Recent Development of Wnt Signaling Pathway Inhibitors for Cancer Therapeutics

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Abstract
Purpose of Review  Review current understanding of both canonical and non-canonical Wnt signaling in cancer and provide updated knowledge in current clinical trials of Wnt signaling drugs.
Recent Findings  Important roles of both canonical and non-canonical Wnt signaling in cancer have been increasingly recognized. Recent clinical trials of several Wnt-signaling drugs have showed promising outcomes. In addition, some drugs that were originally approved for the treatment of other diseases have been recently found to block Wnt signaling, highlighting their potential to treat Wnt-dependent cancer.
Summary  Dysfunction of Wnt signaling is implicated in cancer, and targeting Wnt signaling represents a useful approach to treat cancer. Current clinical trials of Wnt signaling drugs have showed promising outcomes, and repurposing the previously approved drugs for other diseases to treat Wnt-dependent cancer requires further studies.

Keywords  Signaling · Cancer · Canonical · Non-canonical · Clinical trial · FDA approved · Wnt/\(\beta\)-catenin · Wnt/Ca\(^{2+}\) · Wnt/PCP · Wnt inhibitor · \(\beta\)-Catenin

Introduction
The evolutionarily conserved Wnt signaling cascade plays fundamental roles during development and homeostasis in virtually every tissue and organ system. Understanding the regulatory functions of this pathway began with the report of the murine proto-oncogene int-1 and subsequent discovery of its homolog Wingless, or Wnt-1, a segment polarity gene in Drosophila [1, 2]. It was observed that manipulation of either int-1 or its ortholog Wnt-1 would result in abnormal developmental conditions [3, 4]. Since then, delineation of the Wnt pathway has provided an insight to the key molecular processes and interacting components underlying this conserved pathway. Tightly concerted regulation of the Wnt pathway ensures normal embryonic development and adult tissue maintenance [5–8], and dysfunction of this signaling pathway may give rise to a plethora of pathologies from human birth deficiencies, neurodegeneration, and skeletal imperfections, to various cancers including gastrointestinal, breast, and epithelial malignancies [9–13]. In this review, we will summarize recent advance in the understanding of both canonical and non-canonical Wnt signaling in cancer as well as progress in the development of Wnt-targeting drugs in clinical trials. In addition, we further discuss the potential of repurposing drug approved for other disease treatment as Wnt inhibitor drugs.

Wnt Signaling Pathways
In mammals, a family of 19 Wnts and 10 Frizzled receptors has been identified, and their interactions lead to activation of the canonical or non-canonical Wnt signaling pathways that governs a myriad of biological processes including stem cell self-renewal, cell proliferation, differentiation, and apoptosis during early embryonic development and adult tissue homeostasis [14]. Classically, the canonical Wnt signaling activation stabilizes cytoplasmic \(\beta\)-catenin which subsequently translocates into nucleus for the transcription of Wnt-specific genes, while the activation of non-canonical Wnt pathway do not use
β-catenin. To date, two of the non-canonical Wnt signaling, the planar cell polarity (PCP) and the Wnt–calcium pathway, have been well characterized [15, 16].

**Canonical Pathway**

The β-catenin-dependent canonical Wnt signaling has been well characterized (Fig. 1A, B). In the absence of extracellular Wnt ligands, β-catenin in the cytoplasm is phosphorylated by an assembly of destruction complex consisted of adenomatous polyposis coli (APC), Ser/Thr kinases glycogen synthase kinase 3-β (GSK3β), and casein kinase 1 α (CK1α) [17]. Phosphorylation of β-catenin by CK1α (Ser45) and GSK3β (at Ser33, Ser37, and Thr41) in humans marks β-catenin for subsequent proteasomal degradation, mediated by β-transducin-repeat-containing protein (β-TrCP) [18]. In the presence of Wnt ligand, the Frizzled receptor interacts with the co-receptor lipoprotein receptor-related protein 5/6 (LRP5/6) which is phosphorylated by CK1γ to create a docking site for Axin [19]. In a mechanism yet to be completely elucidated, Dishevelled (Dsh) is activated and binds to the cytoplasmic tail of the Frizzled receptor, leading to effective sequestration of Axin near the plasma membrane and simultaneous inhibition of GSK3β activity [20]. Localization of the destruction complex near the plasma membrane disrupts β-catenin phosphorylation, resulting in accumulation of unphosphorylated β-catenin molecules which then translocate into the nucleus to interacts with transcriptional factors T cell factor (TCF)/lymphocyte enhancer factor (LEF) for specific gene transcription [21].

