olaparib for germline *BRCA*-mutated metastatic pancreatic cancer. N Engl J Med. 2019;381:317-327.
64. AstraZeneca Pharmaceuticals LP. Lynparza (olaparib) [package insert]. U.S. Food and Drug Administration website. Updated March 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/208558s023lbl.pdf. Accessed March 13, 2022.
65. Golan T, Hammel P, Reni M, et al. Overall survival from the phase 3 POLO trial: Maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer. J Clin Oncol. 2021;39(suppl 3):378.
66. Nishikawa G, Booth C, Prasad V. Olaparib for BRCA mutant pancreas cancer: should the POLO trial change clinical practice? Cancer. 2020;126:4087-4088.
67. Puccini A, Bregni G, Sciallero S. Maintenance olaparib for metastatic pancreatic cancer. N Engl J Med. 2019;381:1491-1492.
68. Turnbull C, Sud A, Houlston RS. Cancer genetics, precision prevention and a call to action. Nat Genet. 2018;50:1212-1218.
69. André T, Shiu KK, Kim TW, et al; KEYNOTE-177 Investigators. Pembrolizumab in microsatellite-instability-high advanced colorectal cancer. N Engl J Med. 2020;383:2207-2218.
70. Casak SJ, Marcus L, Fashoyin-Aje L, et al. FDA approval summary: pembrolizumab for the first-line treatment of patients with MSI-H/dMMR advanced unresectable or metastatic colorectal carcinoma. Clin Cancer Res. 2021;27:4680-4684.
71. Grothey A. Pembrolizumab in MSI-H-dMMR advanced colorectal cancer - a new standard of care. N Engl J Med. 2020;383:2283-2285.
72. Reiss KA, Forde PM, Brahmer JR. Harnessing the power of the immune system via blockade of PD-1 and PD-L1: a promising new anticancer strategy. Immunotherapy. 2014;6:459-475.
73. Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med. 2015;372:2509-2520.
74. Ricciardiello L, Ceccarelli C, Angiolini G, et al. High thymidylate synthase expression in colorectal cancer with microsatellite instability: implications for chemotherapeutic strategies. Clin Cancer Res. 2005;11:4234-4240.
75. Liu J, Wang B, Fang W. Microsatellite instability and sensitivity to fluoropyrimidine and oxaliplatin containing first-line chemotherapy in metastatic colorectal cancer. Eur J Hosp Pharm Sci Pract. 2020;27:267-270.
76. Aarnio M, Sankila R, Pukkala E, et al. Cancer risk in mutation carriers of DNA-mismatch-repair genes. Int J Cancer. 1999;81:214-218.
77. Marcus L, Lemery SJ, Keegan P, et al. FDA approval summary: pembrolizumab for the treatment of microsatellite instability-high solid tumors. Clin Cancer Res. 2019;25:3753-3758.
78. Jonasch E, Donskov F, Iliopoulos O, et al; MK-6482-004 Investigators. Belzutifan for renal cell carcinoma in von Hippel-Lindau disease. N Engl J Med. 2021;385:2036-2046.
79. Crossey PA, Foster K, Richards FM, et al. Molecular genetic investigations of the mechanism of tumourigenesis in von Hippel-Lindau disease: analysis of allele loss in VHL tumours. Hum Genet. 1994;93:53-58.
80. Duan DR, Pause A, Burgess WH, et al. Inhibition of transcription elongation by the VHL tumor suppressor protein. Science. 1995;269:1402-1406.
81. Kibel A, Iliopoulos O, DeCaprio JA, et al. Binding of the von Hippel-Lindau tumor suppressor protein to Elongin B and C. Science. 1995;269:1444-1446.
82. Kishida T, Stackhouse TM, Chen F, et al. Cellular proteins that bind the von Hippel-Lindau disease gene product: mapping of binding domains and the effect of missense mutations. Cancer Res. 1995;55:4544-4548.
83. Maxwell PH, Wiesener MS, Chang GW, et al. The tumour suppressor protein VHL targets hypoxia-inducible factors for oxygen-dependent proteolysis. Nature. 1999;399:271-275.
84. Hasanov E, Chen G, Chowdhury P, et al. Ubiquitination and regulation of AURKA identifies a hypoxia-independent E3 ligase activity of VHL. Oncogene. 2017;36:3450-3463.
85. Hon WC, Wilson MI, Harlos K, et al. Structural basis for the recognition of hydroxyproline in HIF-1 alpha by pVHL. Nature. 2002;417:975-978.
86. Min JH, Yang H, Ivan M, et al. Structure of an HIF-1alpha -pVHL complex: hydroxyproline recognition in signaling. Science. 2002;296:1886-1889.
87. Ohh M, Park CW, Ivan M, et al. Ubiquitination of hypoxia-inducible factor requires direct binding to the beta-domain of the von Hippel-Lindau protein. Nat Cell Biol. 2000;2:423-427.
88. Bruick RK, McKnight SL. A conserved family of prolyl-4-hydroxylases that modify HIF. Science. 2001;294:1337-1340.

