激酶小分子抑制剂研究进展

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摘要: 蛋白激酶与肿瘤、炎症、自身免疫病、神经性疾病等众多疾病的发病机制密切相关, 近30年以来激酶作为一个非常有潜力的药物靶点受到了广泛研究。截止2020年4月, FDA批准了59个激酶小分子抑制剂上市, 再次激发了针对癌症和其他疾病治疗领域的靶向药物的兴起。本文重点分析了59个已获批上市的药物以及处于II期和III期临床试验的121个 (能检索到分子结构的) 激酶小分子抑制剂, 按照靶点和适应证等信息进行了汇总和分类分析。此外, 本文还简单列举了几类热门靶点及其抑制剂的研究概况。

关键词: 蛋白激酶; 小分子抑制剂; 抗肿瘤; 批准上市

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Research progress on small molecule kinase inhibitors

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Abstract: Protein kinases are intimately involved in the pathogenesis of many diseases such as cancer, inflammation, and autoimmune and neurological diseases. Therefore, kinases have been widely studied as drug targets over the past three decades. As of April, 2020, the FDA had approved 59 small molecule kinase inhibitors (SMKIs) in the emerging field of targeted drug therapy. This paper focuses on the biochemistry and pharmacology of these 59 SMKIs and 121 SMKIs for which structures can be retrieved and that are now in phase II and III clinical trials. In addition, this paper also conducts a simple analysis of several popular targets and their inhibitors.

Key words: protein kinase; small molecule kinase inhibitor; anticancer; approved

蛋白激酶与肿瘤、炎症、自身免疫病、神经性疾病等众多疾病的发病机制密切相关, 近30多年来, 激酶作为一个非常有潜力的药物靶点受到了广泛的研究。全世界高达20%～33%的药物发现都和蛋白激酶超家族相关[1]。本文通过对已上市的以及正处在III期和II期临床试验的激酶小分子抑制剂进行统计分析。针对已上市的抑制剂的靶点和适应证进行统计。针对II期和III期在研的激酶小分子抑制剂, 则是筛选出能够查找到化合物结构的药物, 然后按照靶点和适应证进行归纳统计, 并将这些数据资料展现出来, 期望对该领域的研究起到参考和辅助作用。

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1　激酶简介

激酶 (kinase) 属于磷酸转移酶大家族, 参与底物磷酸化的过程, 把磷酸基团从能量高的分子如ATP转移到能量相对较低的特定靶分子 (如蛋白质、脂质、糖、氨基酸和核苷等) 上。目前在人体中发现的激酶有518种[2,3]。蛋白激酶 (protein kinases, PK) 是激酶家族里面最大的族群, 可通过催化特定底物蛋白的磷酸化 (将ATP末端的γ-磷酸基团转移到底物蛋白质的特定氨基酸上) 影响底物的结构和活性, 进而参与了一系列细胞信号传导和调节过程[4]。基因改变引起的蛋白激酶的突变、易位、失调和过表达等和肿瘤、心血管疾病、炎症、退化、传染病等众多疾病的发病机制有着非常密切的关系。后文所提到的激酶无特别注明则均

默认为蛋白激酶。蛋白激酶主要分为丝氨酸/苏氨酸激酶和酪氨酸激酶。丝氨酸/苏氨酸包含TKL、STE、CK1、AGC、CAMK和CMGC六个亚家族[5]。酪氨酸激酶 (TK) 根据其是否存在于细胞表面, 分为受体型酪氨酸激酶 (receptor tyrosine kinase, RTKs) 和非受体型酪氨酸激酶 (non receptor tyrosine kinase, NRTKs)。

1.1 激酶结构与作用机制

激酶尽管在一级序列上有所差异, 但在三维结构上却具有高度的保守性, 特别是由250～300个氨基酸残基构成的功能域折叠形成的含有12个高度保守亚区的催化结构域。激酶的催化区域可以分为铰链区 (hinge) 以及由铰链区连接的较小的N端区域 (N-lobe) 和较大的C端区域 (C-lobe) (图1A)[6,7]。N-端区域包含5个反向平行的β折叠 (β1～β5) 和一个以“盐桥”连接的αC螺旋[8,9]。β1和β2间包含有1个保守的富含甘氨酸的环 (GXGXΦG, Φ代表疏水残基), 又叫P环 (P-loop), 它可以与ATP分子中的磷酸根形成氢键 (图1B), 从而起到稳定ATP的作用。此外, 柔性的P环可以根据蛋白激酶的构象状态和配体的形状灵活变化从而适应不同的配体。P环之后的β2链上存在1个缬氨酸残基, 它能和ATP的腺嘌呤碱基以及许多小分子激酶抑制剂形成疏水相互作用。在β3链上有1个保守的AXK特征序列, 该序列中的赖氨酸 (以FGFR2中的K517为例, 下同) 能够与ATP的α-和β-磷酸基团形成氢键, 且能与αC螺旋中部的1个保守的谷氨酸 (E534) 以“盐桥”连接 (图1A), 此时的结构称为“αC_{in}”构象。如果没有这个盐桥, 此时的激酶代表一种无活性状态的“αC_{out}”构象。“αC_{out}”构象转化为“αC_{in}”构象是激酶获得催化活性所必需的过程[9]。

C-端区域占主导地位的是8个保守的α螺旋 (αD～αI, αEF1/2), 此外还包含位于αE和αF间的4个小的β链 (β6～β9)。β6之后是一条催化回环 (catalytic loop), 包含$HRD(x)_4N$基序, 主要起到催化和稳定镁离子的作用。天冬酰胺 (N631) 能够稳定镁离子, 天冬氨酸 (D626) 能够夺取底物蛋白羟基的质子, 从而有助于γ-磷酸基从ATP转移到底物上 (图1B)。此外, 位于ATP腺嘌呤结合口袋底部的β7链上的第二个残基能够跟几乎所有ATP竞争性的激酶抑制剂发生疏水相互作用[1]。

ATP结合区域位于N端和C端之间的裂口处, 在该处铰链区的氨基酸与ATP分子中的腺嘌呤形成氢键相互作用 (图1B)。在ATP活性位点附近, 还存在一条保守的活化环 (activation loop), 其前端通常存在一个保守的Asp-Phe-Gly (DFG) 结构基序, 末端为Ala-Pro-Glu (APE) 序列, 当激酶处于活性构象时, DFG基序的Asp (D644) 指向ATP结合空腔与镁离子结合 (“DFG-D_{in}”, 图1B), 并且活化环处于开放状态 (activation loop-open)[10]。

1.2 激酶与药物的结合口袋

大多数激酶小分子抑制剂都是结合在ATP位点, 与ATP竞争结合 (ATP竞争抑制剂), 因此N-端和C-端间的催化裂口是激酶抑制剂开发的主要焦点。该裂口可分为前端、守门区域和后端3部分 (图2)[11]。裂口前端主要包含铰链残基、催化回环以及P-loop, 组成了腺嘌呤结合口袋 (AP)、位于DFG和暴露于溶剂区的铰链残基间的前口袋-I (FP-I) 以及位于P-loop和裂口顶部β3链间的前口袋-II (FP-II)。守门区域起着药物从前端进入后端的门控作用[12], 该区域主要包含β3链和包含DFG在内的活化环的近端部分, 组成了靠上端的后口袋-I-A (BP-I-A) 和中部的相对较大的后口袋-I-B (BP-I-B)。裂口后端主要包含αC螺旋、β4链、β5链以及αE螺旋, 其主要作用是调节激酶催化。当激酶处于DFG-D_{in}构象时, 其裂口后端的口袋由后口袋-II-A-in (BP-II-A-in)、后口袋-II-in (BP-II-in) 及后口袋-II-B