**Non-canonical Pathways**

Non-canonical Wnt signaling pathways are β-catenin-independent, and two well-characterized non-canonical Wnt pathways have been classified into either the PCP pathway or the Wnt/Ca2+ pathway according to specific Wnt ligands and their binding receptors and co-receptors (Fig. 1C, D). The PCP signaling is involved in cell division, acquisition of asymmetric cellular morphology, and directional cell migration [22]. Activation of the PCP pathway is initiated by the binding of Wnt to Frizzled receptor and the co-receptors such as PTK7 or ROR2 [8, 23]. Signal transduction through Frizzled receptor attracts Dsh to the cell membrane, where activation is
facilitated through Dishevelled Associated Activator of Morphogenesis 1 (Daam1), leading to downstream signaling by small GTPases Ras-homology gene family member A (RHOA), Ras-Related C3 Botulinum Toxin Substrate 1 (RAC1), and e-JUN-N terminal kinase (JNK) [24]. The culmination of these downstream effects provides a cellular output that coordinates the cytoskeletal scaffolding and the spatial arrangement of cells in multiple developmental processes including embryonic heart induction, cochlear hair cell anatomy, tissue segregation, neuronal arrangement through radial/tangential migration, and dorsoventral regionalization [25, 26].

Wnt/Ca²⁺ signaling is another well-characterized non-canonical Wnt pathway, which helps regulate calcium release from the endoplasmic reticulum to control intracellular calcium levels. Activation of the Wnt/Ca²⁺ pathway is initiated by specific Wnt proteins-stimulated Frizzled receptor to attract and activate Dsh, mediated by g-coupled proteins [27]. Activated heterotrimeric g-proteins prompt the activation of phospholipase C (PLC), which stimulates downstream effectors inositol-1,4,5-triphosphate (IP₃) and diacyl glycerol (DAG) to elicit the intracellular release of calcium [20, 28]. Amplified calcium levels within the cell in turn modulate the activation of calcineurin, Ca²⁺/calmodulin-dependent kinase II (CAMKII), and protein kinase C (PKC), which together stimulate nuclear factor of activated T-cells (NFAT), a transcriptional regulator critical to ventral cell fate determination [20, 29]. Other downstream effects include the impediment of β-catenin/TCF signaling, mediated by (CAMKII) activation of TGFB activated kinase (TAK1) and Nemo-like kinase (NLK), and the polarization of cells during gastrulation moderated through the activation of the cell division control protein 42 homolog (CDC42) GTPase [27, 30].

**Wnt Pathway and Cancer**

It is now well established that dysfunction of the canonical Wnt/β-catenin signaling plays a major role in various human malignancies including mammary, gastrointestinal, hematologic, epithelial, and respiratory cancers [31–35]. The delineation of cancer biology reveals that Wnt signaling activation can be achieved through either mutational or non-mutational alterations [36]. For instance, both gain-of-function mutations in β-catenin and TCF transcriptional regulators and loss-of-function mutations in the destruction complex (such as APC, Axin) can aberrantly activate Wnt signaling [37]. In contrast to mutational activation of Wnt signaling, non-mutational alterations can also activate Wnt signaling by epigenetic silencing of extracellular WNT antagonists [38–40]. Dysfunction of Wnt signaling implicated in cancer has led to the development of signaling modulators to inhibit tumor growth in preclinical models and clinical trials.

In contrast to the canonical Wnt/β-catenin signaling in cancer, whether the non-canonical Wnt pathways also play major roles in oncogenic transformation is still in discussion. However, some recent evidence suggests that cancer cells may hijack the non-canonical Wnt signaling to acquire the ability to migrate and metastasize. For example, the expression of non-canonical Wnt-5a was found to correlate with advanced stages and poor prognosis of gastric cancer, melanoma and mammary cancer [41–43]. Moreover, effects of Wnt5a expression have further been observed in non-small cell lung (NSCLC) and colorectal cancers, with a tendency of increased expression of Wnt5a contributing to the unregulated migration of cancer cells compared to normal tissues [28, 44]. Additional to Wnt5a, other components of the non-canonical Wnt signaling pathways including Vangl-1, Pk1, Dvl1, and Fzd6 have also been observed to be implicated in malignancies [45, 46].

