Wnt pathways in focus: mapping current clinical trials across cancer spectrum

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Wnt pathways in focus – mapping current clinical trials across cancer spectrum

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The Wnt pathway has a pivotal function in tissue development and homeostasis, overseeing cell growth or differentiation. Aberrant Wnt signalling pathways have been associated with the pathogenesis of diverse malignancies, influencing cell proliferation, differentiation, cancer stem cell renewal, tumor microenvironment and thereby significantly impacting tumour development and therapeutic responsiveness. Promisingly, current research underscores the potential therapeutic value of targeting Wnt pathways, particularly the canonical Wnt/β-catenin signalling, in the context of numerous cancer types.

Key constituents of the Wnt pathway, such as the Wnt/receptor, β-catenin degradation or transcription complexes, have been focal points for interventions in preclinical studies. To comprehend potential therapeutic strategies, we conduct an analysis of ongoing clinical trials that specifically aim to target components of the Wnt pathways across a diverse spectrum of cancer types. By scrutinizing these trials, including their respective phases, targeted patient populations, and observed outcomes, this review provides a consolidated overview of the current translational landscape of Wnt-targeted therapies, thus offering a roadmap for future research endeavours.

Key words: cancer, clinical trials, Wnt signalling pathways, targeted therapy
Introduction

Cancer is one of the main cause of death worldwide [1]. While chemotherapy remain the backbone of systemic treatment for both radically and palliatively treated cancer patients population new options including growing number of molecularly targeted drugs enter the market with new and new indications [2]. The journey from the initial discovery of a compound to its approval by regulatory bodies like the Food and Drug Administration (FDA) or the European Medicines Agency (EMA) is an extensive process. It initiates with preclinical evaluations and advances through a multi-stage series of clinical trials involving human subjects. A significant proportion of compounds displaying promise in the preclinical phase ultimately do not achieve the specified endpoints during the clinical trial phases [3–6]. Figure 1 succinctly outlines this intricate progression.

There are numerous signaling pathways abruptlyed in cancer cells that have been already used as targets for different therapeutic strategies including kinase inhibitors (Kis), monoclonal antibodies (mAbs), antibody-drug conjugates (ADCs), drugs' nanoforms [2]. Activation of these pathways can induce alterations in cell survival capabilities, metabolic processes, cellular proliferation, differentiation, and impact the tumor microenvironment. Moreover, it plays a role in angiogenesis, epithelial to mesenchymal transition, and the formation of metastases [7–10]. Among the numerous pathways with key components that are established targets for treatment, prominent examples comprise epidermal growth factor receptor/RAS/rapidly accelerated fibrosarcoma/mitogen-activated protein kinase kinase (EGFR/RAS/RAF), human epidermal growth factor receptor 2 (HER2), Sonic hedgehog (SHH), vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and protein kinase B/mammalian target of rapamycin (AKT/mTOR). It is noteworthy that these pathways' elements often intersect during signal transduction [7–10]. Wnt represents a fundamental pathway crucial in both embryonic development and the onset of tumorigenesis [11]. Presently, there are no registered drugs specifically targeting the elements of this pathway, despite it presenting an apparent target for innovative anticancer agents. The objective of this review is to delve into the prospects of translating elements of the Wnt pathway from preclinical research to clinical applications. Through meticulous examination of these trials, encompassing their phases, targeted population, and the active drug studied the review furnishes a comprehensive summary of the present translational panorama concerning therapies directed at the Wnt pathways.
Canonical and non-canonical Wnt signalling

The Wnt pathway plays a pivotal role in numerous developmental and homeostatic processes. Aberrations within this pathway have been implicated in a spectrum of pathological conditions, including cancers. The intricate balance and regulation of the Wnt pathway underscore its paramount importance in cellular homeostasis, presenting a potential target for therapeutic interventions in malignancies and other diseases.

There are in fact several signaling pathways that can be activated with the elements of Wnt. The canonical pathway is the most well-known (fig. 2). At the core of this pathway lies β-catenin, a key protein acting as a linchpin orchestrating downstream signaling events. Two other pathways are planar cell polarity (PCP) and calcium-related pathways [11–16].