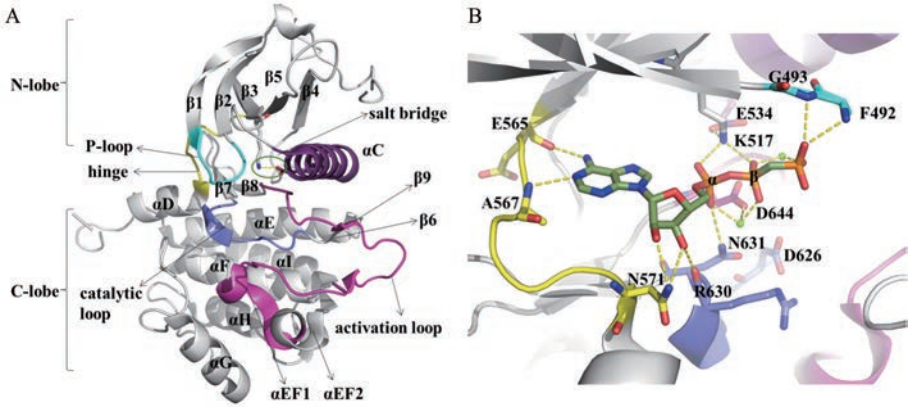

Figure 1 Structure of the protein kinase domain (A) and cocrystal structure of ATP analog bound to the site of FGFR2 (B, PDB ID: 2pvf). Mg^{2+} is shown as green balls and hydrogen bonds are shown as yellow dashes

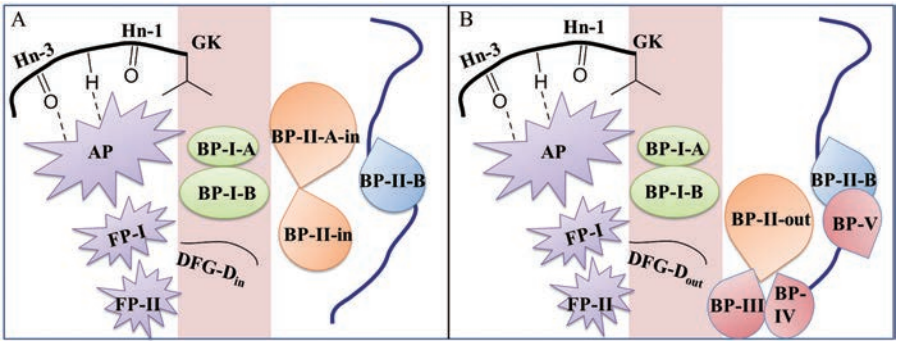

Figure 2 The two binding modes of ATP-competitative protein kinase inhibitors. A is for DFG-D_{in} and B is for DFG-D_{out} conformations

(BP-II-B) 组成。当激酶处于 DFG-D_{out} 构象时, 苯丙氨酸的位置发生了反转, 因此其裂口后端的结合口袋与 DFG-D_{in} 存在差异, 由后口袋-II-out (BP-II-out)、后口袋-II-B (BP-II-B)、后口袋-III (BP-III)、以及部分暴露于溶剂区的后口袋-IV (BP-IV) 和后口袋-V (BP-V) 组成。

1.3 激酶抑制剂分类

目前报道的小分子激酶抑制剂主要通过3种模式进行激酶活性的抑制[13]。① 直接和 ATP 结合位点结合, 阻断后续信号通路。目前研发的大部分小分子激酶抑制剂都是结合激酶的 ATP 结合位点即 ATP 竞争抑制剂。ATP 竞争抑制剂按照结合类型分为可逆抑制剂和共价抑制剂, 其中可逆抑制剂根据激酶的活性/非活性状态主要分为 Type I 型、Type $I_{1/2}$ 型和 Type II 型抑制剂 (表 1)[14]。DFG-D_{in} 为激酶处于活性构象的必要但不充分条件, 激酶处于 DFG-D_{in} 状态的活性构象时结合的抑制剂即为 Type I 型抑制剂, 激酶处于 DFG-D_{in} 状态的非活性构象时结合的抑制剂即为 Type $I_{1/2}$ 型抑制剂。当激酶处于 DFG-D_{out} 状态的非活性构象时, 此时结合的抑制剂即为 Type II 型抑制剂。此外, 根据 Type $I_{1/2}$ 型和 Type II 型抑制剂是否延伸至裂口后端, 又将其分为 A 型和 B 型。共价抑制剂即为 Type VI 型抑制剂; ② 与非活化构象的变构位点相结合, 间接与 ATP 竞争, 即变构抑制剂, 其结合位点接近于 ATP 结合位点的为 Type III 型抑制剂, 远离 ATP 结合位点的为 Type IV 型抑制剂。此外, 一些变构抑制剂还可与假激酶域结合或与激酶的胞外域结合[15]; ③ 同时结合激酶的 ATP 结合位点和表面的另外一个位点 (如变构位点)[16], 即 Type V 型抑制剂。在获批的小分子中大多数是 ATP 竞争型抑制剂, 变构抑制剂目前只有 MEK1 激酶的 4 个抑制剂被获批。

2 FDA 批准的激酶小分子抑制剂

2001 年 FDA 批准了由诺华公司开发的第一个激酶小分子抑制剂伊马替尼 (imatinib), 作用靶点为 Ab1 激酶, 用于慢性粒细胞白血病的治疗, 这是肿瘤靶向治疗的一个重要突破。从 2001 年到 2020 年 4 月累计有 59 个激酶小分子抑制剂获得了 FDA 的批准, 且每年的批准量呈现出总体上升的趋势 (图 3)。

初步分析, 59 个激酶小分子抑制剂中属于酪氨酸激酶抑制剂的有 43 个, 其次为丝氨酸/苏氨酸激酶抑制剂 11 个, 剩下的为 3 个脂激酶抑制剂和 2 个双特异性激酶抑制剂 (图 3)。若按适应证 (肿瘤药和非肿瘤药) 分类, 其中肿瘤药占到了 86%, 即有 51 个用于肺癌、乳腺癌、白血病等肿瘤疾病的药物, 有 8 个用于非肿瘤疾病 (fedratinib 用于骨纤维化; ruxolitinib 用于骨纤维化和红细胞增多症; fostamatinib 用于慢性免疫性血小板减少症; upadacitinib、baricitinib 用于类风湿关节炎; nintedanib 用于特发性肺纤维化; netarsudi 用于青光眼; tofacitinib 用于类风湿关节炎、克罗恩病、溃疡性结肠炎)。这些药物除了极个别外, 几乎都是口服用药。关于这 59 个药物的结构信息见图 4, 靶点信息见网络版支持材料中的表 S1。

Table 1 Classification of protein kinase inhibitors

Property	Type I	Type $I_{1/2}$ (A/B)	Type II (A/B)	Type III	Type IV	Type V	Type VI
Extends into back cleft	No	(A) Yes / (B) No	(A) Yes / (B) No	Yes	No	Variable	Variable
DFG-D	In	In	Out	Variable	Variable	Variable	Variable
Activation loop	Open	Variable	Variable	Variable	Variable	Variable	Variable
αC	In	Variable	Variable	Out	Variable	Variable	Variable
ATP-competitive	Yes	Yes	Yes	No	No	Variable	No
Reversible	Yes	Yes	Yes	Yes	Yes	Yes	Usually not