**Therapeutic Agents in Clinical Trials**

Dysfunction of Wnt signaling leads to various types of cancer, and significant efforts have been made to develop potential therapeutic agents to target the various cascade components of Wnt pathway for cancer treatment. As we and others have recently extensively reviewed preclinical agents for the Wnt signaling inhibition, in this article, we mainly focus on the Wnt signaling therapeutic agents which are undergoing clinical trials listed in Table 1 [57*].

**Porcupine Inhibitors**

Porcupine, the membrane bound O-acyltransferase, is essential for Wnt ligand secretion. Among the inhibitors developed to target porcupine for Wnt signaling inhibition [58], two are currently under clinical trials. LGK974 developed by Novartis was shown to effectively block Wnt signaling in vitro and is efficacious in vivo in multiple murine and rat tumor models of breast cancer and head and neck squamous cell carcinoma [52*]. LGK974 is currently under clinical phase 1 trial for the treatment of solid malignancies in patients affected by pancreatic, skin, mammary, head and neck squamous, cervical squamous, and lung squamous cancers [52*, 53]. Recruitment for phase 1 clinical trials is ongoing and the trial is expected to complete in January 2020 (#NCT01351103).

ETC-159 is another porcupine inhibitor that selectively inhibits Wnt modification and secretion [59, 60]. In an ongoing phase 1 clinical trial, ETC-159 is used to treat patients with advanced solid tumors [51*]. To assess its safety and dose tolerance, ETC-159 was given to patients orally once every other day. A dose escalation administration was implemented among 16 patients in 6 cohorts (cohort 1 1 mg; cohort 2 2 mg; cohort 3 4 mg; cohort 4 8 mg; cohort 5 16 mg; cohort 6
Fusion Protein and Wnt Antibody

As overexpression of Wnt ligands or receptors is associated with many tumors, recombinant fusion proteins or antibodies to block the binding of Wnt ligands to receptors or target specific Wnt receptors have been developed, and two of them are under clinical trials [61, 62]. Ipafricept (also known as OMP-54F28) is a truncated Frizzled 8 receptor fused to the IgG1 Fc region to bind Wnt ligands. The preclinical study showed that ipafricept reduces the frequency of cancer stem cells, and results in a metastatic decrease in both liver and lung metastases as well as suppresses pancreatic tumor growth in combination with gemcitabine [63]. In phase 1 study, ipafricept was given intravenously every 3 weeks in 7 dose-escalation cohorts (0.5, 1, 2.5, 5, 10, 15, and 20 mg/kg) for a total of 26 patients with solid tumors. Dose limiting toxicities were assessed every 28 days, and tumor assessment was done every 8 weeks. The result showed that patients well tolerate ipafricept with common adverse effects of dysgeusia, decreased appetite, fatigue, and muscle spasms. Fifteen milligrams per kilogram dose every 3 weeks was recommended for phase 2 study [63, 64]. Recently, three phase 1b studies have been performed to assess the combination of ipafricept with nabcisplatin and gemcitabine for pancreatic cancer treatment, with carboplatin and paclitaxel for ovarian cancer treatment, and with sorafenib for hepatocellular cancer treatment [62]. Primary objectives of all these phase 1b trial are to determine dose limiting toxicities and maximum tolerated dose of ipafricept in the combination therapy as well as assess pharmacokinetics, pharmacodynamics, and efficacy of the drug combination. Though the phase 1b trials were finished recently, complete and detailed clinical outcomes have not been published yet.