Wnt proteins are categorized into canonical and noncanonical types, instigating both respective pathways by engaging Frizzled (FZD) receptors (tab. 1). Frizzled receptors require a co-receptor, low-density lipoprotein receptor-related protein 5/6 (LRP5/6) for canonical signaling, and receptor tyrosine kinase-like orphan receptor 1/2 (ROR1/2) for non-canonical signaling, to transmit signals effectively [11–17].

Within the canonical pathway, upon activation, Wnt binding disrupts the β-catenin destruction complex, preventing the phosphorylation of β-catenin by GSK3β, thereby averting its proteasomal degradation. Key components of the destruction complex include:

- adenomatous polyposis coli (APC),
- glycogen synthase kinase 3-beta (GSK-3β),
- axin, casein kinase 1-alpha (CK1-α).

The accumulation of β-catenin in the cytoplasm enables its translocation into the nucleus, where it forms complexes with various transcription factors, primarily lymphoid enhancer factor/T-cell factor (LEF/TCF), initiating the transcription of vital Wnt/β-catenin target genes such as: cMyc, cyclin D1 (CCND1), and VEGF or programmed death-ligand 1 (PD-L1) [11–16].

Non-canonical Wnt pathways are Wnt / PCP and Wnt-cyclic guanosine monophosphate / calcium ion (Wnt-cGMP/Ca2+) signaling. The targets for these non-canonical pathways can include matrix metalloproteinases (MMPs) or AKT / mTOR. These pathways are believed to exert influence on processes such as epithelial-mesenchymal
transition (EMT), cell migration, cell metabolism, chemo-resistance, or the formation of metastases [11, 16, 17].

**Preclinical and clinical cancer studies regarding Wnt elements**

Inhibition of the Wnt pathway represents an interesting and promising molecular target for novel anticancer therapies in various malignancies. Many new molecules have been investigated in preclinical studies or in clinical trials – mainly phase 1 (tab. II). Some of them have reached phase 2 clinical trials in the treatment of solid malignancies, as well as hematologic, but recruitment is ongoing or the results of those trials are expected to be published. The interesting approach represents the combination of Wnt inhibitors with chemotherapy of targeted therapies – PD-1/PD-L1 inhibitors (nivolumab / pembrolizumab) or EGFR inhibitors (cetuximab).

Katoh and Katoh divided Wnt-targeted agents into pan-Wnt inhibitors (like porcupine inhibitors), canonical (like β-catenin protein-protein inhibitor) and non-canonical (like ROR1 inhibitors) [12]. However, there is a significant group of compounds that modulate the signal indirectly or influence Wnt signalling by interfering with other pathways (like SHH). β-catenin itself plays an important role as signal transducer in other pathways including Trophoblast Cell Surface Antigen 2 (TROP-2) [138].

Current trials, as shown in table II, involve drugs acting on numerous levels of these signaling pathways:

- **Outside the cancer cell / on the cell membrane level**: Wnt-mimicking agents [79, 80]; monoclonal antibody against ROR1 (cirmtuzumab) [82–86]; Wnt proteins / receptors inhibitors like: porcupine inhibitors LGK974, ETC-1922159, CGX1321, RXC004, XNW7201 [31–41] or FZD inhibitors (vantictumab, ipafricept, OTSA101) [42–53]. Porcupine serves as a vital enzyme within the Wnt signaling pathway, aiding in the palmitoylation of Wnt proteins. This alteration is pivotal for the appropriate secretion of Wnt proteins and the initiation of the Wnt signaling pathway [139]. Monoclonal antibodies against protein tyrosine kinase 7 (PTK7), can also be included into that group. PTK-7 is a transmembrane receptor protein that has been implicated in the regulation of the Wnt signaling pathway (cofetuzumab pelidotin) [94–102].
In the cytoplasm: dikkopf-1 (DKK1) modulators (DKN-01) [66–71]. Functioning as an extracellular antagonist, DKK1 binds to LRP5/6 co-receptors, interrupting their engagement with Wnt ligands and obstructing the activation of the canonical Wnt pathway. This impediment leads to a halt in the accumulation and nuclear movement of β-catenin [140].

Within the nucleus e.g. inhibiting the target canonical pathway genes [125, 126] or CREB-binding protein (CBP) / β-catenin inhibitors (ICG-001, PRI-724, PRI-724 [26,56-60, 89-96]. CBP serves as a coactivator for transcription within the canonical Wnt pathway, collaborating with transcription factors such as β-catenin. It amplifies the transcription of Wnt target genes by modifying chromatin structure through the acetylation of histones [141].