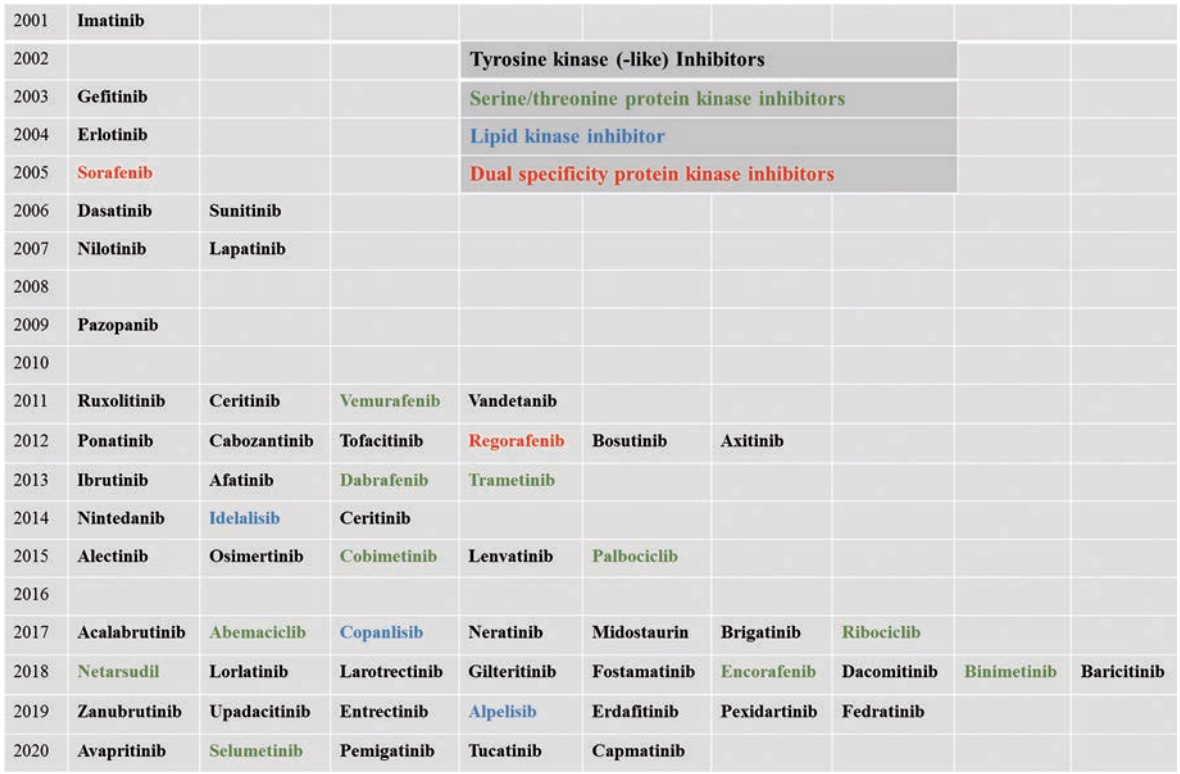

Figure 3 FDA-approved small molecule kinase inhibitors from 2001 to April 2020

3 处于临床II和III期阶段的激酶小分子抑制剂

目前在人体发现的激酶有518种, 有大量的激酶抑制剂处在临床试验阶段。下面将对统计到的121个处于III和II期临床试验阶段的激酶小分子抑制剂按照靶点类型进行简单地综合分析。这121个小分子抑制剂中酪氨酸激酶抑制剂共有63个 (受体型41个和非受体型22个)、丝氨酸/苏氨酸激酶抑制剂44个、其他激酶抑制剂14个。本次统计只选用了化合物结构公开的且能检索到的小分子抑制剂。

3.1 酪氨酸激酶抑制剂

酪氨酸激酶 (protein tyrosine kinase, PTK) 因为其确切的药物作用效果占据了激酶抑制剂药物中的很大一部分, 是激酶抑制剂开发中当之无愧的主力军。按其是否分布在细胞膜上, 酪氨酸激酶可以分为受体型和非受体型两类。

3.1.1 受体型酪氨酸激酶抑制剂 受体型酪氨酸激酶是一类具有内源性蛋白酪氨酸激酶活性的细胞表面跨膜蛋白受体, 一般由1个可以与特定配体结合的细胞外结构域、1个跨膜区及1个可以选择性地与底物结合并将其磷酸化的细胞内区域组成。配体和受体型酪氨酸激酶的细胞外结构域结合, 引起其结构改变而产生酶催化活性[17]。图5是目前处于临床试验的受体型酪氨酸激酶抑制剂的药物结构, 网络版支持材料中的表S2展示了这些药物具体的临床试验阶段和靶点信息。

3.1.2 非受体型酪氨酸激酶抑制剂 非受体酪氨酸激酶通常没有细胞外结构域, 一般存在于细胞膜或者细胞质中, 持续或暂时位于胞浆, 或者在细胞膜内侧与跨膜受体结合, 主要通过细胞因子受体、T细胞受体及其他信号通路执行信号转导[18]。图6是目前处于III期和II期临床试验的非受体型酪氨酸激酶抑制剂的药物结构, 具体的临床试验阶段, 靶点等信息见网络版支持材料中的表S3。

3.2 丝氨酸/苏氨酸激酶抑制剂

受体丝氨酸/苏氨酸激酶 (receptor serine/theonine kinase) 是一类跨膜受体蛋白, 在细胞内具有丝氨酸/苏氨酸蛋白激酶活性, 通过磷酸化下游信号蛋中的丝氨酸/苏氨酸残基而进行信号转导。图7是目前处于II期和III期临床试验的丝/苏氨酸蛋白激酶抑制剂的结构, 具体的临床试验阶段, 靶点等信息见网络版支持材料中的表S4。

3.3 其他激酶抑制剂

除了前面提到的酪氨酸激酶抑制剂和丝/苏氨酸激酶抑制剂, 还有一小部分为脂激酶抑制剂以及其他类型的激酶抑制剂, 药物结构如图8, 靶点和适应证等信息见网络版支持材料中的表S5。

4 几类热门靶点的抑制剂研究

4.1 表皮生长因子受体 (EGFRs)