Vantictumab (OMP-18R5) is a humanized antibody developed by OncoMed, and it inhibits Wnt signaling by interaction with five Frizzled receptors [1, 2, 5, 7, 8] [65]. Similar to ipafricept, vantictumab inhibits the growth of a range of tumor types, reduces cancer stem cell frequency and exhibits synergistic activity with chemotherapeutic agents in xenograft models [65]. In a phase 1 trial (NCT01345201), 18 patients with advanced solid tumors received vantictumab intravenously in 5 dose-escalation cohorts (0.5 and 1 mg/kg weekly; 0.5 mg/kg every 2 weeks; 1 and 2.5 mg/kg every 2 weeks). Most common adverse events included fatigue, vomiting, abdominal pain, constipation, diarrhea, and nausea. One patient receiving 0.5 mg/kg every week displayed a bone fracture on day 110, and bone toxicity can be effectively resolved by the administration of bisphosphonate zoledronic acid [49]. In conclusion, vantictumab is well tolerated up to 2.5 mg/kg every 3 weeks, and bone toxicity appears manageable and reversible.

In a phase 1b trial to study vantictumab in combination with paclitaxel (at 90 mg/m² on days 1, 8, and 15 of each 28-day cycle) to treat patients with locally recurrent or metastatic breast cancer (NCT01973309), 11 patients in three cohorts received vantictumab in increasing dosages (cohort 1 3.5 mg/kg; cohort 2 7.0 mg/kg; cohort 3 14 mg/kg) in a biweekly manner. Complication with grade 2 fragility fractures was observed in two patients of cohort 3 (14 mg/kg vantictumab treatment), and thus, an enhanced bone safety plan was implemented with 12 patients treated with vantictumab every 4 weeks at 3.5 mg/kg in cohort 4 and at 5.0 mg/kg cohort 5. No further bone fragility fractures were seen in cohorts 4 and 5. Vantictumab is well tolerated in combination with paclitaxel in breast cancer patients, and a number of adverse effects were observed including weakness, fecal impaction, diarrhea, revulsions, neutropenia, and abdominal discomfort [48]. Enrollment for phase 1 clinical experiment continues for implementation of a modified dose

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Table 1 Several potential drugs targeting Wnt signaling are under clinical trial

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>Clinical trial stage</th>
<th>Clinicaltrials.Gov identifier</th>
<th>Condition</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipafricept [OMP-54F28]</td>
<td>Wnt antibody</td>
<td>Phase 1B</td>
<td>NCT02092363</td>
<td>Refractory solid tumors, ovarian cancers</td>
<td>[47]</td>
</tr>
<tr>
<td>Vantictumab [OMP-18R5]</td>
<td>Wnt antibody</td>
<td>Phase 1B/phase 1B</td>
<td>NCT01973309, NCT02005315</td>
<td>Mammary, pancreatic cancers</td>
<td>[48, 49, 50]</td>
</tr>
<tr>
<td>ETC-159</td>
<td>Porcupine</td>
<td>Phase 1A/B</td>
<td>NCT02521844</td>
<td>Advanced solid tumors</td>
<td>[51]</td>
</tr>
<tr>
<td>LGK974</td>
<td>Porcupine</td>
<td>Phase 1</td>
<td>NCT01351103</td>
<td>Pancreatic, melanoma, mammary, head and neck, cervical, and respiratory cancers</td>
<td>[52, 53]</td>
</tr>
<tr>
<td>PRI-724 [ICG-001]</td>
<td>β-Catenin</td>
<td>Phase 1</td>
<td>NCT01764477</td>
<td>Pancreatic cancers</td>
<td>[54]</td>
</tr>
<tr>
<td>CWP232291</td>
<td>β-Catenin</td>
<td>Phase 1A/B</td>
<td>NCT02424723, NCT01398462</td>
<td>Relapsed or refractory multiple myeloma, Acute myeloid leukemia</td>
<td>[55, 56]</td>
</tr>
</tbody>
</table>

30 mg). The study was completed in January 2017, and less than 20% of patients displayed adverse effects including re-gurgitation, weakness, anorexia, dysgeusia, and inability to defecate [51]. Overall, ETC-159 was well tolerated in patients with advanced solid tumors, and next stage of clinical trial is expected to initiate soon.
escalation method (8 mg/kg), specifically adjusted for negating the adverse effects seen in bone composition.