Within other signaling pathways that interact with Wnt including SHH (vismodegib, sonidegib, itraconazole, glasdegib, patidegib, LY2940680, ENV-101) as the most visible example [101–121].

While compounds acting on β-catenin degradation complex show activity in preclinical studies their clinical activity has not been confirmed yet (NVP-TNKS656, XAV939) [54, 55]. Numerous limitations accompany development of Wnt pathways’ inhibitors. They include: non-obvious role of Wnt elements in cancer development and progression, its role in physiological processes, its complexity. Notably, WNT inhibitors have the potential to serve not only in cancer therapy but also in a supportive capacity to mitigate treatment-related toxicity [11–17, 142].

Numerous novel molecules have undergone scrutiny in either preclinical investigations or clinical trials. A portion of these compounds has progressed to phase 2 clinical trials, marking the mid-point in the translational process depicted in figure 1.

Conclusions

The precise equilibrium and meticulous regulation observed in the Wnt pathway underline its paramount importance in maintaining cellular homeostasis, thereby delineating it as a
promising focal point for therapeutic interventions directed at malignancies. The Wnt pathway branches into canonical and noncanonical categories, each instigating distinctive signaling cascades through specific receptor engagement. A comprehensive understanding of these pathways and their constituent elements is imperative for discerning their potential therapeutic ramifications. Presently, preclinical and clinical inquiries into Wnt elements are progressing, presenting an enticing trajectory for the development of novel anticancer therapies. However, the intricate nature of Wnt signaling, its dual role in both disease and physiological homeostasis, and the complexities surrounding its inhibitors pose formidable challenges. The number of trials and the variety of molecular targets related to Wnt pathways, as well as different cancer indications within the patient population (tab. II) provide grounds for optimism regarding the possibility of advancing beyond the early phases of clinical trials in the journey from bench to bedside (fig. 1).

**Article information and declarations**

**Author contributions**

Renata Pacholczak-Madej – study conception and design, material collection, analysis and interpretation of results: all authors; manuscript preparation.

Mirosława Püsküllüoğlu – study conception and design, material collection, analysis and interpretation of results: all authors; manuscript preparation.

Paulina Frączek – manuscript critical review.

Klaudia Skrzypek – manuscript critical review.

All authors have approved the final version of the paper.

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**Conflict of interest**

None declared
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References


[102] CHMP. VISMODEGIB- ANNEX I SUMMARY OF PRODUCT CHARACTERISTICS.


[104] CHMP. SONIDEGIB- ANNEX I SUMMARY OF PRODUCT CHARACTERISTICS.


Figure 1. Sequential stages of drug discovery and registration [3–6]
Figure 2. Canonical Wnt pathway inactive (on the left hand side) and active (on the right hand side) (created with BioRender) [11–16]

APC – *adenomatous polyposis coli*; CBP – CREB-binding protein; CK1-α GSK3β – casein kinase 1-alpha; GSK – glycogen synthase kinase 3-beta; LEF – lymphoid enhancer factor; LRP – low-density lipoprotein receptor-related protein; TCF – T cell factor

Table I. Canonical and non-canonical elements of the Wnt family [11, 16]

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Proteins</th>
</tr>
</thead>
<tbody>
<tr>
<td>canonical</td>
<td>Wnt / β-catenin</td>
</tr>
<tr>
<td></td>
<td>Wnt1, Wnt2, Wnt3, Wnt3a,</td>
</tr>
<tr>
<td></td>
<td>Wnt8a, Wnt8b, Wnt10a,</td>
</tr>
<tr>
<td></td>
<td>Wnt10b</td>
</tr>
<tr>
<td>non canonical</td>
<td>PCP</td>
</tr>
<tr>
<td></td>
<td>Wnt3, Wnt4, Wnt5a, Wnt5b,</td>
</tr>
<tr>
<td></td>
<td>Wnt6, Wnt7a, Wnt7b, Wnt11</td>
</tr>
</tbody>
</table>

PCP – planar-cell polarity
Table II. Agents inhibiting Wnt pathway which are under investigation. Complied on a basis of clinicaltrials.gov as of April 2023, unless otherwise specified