表皮生长因子受体 (EGFR) 是一类受体型酪氨

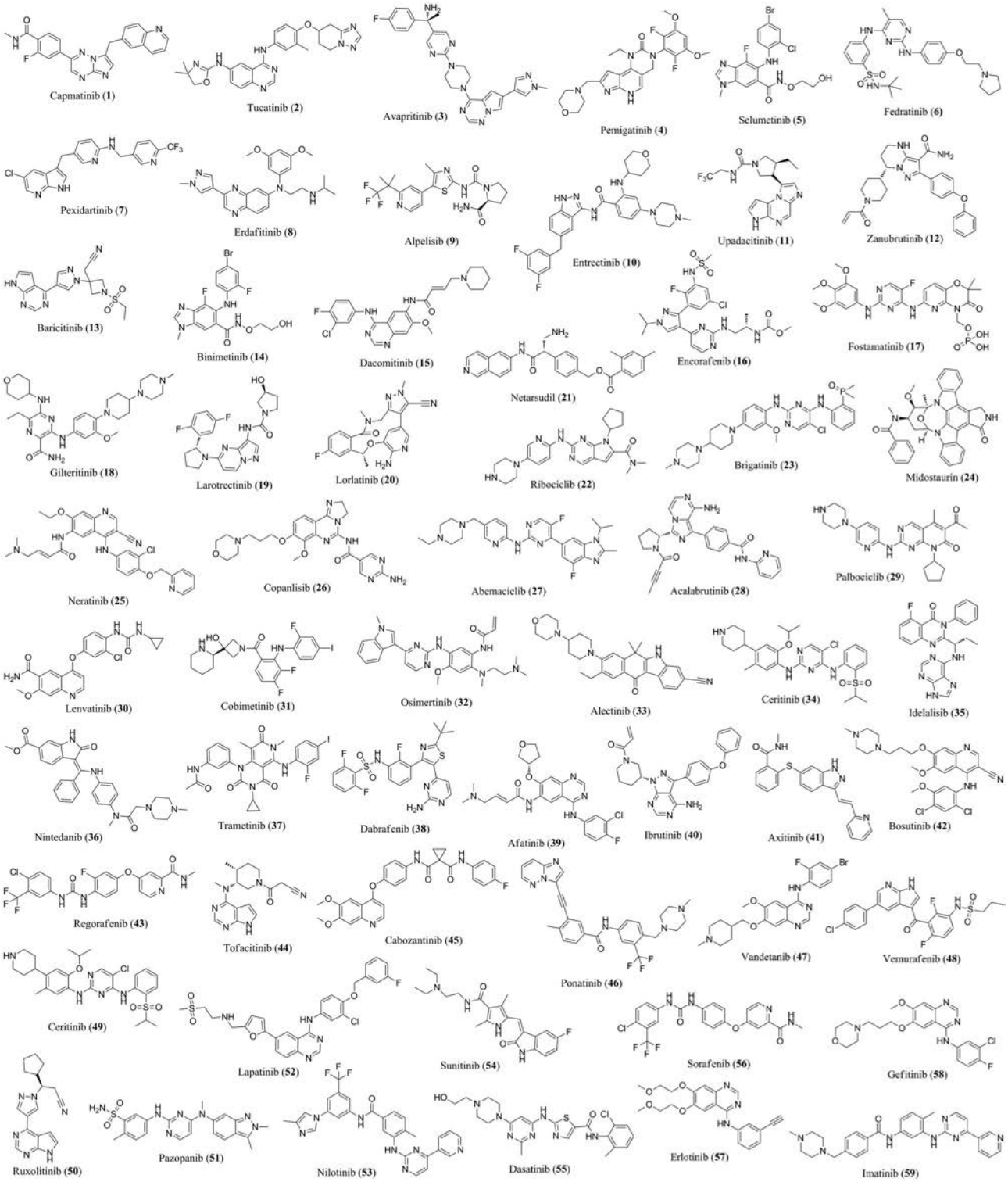

Figure 4 Structures of small molecule kinase inhibitors (**1**−**59**) approved by FDA from 2001 to April 2020

酸, 家族成员有HER1、HER2、HER3、HER4四种分型, 位于细胞膜上, 分为膜内、跨膜和膜外3个区域[19]。EGFR家族成员能两两形成同源和异源两种二聚体, 其中同源二聚体不需要配体, 异源二聚体需要配体。形成二聚体之后与ATP结合, 然后进行自磷酸化, 激活下游Ras/Raf/MAPK和PI3K/Akt/mTOR等信号通路, 参与细胞的生长、分裂、分化等活动。EGFR酪氨酸激酶抑制剂选择性地竞争细胞内结构域中Mg-ATP结合位点, 导致酪氨酸残基不能磷酸化, 进而阻断了下游通路的信号转导。目前经FDA批准上市的涉及到EGFR靶点有tucatinib (HER2阳性乳腺癌)[20]、dacomitinib (非小细胞肺癌)[21]、brigatinib (非小细胞肺癌)[22]、neratinib

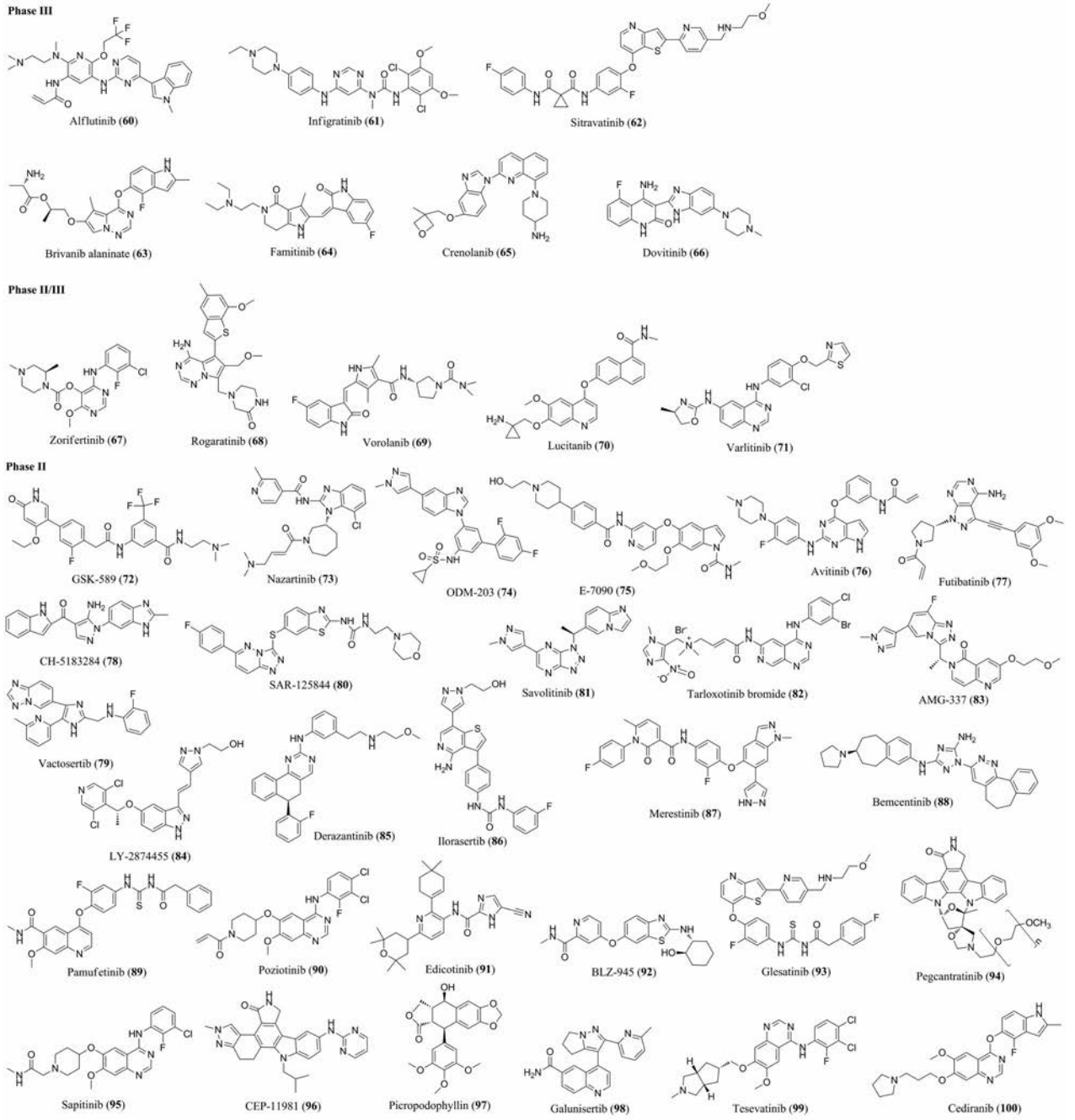

Figure 5 Structures of receptor tyrosine kinase inhibitors (**60**–**100**) currently in clinical phase II and III trials

(HER2阳性乳腺癌)[23]、osimertinib (非小细胞肺癌)[24]、afatinib (非小细胞肺癌)[25]、vandetanib (甲状腺癌)[26]、lapatinib (乳腺癌)[27]、dasatinib (CML)[28]、erlotinib (非小细胞肺癌, 胰腺癌)[29]、gefitinib (非小细胞肺癌)[30]。从上面的列举可以看出针对该靶点开发出的药物主要适应证以非小细胞肺癌为主, 研究表明EGFRs在癌细胞表面高度表达, 其中非小细胞肺癌表达阳性率40%～80%[31]。在本综述统计的处于临床试验的药物中有10个药物涉及到该靶点, 其主要针对疾病仍然是非小细胞肺癌 (因部分药物治疗组很多, 此处不一一列举, 具体见表2)。

4.2 成纤维细胞生长因子受体 (FGFRs)

成纤维细胞生长因子受体 (FGFRs) 跟EGFR类似, 也分为胞外、跨膜和胞内3个区域。其中胞外区域是与配体结合的地方, 包含3个免疫球蛋白 (Ig) 样区; 胞内为酪氨酸激酶区, 能够进行信号转导[32]。FGFR有FGFR1、FGFR2、FGFR3、FGFR4四位家族成员, 因Ig-III样结构域的剪切体的不同又可将其分为FGFR1b、FGFR1c、FGFR2b、FGFR2c、FGFR3b、FGFR3c和FGFR4七种亚型, 因此FGFRS与配体结合

Figure 6 Structures of non receptor tyrosine kinase inhibitors (**101**–**122**) currently in clinical phase II and III trials