89. Jaakkola P, Mole DR, Tian YM, et al. Targeting of HIF-alpha to the von Hippel-Lindau ubiquitylation complex by O2-regulated prolyl hydroxylation. Science. 2001;292:468-472.

90. Yu F, White SB, Zhao Q, et al. HIF-1alpha binding to VHL is regulated by stimulus-sensitive proline hydroxylation. Proc Natl Acad Sci USA. 2001;98:9630-9635.

91. Clifford SC, Cockman ME, Smallwood AC, et al. Contrasting effects on HIF-1alpha regulation by disease-causing pVHL mutations correlate with patterns of tumourigenesis in von Hippel-Lindau disease. Hum Mol Genet. 2001;10:1029-1038.

92. Knauth K, Bex C, Jemth P, et al. Renal cell carcinoma risk in type 2 von Hippel-Lindau disease correlates with defects in pVHL stability and HIF-1alpha interactions. Oncogene. 2006;25:370-377.

93. Li L, Zhang L, Zhang X, et al. Hypoxia-inducible factor linked to differential kidney cancer risk seen with type 2A and type 2B VHL mutations. Mol Cell Biol. 2007;27:5381-5392.

94. Schödel J, Oikonomopoulos S, Ragoussis J, et al. High-resolution genome-wide mapping of HIF-binding sites by ChIP-seq. Blood. 2011;117:e207-e217.

95. Semenza GL. Hypoxia-inducible factors: mediators of cancer progression and targets for cancer therapy. Trends Pharmacol Sci. 2012;33:207-214.

96. Wang GL, Jiang BH, Rue EA, et al. Hypoxia-inducible factor 1 is a basic-helix-loop-helix-PAS heterodimer regulated by cellular O2 tension. Proc Natl Acad Sci USA. 1995;92:5510-5514.

97. Xia X, Lemieux ME, Li W, et al. Integrative analysis of HIF binding and transactivation reveals its role in maintaining histone methylation homeostasis. Proc Natl Acad Sci USA. 2009;106:4260-4265.

98. Hasanov E, Gao J, Tannir NM. The immunotherapy revolution in kidney cancer treatment: scientific rationale and first-generation results. Cancer J. 2020;26:419-431.

99. Jonasch E, Slack RS, Geynisman DM, et al. Phase II study of two weeks on, one week off sunitinib scheduling in patients with metastatic renal cell carcinoma. J Clin Oncol. 2018;36:1588-1593.

100. Jonasch E, McCutcheon IE, Waguespack SG, et al. Pilot trial of sunitinib therapy in patients with von Hippel-Lindau disease. Ann Oncol. 2011;22:2661-2666.

101. Pilié P, Hasanov E, Matin SF, et al. Pilot study of dovitinib in patients with von Hippel-Lindau disease. Oncotarget. 2018;9:23390-23395.

102. Jonasch E, McCutcheon IE, Gombos DS, et al. Pazopanib in patients with von Hippel-Lindau disease: a single-arm, single-centre, phase 2 trial. Lancet Oncol. 2018;19:1351-1359.

103. Hoffman MA, Ohh M, Yang H, et al. von Hippel-Lindau protein mutants linked to type 2C VHL disease preserve the ability to downregulate HIF. Hum Mol Genet. 2001;10:1019-1027.