In another clinical phase 1b study (NCT02005315), vantictumab was given intravenously to stage IV pancreatic cancer patients in combination with 125 mg/m² nab-paclitaxel (Nab-P) at and 1000 mg/m² gemcitabine that were administered on days 1, 8, and 15 of 28-day cycles [49, 50]. Among 19 patients treated with vantictumab in four dose escalation cohorts, eight patients in cohort 1 (n = 3) and cohort 2 (n = 5) were administrated vantictumab (3.5 mg/kg in cohort 1 and 7.0 mg/kg in cohort 2 in a biweekly manner with combination of Nab-P and gemcitabine). Two patients experienced grade 2 bone fragility fractures. Subsequently, 11 patients were treated in two cohorts (cohort 3, n = 7; 3.0 mg/kg vantictumab) and cohort 4, n = 9; 5.0 mg/kg vantictumab) contingent upon enhanced bone safety protocols. Common adverse effects in this clinical trial include nausea, fatigue, and dysgeusia, reported in less than 10% of patients [49].

**β-Catenin Inhibitors**

PRI-724 is a small molecule Wnt signaling inhibitor that blocks the interaction between β-catenin and its transcriptional coactivator CREB-binding protein (CBP) [66]. PRI-724 was shown to induce cancer stem cell differentiation and increase sensitivity to cytotoxic or targeted drugs in preclinical studies [67]. In the treatment of patients with advanced solid tumors (NCT01302405), PRI-724 was shown to have an acceptable toxicity and downregulated survivin expression in tumors (NCT01302405), PRI-724 was shown to have an acceptable toxicity and downregulated survivin expression in circulating tumor cells. Studies combining PRI-724 with chemotherapy are underway [68].

In an ongoing phase 1b clinical trial (NCT01764477), PRI-724 in combination with chemotherapy drug, gemcitabine, is implemented as a second-line therapy following original therapeutic intervention with FOLFIRINOX or FOLFOX, in the treatment of patients with metastatic pancreatic cancer [54]. In an escalation design of drug administration, patients were administered gemcitabine at dose 1000 mg/m² in combination with escalating doses of PRI-724 infusions that were given for seven consecutive days, in a biweekly manner. Twenty patients were divided into three dose-dependent cohorts (cohort 1 320 mg/m²/day; cohort 2 640 mg/m²/day; cohort 3 905 mg/m²/day), and eight patients showed responses characterized by stable disease, with five of those eight patients experiencing decreased carbohydrate antigen 19-9 levels [54]. This phase 1b trial concluded that PRI-724 combined with gemcitabine is safe with modest clinical activity, warranting next phase clinical trial.

CWP232291 (CWP291) is a peptide mimetic selectively acting on Wnt/β-catenin transcriptional products, effectively lowering the expression of genes including survivin and cyclin D1. In a phase 1a study of CWP291, patients with relapsed or refractory myeloma were treated with CWP291 in a biweekly through intravenous administration for three in a 4-week cycle [55]. This method of design was observed to be well taken by patients, and continuation of this study will observe the effects of CWP291 in combination with immunomodulatory agents lenalidomide and corticosteroid dexamethasone in phase 1b trials [55]. In a recently completed clinical trial involving the implementation of CWP291 in patients with acute myeloid leukemia, individuals under study were administered CWP291 through intravenous infusion every day for 3 weeks, following standard 3 + 3 dose escalation [56]. Common adverse effects of this drug include biliousness, infusion-associated event, heaving, diarrhea, and eating disorders [56]. This increased dosage administration yields a complete remission in one acute myeloid leukemia patient at doses of 153 and 118 mg/m², although no other significant responses were seen among the 56 patients reported, of which 53 patients had acute myeloid leukemia, while 3 patients were affected by myelodysplastic syndrome [56].

**Drugs Repurposed for Wnt-Dependent Cancer**

Although several Wnt signaling inhibitors have gone to clinical trials, to date, no specific Wnt signaling drugs have been approved for clinical use. However, several drugs (Table 2), which were originally approved to treat other diseases, have been recently found to inhibit Wnt signaling, and thus, they could be repurposed for Wnt-dependent cancer treatment in the future. A few important examples of such drugs are elaborated below.

**Ethacrynic Acid**

Originally approved as a loop diuretic drug, ethacrynic acid has been recently found to dose-dependently inhibit Wnt signaling specific luciferase assay. Further experiments indicated that ethacrynic acid disrupts the formation of the LEF-1/β-catenin complex required for the transcription of Wnt target genes in the nucleus [86]. Multiple reports showed that ethacrynic acid effectively increases cell apoptosis of chronic lymphocytic leukemia cells, a disease associated with aberrant activation of lymphoid LEF1 [86, 87]. Additionally, it was observed that ethacrynic acid effectively restricts aberrant cell growth in Hep3B and HepG2 hepatic cancer lines [70].