具有多样性[33,34]。除FGF-7只能激活FGFR2b一种受体, 其他FGFs一般可以激活多种FGFR, 而FGFR也能被多种FGF激活[35,36]。硫酸肝素蛋白多糖 (HSPGs) 能够协助FGFRs与FGFs结合, 然后使得FGFRs磷酸化, 从而激活下游一系列的相关信号通路如磷酸肌醇、MAPK和PI3K/Akt等, 进而参与细胞的生长、增殖、分化和血管生成等各种生理活动[37]。在经FDA批准上市中涉及到FGFR受体的药物有pemigatinib (胆管癌)[38]、erdafitinib (泌尿道上皮细胞癌)[39]、lenvatinib (多靶点, 分化型甲状腺癌)[40]、nintedanib (多靶点, 肺纤维化)[41]、regorafenib (多靶点, 结肠直肠癌, 肺细胞癌, 胃肠道间质瘤)[42]、ponatinib (多靶点, 慢性粒细胞性白血病, 急性淋巴细胞性白血病)[43]和pazopanib (肾细胞癌, 软组织肉瘤)[44] 7个, 大多数为多靶点药物。在本综述统计的处于II和III期临床试验的药物中有12个药物靶点涉及到FGFR, 其中5个是多靶点药物 (表3)。

4.3 血管内表皮生长因子受体 (VEGFRs)

血管内表皮生长因子 (VEGF) 由VEGF-A、VEGF-B、VEGF-C、VEGF-D、VEGF-E、VEGF-F和胎盘生长因子PIGF等7个成员组成, 它在血管生成、促进细胞存活以及通过与特定受体结合而促进内皮细胞生长和生存等方面发挥关键作用[45,46]。VEGFR是VEGF的受体酪氨酸激酶跨膜蛋白, 由胞外7个免疫蛋白结构域、跨膜结构域和胞内酪氨酸激酶结合域3部分组成, 有VEGFR-1 (FLT-1)、VEGFR2 (KDR)、VEGFR3 (FLT-4) e3种亚型[47]。VEGFR与VEGF结合后首先发生二聚化, 然后进行自身磷酸化, 进而激活下游信号通路, 促进血管内皮细胞的生成。由于肿瘤细胞的大量增殖需要新生血管来供应营养物质和新陈代谢, 因此VEGFR表达会比较高。它与受体结合诱导肿瘤血管生成, 能够促进肿瘤生长, 参与肿瘤的转移和耐药机制形成[48]。在FDA批准的已上市药物中有11个涉及到VEGFR靶

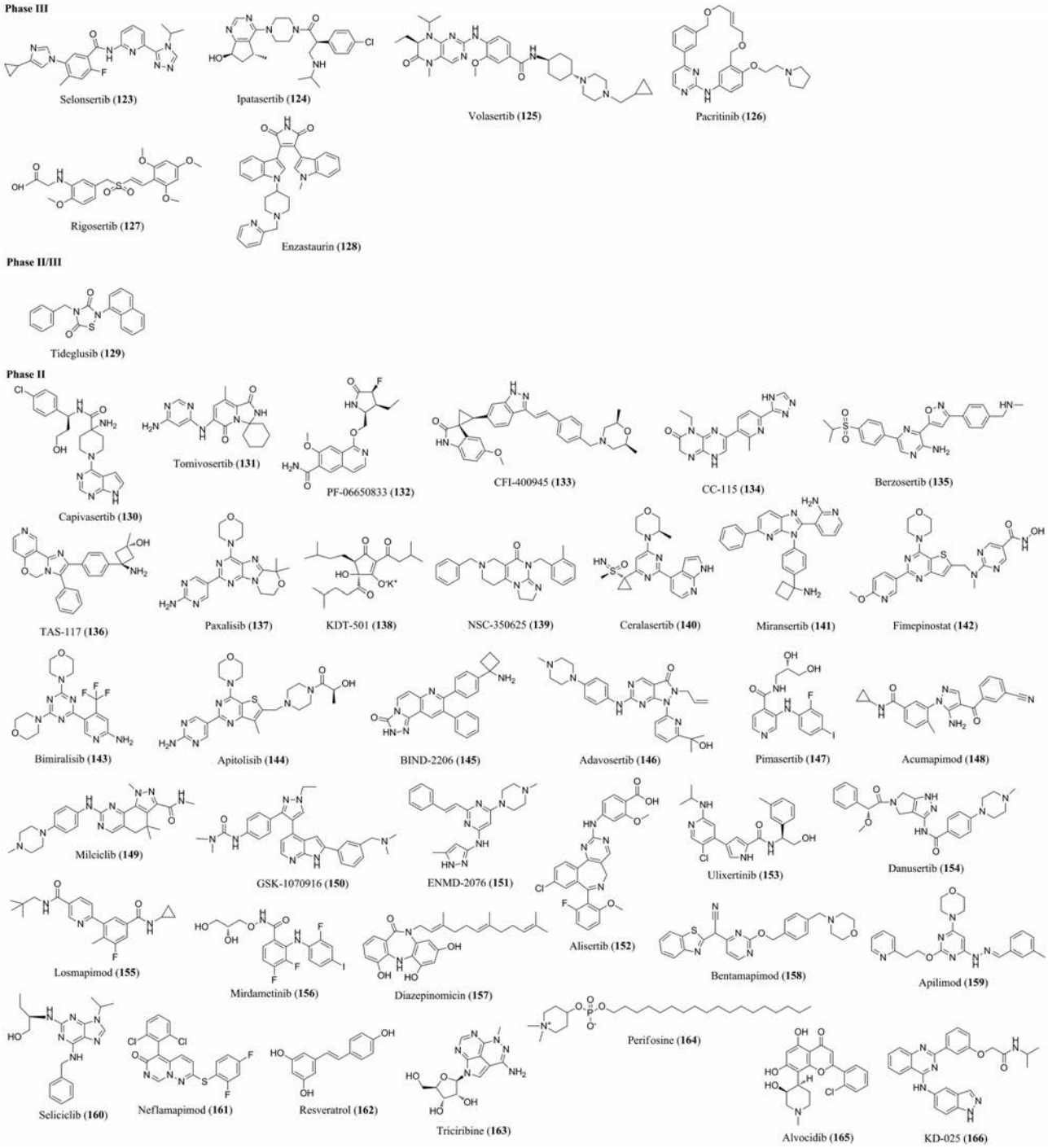

Figure 7 Structures of receptor serine/theonine kinase inhibitors (**123**–**166**) currently in clinical phase II and III trials

点, 分别为midostaurin (急性髓细胞性白血病、肥大细胞白血病)[49]、lenvatinib (分化型甲状腺癌)[40]、nintedanib (特发性肺纤维化)[41]、axitinib (肾细胞癌)[50]、regorafenib (结肠直肠癌、肺细胞癌、胃肠道间质瘤)[42]、cabozantinib (肾细胞癌、肺细胞癌、髓甲状腺癌)[51]、ponatinib (慢性粒细胞性白血病、急性淋巴细胞性白血病)[52]、vandetanib (甲状腺癌)[26]、pazopanib (肾细胞癌、软组织肉瘤)[43]、sunitinib (肾细胞癌、胃肠道间质瘤、胰腺神经内分泌肿瘤)[53]和sorafenib (甲状腺癌、肾细胞癌)[54]。值得注意的是这11个药物全部是多靶点药物。本综述统计的处于临床的药物中有12个药物涉及到该靶点, 也均为多靶点药物 (表4)。

4.4 布鲁顿酪氨酸激酶 (BTK)

布鲁顿酪氨酸激酶 (BTK) 属于非受体酪氨酸Tec家族, 是人类非受体激酶的第二大家族, 广泛表达于造血系统的所有细胞系中 (除T细胞外), 分布在骨髓、脾

Table 2 EGFR inhibitors, their protein kinase targets, and therapeutic indications