<table>
<thead>
<tr>
<th>Name of agent</th>
<th>Mechanism of action</th>
<th>Development stage</th>
<th>Indications</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>PKF115–584, CGP049090, PKF222–815, PKF118–310, PKF118–744, ZTM000990</td>
<td>β-catenin – TCF antagonists</td>
<td>preclinical</td>
<td>colorectal cancer, breast cancer</td>
<td>[18, 19]</td>
</tr>
<tr>
<td>iCRT3, iCRT5, iCRT14</td>
<td>β-catenin – TCF antagonists</td>
<td>preclinical</td>
<td>colorectal cancer, triple negative breast cancer</td>
<td>[20, 21]</td>
</tr>
<tr>
<td>BC21</td>
<td>β-catenin – TCF antagonists</td>
<td>preclinical</td>
<td>colorectal cancer</td>
<td>[22]</td>
</tr>
<tr>
<td>CWP232228</td>
<td>β-catenin – TCF antagonists</td>
<td>preclinical</td>
<td>breast cancer</td>
<td>[25]</td>
</tr>
<tr>
<td>ICG-001</td>
<td>β-catenin / CBP inhibitor</td>
<td>preclinical</td>
<td>triple negative breast cancer</td>
<td>[26]</td>
</tr>
<tr>
<td>CG0009</td>
<td>glycogen synthase kinase 3α/β inhibitor</td>
<td>preclinical</td>
<td>breast cancer</td>
<td>[27]</td>
</tr>
<tr>
<td>niclosamide</td>
<td>inhibition the binding of a WNT ligand to LRPS/6 receptors</td>
<td>preclinical</td>
<td>breast cancer</td>
<td>[28]</td>
</tr>
<tr>
<td>salinomycin</td>
<td>inhibition the binding of a WNT ligand to LRPS/6 receptors</td>
<td>preclinical</td>
<td>breast cancer, prostate cancer, chronic lymphocytic leukemia</td>
<td>[29, 30]</td>
</tr>
<tr>
<td>LGK974 (WNT974)</td>
<td>inhibitor of the WNT-receptor complex (porcupine inhibitor)</td>
<td>phase 1 clinical trial, recruiting phase 1 and 2 clinical trial + cetuximab, completed</td>
<td>pancreatic cancer, BRAF-mutant colorectal cancer, melanoma, triple negative breast cancer, head and neck squamous cell cancer, cervical squamous cell cancer, esophageal squamous cell cancer, lung squamous cell cancer</td>
<td>[31]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>braf-mutant metastatic colorectal cancer</td>
<td>[32]</td>
</tr>
<tr>
<td><strong>Chemical Name</strong></td>
<td><strong>Pharmacological Action</strong></td>
<td><strong>Clinical Trial Phase</strong></td>
<td><strong>Tumor Type</strong></td>
<td><strong>References</strong></td>
</tr>
<tr>
<td>------------------</td>
<td>---------------------------</td>
<td>-------------------------</td>
<td>----------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Ewing sarcoma</td>
<td></td>
<td>preclinical</td>
<td></td>
<td>[33]</td>
</tr>
<tr>
<td>clear cell, renal cell carcinoma</td>
<td></td>
<td>preclinical</td>
<td></td>
<td>[34]</td>
</tr>
<tr>
<td>ETC-1922159</td>
<td>inhibitor of the WNT-receptor complex (porcupine inhibitor)</td>
<td>phase I clinical trial +/- pembrolizumab, recruiting</td>
<td>advanced solid tumors</td>
<td>[35]</td>
</tr>
<tr>
<td>CGX1321</td>
<td>Inhibitor of the WNT-receptor complex (porcupine inhibitor)</td>
<td>phase I clinical trial +/- pembrolizumab or encorafenib + cetuximab, recruiting</td>
<td>advanced gastrointestinal tumors</td>
<td>[36]</td>
</tr>
<tr>
<td>REX1711</td>
<td>inhibitor of the WNT-receptor complex (porcupine inhibitor)</td>
<td>phase I clinical trial +/- nivolumab, recruiting</td>
<td>advanced solid tumors</td>
<td>[38]</td>
</tr>
<tr>
<td>XNW7201</td>
<td>inhibitor of the WNT-receptor complex (porcupine inhibitor)</td>
<td>phase 1 clinical trial, active, not recruiting</td>
<td>advanced solid tumors</td>
<td>[41]</td>
</tr>
<tr>
<td>OMP-18R5 (vantiectumab)</td>
<td>inhibitor of the WNT-receptor complex (antibody against WNT family proteins - namely FZD1, FZD2, FZD5, FZD7 and FZD8)</td>
<td>phase 1 clinical trial, completed</td>
<td>advanced solid tumors</td>