**Pyrvinium Pamoate**

Pyrvinium pamoate was originally approved as an antiparasitic drug, and its role in the Wnt signaling pathway has not been revealed until recently. Early report showed that pyrvinium pamoate selectively activates casein kinase 1α (CK1α) kinase activity to suppress the Wnt pathway [88]. However, recent data support that pyrvinium pamoate does not activate CK1α inhibition of β-catenin.
but rather activates GSK-3β to phosphorylate β-catenin for degradation [89]. In addition, several studies demonstrated that pyrvinium pamoate dose-dependently decreases the cell viability and restricts cancer stem cell regeneration and proliferation in the various breast cancer lines and melanoma lines [75–77].

### Pimozide

Pimozide is a FDA-approved clinical drug for the treatment of psychotic diseases, Tourette syndrome and resistant tics. Recent several studies showed that pimozide suppresses the growth of hepatocellular carcinoma colorectal cancer in mouse models though inhibition of canonical Wnt/β-catenin signaling pathway [71, 90]. However, the molecular target of pimozide in Wnt/β-catenin signaling still remains unknown.

### Non-steroidal Anti-inflammatory Drugs

Celecoxib is a NSAID drug and was initially approved as a selective cyclooxygenase-2 (COX-2) inhibitor to treat rheumatoid arthritis and inflammation disorders [91–94]. Previous studies detailed the use of celecoxib in patients with familial adenomatous polyposis and showed significant attenuation of the amount of colorectal polyps, indicating celecoxib as a plausible agent for cancer therapy [72]. More recently, celecoxib has been shown to suppress mammary cancer stem cell renewal, enhance responsiveness to chemotherapeutic agents, impede epithelial to mesenchymal transition, and mitigate metastatic potential in MCF-7 and MDA-MB-231 cells by inhibiting the synthesis of prostaglandin E2 to promote β-catenin degradation [73]. In addition, a study of a celecoxib analog, 2,5-dimethylcelecoxib (DM-celecoxib) showed the growth attenuation of Wnt-dependent colorectal cancer lines in vitro and suppression of the intestinal cancer growth in Mutyh−/− mice in vivo [74]. In addition, sulindac, another NSAID, was shown to increase β-catenin degradation for Wnt signaling inhibition and its anti-cancer property was reported in multiple studies [95–97]. For instance, sulindac effectively induces colorectal cancer cell growth and apoptosis in vitro [81] and reduces tumor growth of and prevent metastasis of colon cancer in mouse model [97].

### Niclosamide

Niclosamide is a FDA-approved anti-parasitic drug, and it was identified to displays anti-tumorigenic effects through the negative regulative of Wnt signaling in various cancer cells lines including colorectal, prostatic, and ovarian [82, 83, 84, 85]. Niclosamide mediates several actions in modulation the Wnt transduction signal including the internalization of membrane receptor Frizzled, reduction of Dishevelled protein activity, and restriction of β-catenin stabilization [98]. Application of niclosamide in cancer treatment has only recently been investigated with limited amount of data available; further, more detailed target study and clinical trials are warranted.

### Conclusions

Wnt signaling is a fundamental regulatory pathway implicated in the maintenance of normal physiological function, and dysregulation of this pathway is implicated in a plethora of diseases including cancer. Consequently, significant efforts have been made to develop therapeutic agents to target Wnt signaling. Though several Wnt-signaling inhibitors are under early clinical trials with promising outcome, to date, no Wnt-specific drugs have been approved for clinical use. Interestingly, recent studies demonstrated that multiple previous drugs approved for the treatment of other diseases can actually inhibit Wnt/β-catenin signaling, supporting the possibility to repurpose these drugs for Wnt-dependent cancer therapy. Despite the significant progress in Wnt signaling drug development, we shall bear in mind that the Wnt signaling is essential in adult tissue homeostasis and repair, and some key targets in Wnt signaling are also implied in other signaling pathways. Therefore, targeting Wnt signaling for cancer treatment may cause other adverse events.
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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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• Of importance


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