Drug (Code) name	Target	Organization	Therapeutic indication
Launched			
Tucatinib	HER2	Seattle Genetics	HER2 positive breast cancers
Dacomitinib	EGFR family	Pfizer	EGFR-mutant NSCLC (non-small cell lung cancer)
Brigatinib	ALK; ROS1; IGF-1R; FLTFLT3; EGFR	Ariad	ALK positive NSCLC
Neratinib	ErbB2/HER2	Puma Biotechnology, Inc.	HER2 positive breast cancers
Osimertinib	EGFR T790M	AstraZeneca	NSCLC
Afatinib	EGFR; ErbB2; ErbB4	Boeh-ringer Ingelheim	NSCLC
Vandetanib	RET; EGFRs; VEGFRs; Brk; Tie2; EphRs; Src family kinases	AstraZeneca	Thyroid cancer
Lapatinib	EGFR; ErbB2	GSK	Breast cancer
Dasatinib	BCR-Abl; EGFR; Src; Lck; Yes; Fyn; Kit; EphA2; PDGFR	Bristol-Myers Squibb	Chronic myelogenous leukemia
Erlotinib	EGFR	Genentech	NSCLC; Pancreatic cancer
Gefitinib	EGFR	Astra Zeneca	NSCLC
Phase III			
Alflutinib	EGFR	Shanghai Allist Pharmaceutical	NSCLC
Dovitinib	EGFR; FGFR1; FGFR3; VEGFR-1; VEGFR-2	Asan Medical Center; Chiron (Novartis Vaccines and Diagnostics); Novartis (Originator); Oncology Venture; Samsung Medical Center (SMC); Seoul National University Hospital; University of Pennsylvania	Bladder cancer; Breast cancer; Colorectal cancer; Digestive/Gastrointestinal cancer; Endocrine cancer; Female reproductive system cancer; Gastric cancer; Glioblastoma multiforme; Head and neck cancer; Liver cancer; Melanoma; Multiple myeloma; Myeloid leukemia; Neurological genetic disorders; NSCLC; Pancreatic cancer; Prostate cancer; Renal cancer; Respiratory/Thoracic cancer
Phase II/III			
Zorifertinib	EGFR	Alpha Biopharma; Astra Zeneca (Originator)	NSCLC
Varlitinib	EGFR	ASLAN Pharmaceuticals; Array BioPharma (Originator); BioGenetics; Hyundai Pharm	Breast cancer; Digestive/Gastrointestinal cancer; Gastric cancer; Liver cancer; Pancreatic cancer; Solid tumors
Phase II			
Nazartinib	EGFR	Novartis	NSCLC; Solid tumors
Avitinib	EGFR	ACEA Biosciences (Originator)	Non-Hodgkin's lymphoma; NSCLC
Tarloxotinib bromide	EGFR	Proacta; Rain Therapeutics; Threshold Pharmaceuticals (Molecular Templates); University of Auckland (Originator);	Head and neck cancer; NSCLC; Skin cancer
Poziotinib	EGFR	Yakult Honsha Hanmi (Originator); Luye Pharma; Spectrum Pharmaceuticals	Breast cancer; Colorectal cancer; Gastric cancer; Head and neck cancer; Lung cancer; Neurologic cancer; NSCLC
Sapitinib	EGFR	AstraZeneca	Breast cancer; Colorectal cancer; Gastric cancer; NSCLC; Solid tumors
Tesevatinib	EGFR; CSK; VEGFR-2/3	Exelixis (Originator); GSK; Kadmon; Symphony Evolution	Brain cancer; Breast cancer; NSCLC; Renal and urinary system genetic disorders

脏和淋巴结组织中[55]。BTK在B细胞发育和功能中起着重要作用, BTK的异常激活与B细胞淋巴瘤的发病机制密切相关, 因此BTK在血液恶性肿瘤的治疗中一直是重要的靶点[56]。BTK由PH (Pleckstrin homology)、TH (Tec homology)、SH3 (Src homology 3)、SH2 (Src homology 2) 和SH1 (Src homology 1) 5个结构域组成[57]。BTK的活化过程比较复杂, 该过程重要的步骤为磷脂酰肌醇三磷酸 (PIP3) 与BTK的PH结构域结合后将后者募集至细胞膜, 然后其Tyr551残基被Syk和Lyn激酶磷酸化, 最后BTK在Tyr223残基进行自磷酸化反应从而获得生理活性[58]。目前FDA批准的上市药物中靶点为BTK的药物有3个: zanubrutinib (套淋巴瘤)[59]、acalabrutinib (套淋巴瘤)[60]和ibrutinib (套淋巴瘤、慢性淋巴细胞白血病)[61]。这几个药物都是单靶点药物, 对BTK有很高的选择性。在本综述统计的处于临床的药物中有6个BTK抑制剂, 均为单

Table 3 FGFR inhibitors, their protein kinase targets, and therapeutic indications

Drug (Code) name	Target	Organization	Therapeutic indication
Launched			
Pemigatinib; Pemazyre	FGFR1/2/3	Incyte	Cholangiocarcinoma
Erdafitinib	FGFRs	Janssen	Urothelial cancer
Lenvatinib	VEGFR1/2/3; PDGFR; FGFR; Kit; RET	Easai	Differentiated thyroid cancer
Nintedanib	FGFR1/2/3; PDGFR*α*/*β*; VEGFR1/2/3; FLTFLT3	Boeh-ringer Ingelheim	Pulmonary fibrosis
Regorafenib	VEGFR1/2/3; BCR-Abl; B-Raf; B-Raf (V600E); Kit; PDGFR*α*/*β*; RET; FGFR1/2; Tie2; Eph2A	Bayer	Colorectal neoplasms; Lung cancer; Adenocarcinoma of the gastroesophageal junction; HCC
Ponatinib	BCR-Abl; BCR-Abl T315I; VEGFR; PDGFR; FGFR; EphR; Src family kinases; Kit; RET; Tie2; FLTFLT3	Ariad	CML or ALL, Philadelphia chromosome positive
Pazopanib	VEGFR1/2/3; PDGFR*α*/*β*; FGFR1/3; Kit; Lck; Fms; Itk	GSK	Renal cell carcinoma; Soft tissue sarcomas
Phase III			
Infigratinib	FGFR1; FGFR2; FGFR3; FGFR4	BridgeBio Pharma; Memorial Sloan-Kettering Cancer Center; Novartis (Originator); QED Therapeutics	Bladder cancer; Bone, muscles and connective tissue genetic disorders; Digestive/Gastrointestinal cancer; Hematological cancer; Melanoma; Neurologic cancer; Solid tumors; Squamous cell carcinoma
Brivanib alaninate	FGFR1; FGFR3; VEGFR-2	Bristol-Myers Squibb (Originator); National Cancer Institute (NCI); National Cancer Institute (US) (National Cancer Institute (NCI)); University of Pennsylvania; ZAI Lab; ZAI Laboratory (ZAI Lab)	Antineoplastic enhancing agents; Cervical cancer; Colorectal cancer; Digestive/Gastrointestinal cancer; Female reproductive system cancer; Liver cancer; Oncolytic drugs; Ovarian cancer; Renal cancer
Dovitinib	EGFR; FGFR1; FGFR3; VEGFR-1; VEGFR-2	Asan Medical Center; Chiron (Novartis Vaccines and Diagnostics);	Bladder cancer; Breast cancer; Colorectal cancer; Digestive/Gastrointestinal cancer; Endocrine cancer; Female reproductive system cancer; Gastric cancer; Glioblastoma multiforme; Head and neck cancer; Liver cancer; Melanoma; Multiple myeloma; Myeloid leukemia; Neurological genetic disorders; NSCLC; Pancreatic cancer; Prostate cancer; Renal cancer; Respiratory/Thoracic cancer
Phase II/III			
Rogaratinib	FGFR	Bayer (Originator)	Genitourinary cancer; Solid tumors
Vorolanib	FGFR; VEGFR-2	Betta Pharmaceuticals; Sundia MediTech; Tyrogenex (Originator); Xcovery	Age-related macular degeneration; Gastric cancer; Melanoma; NSCLC; Ophthalmic drugs; Pancreatic cancer; Renal cancer; Respiratory/Thoracic cancer; Small cell lung cancer; Solid tumors
Lucitanib	FGFR1; FGFR2; FGFR3; KIT; CSF1R; PDGFR; Raf; VEGFR-1; VEGFR-2; VEGFR-3	Advenchen Laboratories (Originator); Clovis Oncology;	Bladder cancer; Breast cancer; Female reproductive system cancer; Head and neck cancer; NSCLC; Oncolytic drugs; Ovarian cancer; Respiratory/Thoracic cancer; Small cell lung cancer
Phase II			
ODM-203	FGFR	Orion (FI) (Originator	Solid tumors
E-7090	FGFR1; FGFR2; FGFR3	Eisai (Originator)	Digestive/Gastrointestinal cancer; Liver cancer; Solid tumors
Futibatinib	FGFR1; FGFR2; FGFR3; FGFR4	Taiho (Originator)	Bladder cancer; Brain cancer; Breast cancer; Digestive/Gastrointestinal cancer; Multiple myeloma; Oncolytic drugs; Solid tumors
CH-5183284; Debio-1347; FF-284	FGFR1; FGFR2; FGFR3	Chugai Pharmaceutical (Originator); Debiopharm; Memorial Sloan-Kettering Cancer Center	Breast cancer; Oncolytic drugs; Solid tumors
LY-2874455	FGFR1; FGFR2; FGFR3; FGFR4	Lilly (Originator)	Myeloid leukemia; Oncolytic drugs
Derazantinib	FGFR; CSF1R	ArQule (Merck & Co.); Basilea Pharmaceutica; Merck & Co. (Originator); Sinovant Sciences	Bladder cancer; Digestive/Gastrointestinal cancer; Gastric cancer; Liver cancer; Solid tumors