<td>[42]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>phase 1 clinical trial +/- nab-paclitaxel and gemcitabine, completed</td>
<td>advanced pancreatic cancer</td>
<td>[43, 44]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>phase 1b clinical trial + docetaxel, completed</td>
<td>non-small cell lung cancer</td>
<td>[45]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>phase 1b clinical trial, completed</td>
<td>metastatic breast cancer</td>
<td>[46]</td>
</tr>
<tr>
<td>OMP-54F28 (ipafricept)</td>
<td>inhibitor of the WNT-receptor complex (antibody against WNT family proteins - namely FZD 8 receptor)</td>
<td>phase 1 clinical trial, completed</td>
<td>advanced solid tumors</td>
<td>[47, 48]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>phase 1 clinical trial + sorafenib, completed</td>
<td>hepatocellular cancer</td>
<td>[49]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>phase 1 clinical trial + paclitaxel and carboplatin, completed</td>
<td>ovarian cancer</td>
<td>[50, 51]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>phase 1 clinical trial + nab-paclitaxel and gemcitabine, completed</td>
<td>pancreatic cancer</td>
<td>[52]</td>
</tr>
<tr>
<td>OTSA101</td>
<td>inhibitor of the WNT-receptor complex</td>
<td>phase 1 clinical trial, recruiting</td>
<td>synovial sarcoma</td>
<td>[53]</td>
</tr>
</tbody>
</table>
| **receptor complex**  
| (antibody against Wnt family proteins – namely FZD 10 receptor) |  |  |
| **NVP-TNKS656**  
| β-catenin-destruction complex inhibitors, namely tankyrase inhibitors (PARP family) | preclinical | colorectal cancer | [54] |
| **XAV939**  
| β-catenin-destruction complex inhibitors, namely tankyrase inhibitors (PARP family) | preclinical | breast cancer | [55] |
| **PRI-724**  
| inhibition of the CBP and β-catenin interaction | phase 1a/1b clinical trial, terminated | advanced solid tumors | [56, 57] |
|  | phase 1 clinical trial + gemcitabine, completed | pancreatic cancer | [58, 59] |
|  | phase 1 and 2 clinical trial, completed | acute myeloid leukemia, chronic myeloid leukemia | [60] |
| **CWP232291**  
| inhibitor of the WNT pathway, induction of apoptosis via activation of caspases | phase 1 clinical trial, completed | refractory acute myeloid leukemia, chronic myelomonocytic leukemia, myelodysplastic syndrome, myelofibrosis | [61, 62] |
|  | phase 1 clinical trial +/- lenalidomide, dexamethasone, completed | multiple myeloma | [63, 64] |
|  | phase 1 and 2 clinical trial, active, not recruiting | acute myeloid leukemia | [65] |
| **DKN-01**  
<p>| monoclonal antibody, inhibitor of the DKK1 activity, a modulator of Wnt / β-catenin signaling | phase 1 clinical trial +/- paclitaxel or pembrolizumab, completed | esophageal cancer gastroesophageal junction cancer, gastric adenocarcinoma with Wnt signaling alterations | [66, 67] |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Phase</th>
<th>Treatment</th>
<th>Eligibility</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>phase 1 clinical trial + gemcitabine/cisplatine, completed</td>
<td>carcinoma primary to the intra- or extra-hepatic biliary system or gallbladder</td>
<td>[68, 69]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>phase 1b/2a clinical trial +/- docetaxel, recruiting</td>
<td>prostate cancer</td>
<td>[70, 71]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>phase 1 and 2 clinical trial +/- sorafenib, recruiting</td>
<td>advanced liver cancer</td>
<td>[72]</td>
</tr>
<tr>
<td></td>
<td>phase 2 clinical trial</td>
<td>+ nivolumab, recruiting</td>
<td>advanced biliary tract cancer</td>
<td>[73]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+/- paclitaxel, completed</td>