104. Kondo K, Kim WY, Lechpammer M, et al. Inhibition of HIF2alpha is sufficient to suppress pVHL-defective tumor growth. PLoS Biol. 2003;1:E83.

105. Erbel PJ, Card PB, Karakuzu O, et al. Structural basis for PAS domain heterodimerization in the basic helix–loop–helix-PAS transcription factor hypoxia-inducible factor. Proc Natl Acad Sci USA. 2003;100:15504-15509.

106. Scheuermann TH, Li Q, Ma HW, et al. Allosteric inhibition of hypoxia inducible factor-2 with small molecules. Nat Chem Biol. 2013;9:271-276.

107. Scheuermann TH, Tomchick DR, Machius M, et al. Artificial ligand binding within the HIF2alpha PAS-B domain of the HIF2 transcription factor. Proc Natl Acad Sci USA. 2009;106:450-455.

108. Chen W, Hill H, Christie A, et al. Targeting renal cell carcinoma with a HIF-2 antagonist. Nature. 2016;539:112-117.

109. Cho H, Du X, Rizzi JP, et al. On-target efficacy of a HIF-2α antagonist in preclinical kidney cancer models. Nature. 2016;539:107-111.

110. Courtney KD, Infante JR, Lam ET, et al. Phase I dose-escalation trial of PT2385, a first-in-class hypoxia-inducible factor-2α antagonist in patients with previously treated advanced clear cell renal cell carcinoma. J Clin Oncol. 2018;36:867-874.

111. Rogers JL, Bayeh L, Scheuermann TH, et al. Development of inhibitors of the PAS-B domain of the HIF-2α transcription factor. J Med Chem. 2013;56:1739-1747.

112. Scheuermann TH, Stroud D, Sleet CE, et al. Isoform-selective and stereoselective inhibition of hypoxia inducible factor-2. J Med Chem. 2015;58:5930-5941.

113. Wallace EM, Rizzi JP, Han G, et al. A small-molecule antagonist of HIF2α is efficacious in preclinical models of renal cell carcinoma. Cancer Res. 2016;76:5491-5500.

114. Wehn PM, Rizzi JP, Dixon DD, et al. Design and activity of specific hypoxia-inducible factor-2α (HIF-2α) inhibitors for the treatment of clear cell renal cell carcinoma: discovery of clinical candidate (S)-3-((2,2-Difluoro-1-hydroxy-7-(methylsulfonyl)-2,3-dihydro-1 H-inden-4-yl)oxy)-5-fluorobenzonitrile (PT2385). J Med Chem. 2018;61:9691-9721.

115. Xu R, Wang K, Rizzi JP, et al. 3-[(1*S*,2*S*,3*R*)-2,3-Difluoro-1-hydroxy-7-methylsulfonylindan-4-yl]oxy-5-fluorobenzonitrile (PT2977), a Hypoxia-Inducible Factor 2α (HIF-2α) Inhibitor for the Treatment of Clear Cell Renal Cell Carcinoma. J Med Chem. 2019;62:6876-6893.

116. Choueiri TK, Bauer TM, Papadopoulos KP, et al. Inhibition of hypoxia-inducible factor-2α in renal cell carcinoma with belzutifan: a phase 1 trial and biomarker analysis. Nat Med. 2021;27:802-805.

117. GlaxoSmithKline. Zejula (niraparib) [package insert]. U.S. Food and Drug Administration website. Updated April 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/209115s004lbl.pdf. Accessed March 13, 2022.

118. Clovis Oncology, Inc. Rubraca (rucaparib) [package insert]. U.S. Food and Drug Administration website. Updated May 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/209115s004lbl.pdf. Accessed March 13, 2022.

119. Bristol-Myers Squibb Company. Opdivo (nivolumab) [package insert]. U.S. Food and Drug Administration website. Updated March 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/225554s112lbl.pdf. Accessed March 13, 2022.

120. Merck & Co. Inc. Keytruda (pembrolizumab) [package insert]. U.S. Food and Drug Administration website. Updated November 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125514s096lbl.pdf. Accessed March 13, 2022.