Table 4 VEGFR inhibitors, their protein kinase targets, and therapeutic indications

Drug (Code) name	Target	Organization	Therapeutic indication
Launched			
Midostaurin	FLT3; PDGFR; VEGFR2; PKC	Novartis	Acute myeloid leukemia; Mastocytosis; Mast cell leukemia
Lenvatinib	VEGFR1/2/3; PDGFR; FGFR; Kit; RET	Easai	Differentiated thyroid cancer
Nintedanib	FGFR1/2/3; PDGFR*α*/*β*; VEGFR1/2/3; FLT3	Boeh-ringer Ingelheim	Pulmonary fibrosis (idiopathic)
Axitinib	VEGFR1/2/3; PDGFR	Pfizer	Renal cell carcinoma
Regorafenib	VEGFR1/2/3; BCR-Abl; B-Raf; B-Raf (V600E); Kit; PDGFR*α*/*β*; RET; FGFR1/2; Tie2; Eph2A	Bayer	Colorectal cancer; Hepatocellular carcinoma; Gastrointestinal stromal tumor
Cabozantinib	RET; MET; VEGFR1/2/3; Kit; TrkB; FLT3; Axl; Tie2	Excelixis	Renal cell carcinoma; Hepatocellular carcinoma; Medullary thyroid cancer
Ponatinib	BCR-Abl; BCR-Abl T315I; VEGFR; PDGFR; FGFR; EphR; Src family kinases; Kit; RET; Tie2; FLT3	Ariad	Chronic myelogenous leukemia or acute lymphoblastic leukemia; Philadelphia chromosome positive
Vandetanib	RET; EGFRs; VEGFRs; Brk; Tie2; EphRs; Src family kinases	AstraZeneca	Thyroid cancer
Pazopanib	VEGFR1/2/3; PDGFRs; Brk; Tie2; EphRs; Src	GSK	Renal cell carcinoma; Soft tissue sarcomas
Sunitinib	PDGFR*α*/*β*; VEGFR1/2/3; Kit; FLT3; CSF-1R; Axl; RET	Pfizer	Renal cell carcinoma; Gastrointestinal stromal tumor; Pancreatic neuro-endocrine tumors
Sorafenib	VEGFR1/2/3; B-/C-Raf; mutant B-Raf; Kit; FLT3; RET; PDGFR*β*	Onyx	Thyroid cancer; Differentiated hepatocellular carcinoma; Renal cell carcinoma
Phase III			
Sitravatinib	DDR2; FLT3; KIT; MERTK; AXL; VEGFR-2; VEGFR-3	BeiGene; Mirati Therapeutics (Originator)	Bladder cancer; Breast cancer; Non-small cell lung cancer; Renal cancer; Sarcoma; Solid tumors
Famitinib	FLT3; KIT; PDGFR*β*; VEGFR-1; VEGFR-2; VEGFR-3	Jiangsu Hengrui (Originator)	Breast cancer; Colorectal cancer; Digestive/gastrointestinal cancer; Female reproductive system cancer; Genitourinary cancer; Head and neck cancer; Non-small cell lung cancer; Osteosarcoma; Renal cancer
Brivanib alaninate	FGFR1; FGFR3; VEGFR-2	Bristol-Myers Squibb (Originator); National Cancer Institute (NCI); National Cancer Institute (US) (National Cancer Institute (NCI))	Antineoplastic enhancing agents; Cervical cancer; Colorectal cancer; Digestive/gastrointestinal cancer; Female reproductive system cancer; Liver cancer; Oncolytic drugs; Ovarian cancer; Renal cancer
Dovitinib	EGFR; FGFR1; FGFR3; VEGFR-1; VEGFR-2	Asan Medical Center; Chiron (Novartis Vaccines and Diagnostics); Novartis (Originator); Oncology Venture; Samsung Medical Center (SMC); Seoul National University Hospital; University of Pennsylvania	Bladder cancer; Breast cancer; Colorectal cancer; Digestive/gastrointestinal cancer; Endocrine cancer; Female reproductive system cancer; Gastric cancer; Glioblastoma multiforme; Head and neck cancer; Liver cancer; Melanoma; Multiple myeloma; Myeloid leukemia; Neurological genetic disorders; Non-small cell lung cancer; Pancreatic cancer; Prostate cancer; Renal cancer; Respiratory/thoracic cancer
Phase II/III			
Vorolanib	FGFR; VEGFR-2	Betta Pharmaceuticals; Sundia MediTech; Tyrogenex (Originator); Xcovery	Age-related macular degeneration; Gastric cancer; Melanoma; Non-small cell lung cancer; Ophthalmic drugs; Pancreatic cancer; Renal cancer; Respiratory/thoracic cancer; Small cell lung cancer; Solid tumors
Lucitanib	VEGFR-2; VEGFR-3	Advenchen Laboratories (Originator); Clovis Oncology; EOS (Clovis Oncology); Servier; Shanghai HaiHe Biopharma	Bladder cancer; Breast cancer; Female reproductive system cancer; Head and neck cancer; Non-small cell lung cancer; Oncolytic drugs; Ovarian cancer therapy; Respiratory/thoracic cancer; Small cell lung cancer
Phase II			
Ilorasertib	ARK1; ARK2; ARK3; FLT3; KIT; CSF1R; PDGFR*α*; PDGFR*β*; VEGFR-1; VEGFR-2	AbbVie (Originator); Abbott; University of Chicago	Lymphocytic leukemia; Myelodysplastic syndrome; Myeloid leukemia; Ovarian cancer; Solid tumors
Pamufetinib	HGFR; VEGFR-2	AbbVie (Originator); Abbott; University of Chicago	Interstitial lung diseases; Prostate cancer