<td>endometrial cancer, uterine cancer, ovarian cancer, carcinosarcoma</td>
<td>[74]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>phase 2 clinical trial + tislelizumab +/- chemotherapy, recruiting</td>
<td>gastric cancer, gastroesophageal cancer</td>
<td>[75]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>phase 1 clinical trial, completed</td>
<td>multiple myeloma, solid tumors, non-small cell lung cancer</td>
<td>[76, 77]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>phase 1 clinical trial + lenalidomide/dexamethasone, completed</td>
<td>relapsed or refractory multiple myeloma</td>
<td>[77]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>phase 1 and 2 clinical trial + atezolizumab, recruiting</td>
<td>metastatic esophageal cancer, metastatic gastric cancer</td>
<td>[78]</td>
</tr>
<tr>
<td>Foxy-5</td>
<td>WNT5A-mimicking peptide</td>
<td>phase 1 clinical trials, completed</td>
<td>breast cancer, colon cancer, prostate cancer</td>
<td>[79, 80]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>phase 2 clinical trial, recruiting</td>
<td>colon cancer (neoadjuvant setting)</td>
<td>[81]</td>
</tr>
<tr>
<td>UC-961 (cirmtuzumab)</td>
<td>monoclonal antibody against ROR1 of the non-canonical Wnt pathway</td>
<td>phase 2 clinical trial + docetaxel, not yet recruiting</td>
<td>metastatic castration resistant prostate cancer</td>
<td>[82]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>phase 1 clinical trial, completed</td>
<td>relapsed or refractory chronic lymphocytic leukemia</td>
<td>[83, 84]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>phase 1 and 2 clinical trial + ibrutinib, active, not recruiting</td>
<td>b-cell lymphoid malignancies</td>
<td>[85, 86]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>phase 2 clinical trial, recruiting</td>
<td>chronic lymphocytic leukemia, consolidation after venetoclax</td>
<td>[87]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>phase 1 clinical trial + paclitaxel, active, not recruiting</td>
<td>breast cancer</td>
<td>[88]</td>
</tr>
<tr>
<td>PRI-724</td>
<td>CBP / β-catenin antagonist</td>
<td>phase 2 clinical trial + FOLFOX and bevacizumab,</td>
<td>metastatic colorectal cancer</td>
<td>[89]</td>
</tr>
<tr>
<td>Compound</td>
<td>Description</td>
<td>Clinical Trials</td>
<td>Target Conditions</td>
<td></td>
</tr>
<tr>
<td>----------</td>
<td>-------------</td>
<td>-----------------</td>
<td>------------------</td>
<td></td>
</tr>
<tr>
<td><strong>PF-06647020</strong>&lt;br&gt;(cofetuzumab pelidotin)</td>
<td>Monoclonal antibody against PTK7 - inhibition of non-canonical WNT pathway</td>
<td>Phase 1 clinical trial + gedatolisib, completed</td>
<td>Advanced solid tumors [94–96]</td>
<td></td>
</tr>
<tr>
<td><strong>GDC-0449</strong>&lt;br&gt;(vismodegib)</td>
<td>Inhibitor of the Hedgehog pathway</td>
<td>FDA and EMA registered</td>
<td>Metastatic/locally advanced basal cell carcinoma [101, 102]</td>
<td></td>
</tr>
<tr>
<td><strong>LDE225</strong>&lt;br&gt;(sonidegib)</td>
<td>Inhibitor of the Hedgehog pathway</td>
<td>FDA and EMA registered</td>
<td>Metastatic/locally advanced basal cell carcinoma [103, 104]</td>
<td></td>
</tr>
<tr>
<td>itraconazole</td>
<td>Antifungal medication, inhibitor of the Hedgehog pathway</td>
<td>Numerous clinical trials phase 1-3</td>
<td>Advanced solid tumors (also advanced breast cancer) hematologic malignancies #</td>
<td></td>
</tr>
<tr>
<td><strong>PF-04449913</strong>&lt;br&gt;(glasdegib)</td>
<td>Inhibitor of the Hedgehog pathway</td>
<td>Phase 1 and 2 clinical trials</td>
<td>Hematologic malignancies [105, 106]</td>
<td></td>
</tr>
<tr>
<td><strong>IPI-926</strong>&lt;br&gt;(patidegib)</td>
<td>Inhibitor of the Hedgehog pathway</td>
<td>Phase 1 clinical trial, completed</td>
<td>Basal cell carcinoma [108]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Phase 1 and 2 clinical trial + gemcitabine, completed</td>
<td>Pancreatic cancer [109, 110]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LY2940680</strong></td>
<td>inhibitor of the Hedgehog pathway</td>
<td>phase 1 + FOLIFIRINOX, completed</td>
<td>pancreatic cancer</td>
<td>[111, 112]</td>
</tr>
<tr>
<td><strong>ENV-101</strong></td>
<td>inhibitor of the Hedgehog pathway</td>
<td>phase 1 clinical trial, completed</td>
<td>solid tumor malignancies</td>
<td>[113, 114]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>phase 1 clinical trial + cetuximab, completed</td>
<td>head and neck cancer</td>
<td>[115, 116]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>phase 2 clinical trial, completed</td>
<td>unresectable chondrosarcoma</td>
<td>[117]</td>
</tr>
<tr>
<td><strong>LY2940680</strong></td>
<td>inhibitor of the Hedgehog pathway</td>
<td>phase 2 clinical trial, completed</td>
<td>advanced solid tumors harboring PTCH1 loss of function mutations</td>
<td>[118]</td>
</tr>
<tr>
<td><strong>ENV-101</strong></td>
<td>inhibitor of the Hedgehog pathway</td>
<td>phase 1 clinical trial, recruiting</td>
<td>breast cancer, colon cancer, cholangiocarcinoma, soft tissue sarcoma</td>
<td>[119]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>phase 1 clinical trial, completed</td>
<td>esophageal or gastroesophageal junction cancer</td>
<td>[120]</td>
</tr>
<tr>
<td><strong>lycopene</strong></td>
<td>naturally synthesized carotenoid (an active component of red fruits and vegetables) – suppression of β-catenin nuclear expression</td>
<td>phase 2 clinical trial, active, not recruiting</td>
<td>skin toxicity in patients with colorectal carcinoma treated with panitumumab</td>
<td>[121]</td>
</tr>
<tr>
<td><strong>artesunate</strong></td>
<td>antimalarial drug – suppression of WNT pathway by downregulation of c-Myc and cyclin D1</td>
<td>phase 2 clinical trial, active, not recruiting</td>
<td>stage II/III colorectal cancer (pre-operative treatment)</td>
<td>[122]</td>
</tr>
<tr>
<td><strong>resveratol</strong></td>
<td>non-flavonoid polyphenol – suppression of WNT pathway by decreased the expression of β-catenin and cyclin D1</td>
<td>phase 1 clinical trial, completed</td>
<td>metastatic breast cancer</td>
<td>[123, 124]</td>
</tr>
<tr>
<td><strong>quercetin</strong></td>
<td>flavonoid (component of onion, red grapes, lettuce, tomato).</td>
<td>phase 1 clinical trial, completed</td>
<td>colon cancer</td>
<td>[125, 126]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>preclinical</td>
<td>breast cancer, gastric cancer</td>
<td>[127, 128]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>phase 1 clinical trial, completed</td>
<td>breast cancer, ovarian cancer, B-cell lymphomas</td>
<td>[129, 130]</td>
</tr>
<tr>
<td>Inhibition of the Notch1, PI3K/AKT and β-catenin signaling pathways</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CBP – CREB-binding protein; BRAF – B-Raf proto-oncogene, serine/threonine kinase; DKK1 – dickkopf-1 protein; EMA – European Medical Agency; FDA – Food and Drug Administration; FOLFOX – folinic acid, 5-fluorouracil and oxaliplatin; FOLFIRINOX – folinic acid, 5-fluorouracil, irinotecan and oxaliplatin; FZD – frizzled receptor; LRP5/6 – low-density lipoprotein receptor-related protein 5/6; PARPs – poly (ADP-ribose) polymerases; PI3K/AKT – phosphoinositide 3-kinase/protein kinase B; PTK7 – protein tyrosine kinase 7; TCF – T cell factor; # – for details see clinicaltrials.gov