Continued

Drug (Code) name	Target	Organization	Therapeutic indication
Glesatinib	TEK; HGFR; MST1R; VEGFR-1; VEGFR-2; VEGFR-3	MethylGene (Mirati Therapeutics); Mirati Therapeutics (Originator)	Head and neck cancer; Non-small cell lung cancer; Solid tumors
CEP-11981; ESK-981; SSR-106462	TEK; VEGFR-2	Barbara Ann Karmanos Cancer Institute; Cephalon (Teva); Sanofi (Originator); Teva; University of Michigan	Oncolytic drugs; Prostate cancer; Renal cancer
Tesevatinib	EGFR; CSK; VEGFR-2; VEGFR-3	Exelixis (Originator); GlaxoSmithKline; Kadmon; Symphony Evolution	Brain cancer; Breast cancer; Non-small cell lung cancer; Renal and urinary system genetic disorders
Cediranib	VEGFR-1; VEGFR-2; VEGFR-3	AstraZeneca (Originator); Canadian Cancer Society Research Inst; Mayo Clinic; National Cancer Institute (NCI); National Cancer Institute (US) (National Cancer Institute (NCI)); National Cancer Institute of Canada (Canadian Cancer Society Research Inst); Radboud Universiteit Nijmegen	Breast cancer; Cancer associated disorders; Colorectal cancer; Digestive/gastrointestinal cancer; Endocrine cancer; Gastric cancer; Glioblastoma multiforme; Head and neck cancer; Leukemia; Liver cancer; Lymphoma; Melanoma; Myelodysplastic syndrome; Myeloid leukemia; NSCLC; Ovarian cancer; Prostate cancer; Renal cancer; Respiratory/thoracic cancer; Sarcoma; Small cell lung cancer; Solid tumors

靶点, 不过值得注意的是这几个药物的治疗组不是针对肿瘤而是炎症性疾病和自身免疫性疾病 (表5)。

4.5 JAK

JAK激酶家族属于非受体酪氨酸蛋白激酶, 目前发现的共有4位家族成员: JAK1、JAK2、JAK3和TYK2[62]。其中JAK1、JAK2和TYK2广泛存在于各种组织和细胞中, JAK3只在淋巴细胞和骨髓中表达。JAK蛋白与不同的受体特异性结合能发挥特定的生理功能。研究表明JAK激酶和血液系统肿瘤关系密切, JAK2跟红细胞和血小板的生成密切相关, JAK1/3则和免疫调节有关[63]。近几年研究发现JAK-STAT信号通路与炎症细胞因子、肿瘤细胞等的信号转导密切相关, 广泛参与人类健康和疾病过程中的细胞活动[64]。FDA批准上市的有fedratinib (骨髓纤维变性)[65]、upadacitinib (中度/重度类风湿性关节炎)[66]、baricitinib (类风湿关节炎)[67]、tofacitinib (银屑病关节炎、类风湿关节炎、溃疡性结肠炎)[68]和ruxolitinib (骨纤维化)[69] 5个药物, 均为单靶点且都不是肿瘤药。本综述统计的处于临床试验的JAK抑制剂有10个, 基本都是单靶点, 炎症和自身免疫性疾病相关适应证占绝大部分 (表6)。

4.6 磷脂酰肌醇3-激酶 (PI3K)

PI3K (磷脂酰肌醇3-激酶) 是一类脂质激酶, 根据其结构特征和底物特异性可分为I、II、III 3种类型[70]。I型又可以分为IA和IB两种分型, 其中IA有PI3Kα、

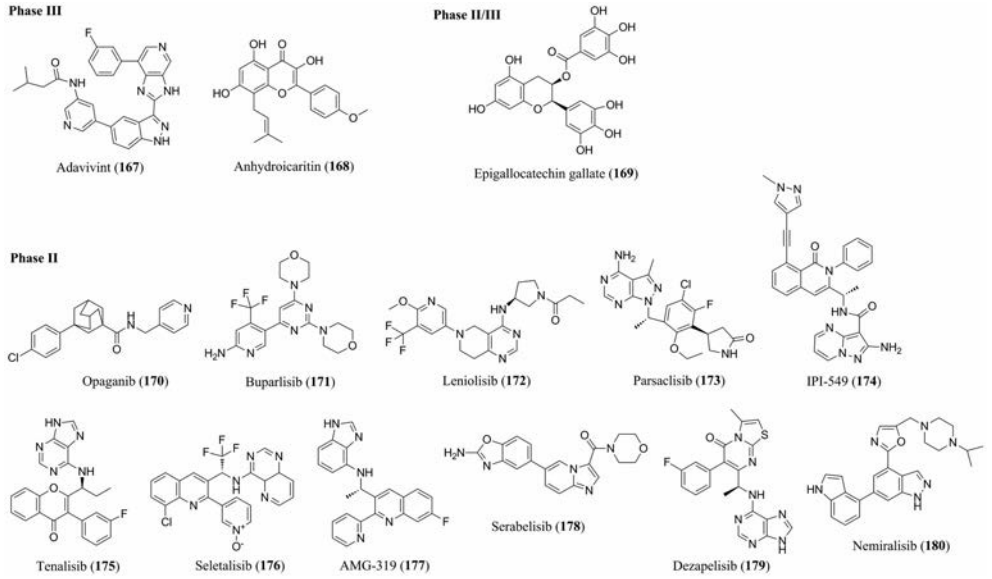

Figure 8 Structures of other kinase inhibitors (**167**–**180**) currently in phase II and III clinical trials

Table 5 BTK inhibitors, their protein kinase targets, and therapeutic indications

Drug (Code) name	Target	Organization	Therapeutic indication
Launched			
Zanubrutinib	BTK	BeiGene	Lymphoma
Acalabrutinib	BTK	Acerta Pharma	Lymphoma
Ibrutinib	BTK	Pharma-cyclics and J&J	Lymphoma; Chronic lymphocytic leukemia
Phase III			
Rilzabrutinib	BTK	Principia Biopharma (Originator)	Skin drugs; Inflammation; Rheumatoid arthritis
Evobrutinib	BTK	EMD Serono (Originator)	Multiple sclerosis; Rheumatoid arthritis; Systemic lupus erythematosus
Phase II			
Branebrutinib	BTK	Bristol-Myers Squibb (Originator)	Multiple sclerosis; Rheumatoid arthritis; Systemic lupus erythematosus
Remibrutinib	BTK	Novartis (Originator)	Asthma; Autoimmune disease; Urticaria
BMS-986142	BTK	Bristol-Myers Squibb (Originator)	Rheumatoid arthritis; Sjogren's syndrome; Systemic lupus erythematosus
Fenebrutinib	BTK	ChugaiPharmaceutical(Originator); Genentech (Originator)	Lymphocytic leukemia; Non-Hodgkin's lymphoma; Rheumatoid arthritis; Systemic lupus erythematosus; Urticaria

Table 6 JAK inhibitors, their protein kinase targets, and therapeutic indications

Drug (Code) name	Target	Organization	Therapeutic indication
Launched			
Fedratinib	JAK2	Celgene	Myelofibrosis
Upadacitinib	JAK1	Abbvie	Moderate/severe rheumatoid arthritis
Baricitinib	JAK1/2	Lilly	Reumatoid arthritis
Tofacitinib	JAK3	Pfizer	Rheumatoid arthritis; Psoriatic arthritis; Ulerative colitis
Ruxolitinib	JAK1/2	Incyte	Myelofibrosis
Phase III			
Abrocitinib	JAK1	Pfizer (Originator)	Antipsoriatics; Atopic dermatitis; Systemic lupus erythematosus;
Itacitinib	JAK1	Incyte(Originator); Innovent Biologics	Antipruritics; Antipsoriatics; Hematopoiesis disorders; Immunosuppressants; Inflammatory bowel disease lymphoma; Melanoma; Non-Hodgkin's lymphoma; NSCLC; Pancreatic cancer; Rheumatoid arthritis; Sarcoma; Solid tumors; Treatment of transplant rejection
Momelotinib	JAK1/2	CresPharmaceuticals; Cytopia (Gilead); Gilead (Originator); Sierra Oncology	Hematopoiesis disorders; Non-small cell lung cancer; Pancreatic cancer
Phase II/III			
PF-06651600	JAK3	Pfizer (Originator)	Dermatologic drugs; Hair growth stimulants; Inflammatory bowel disease; Rheumatoid arthritis
Phase II			
Brepocitinib	JAK1/2	Pfizer (Originator)	Antipsoriatics; Atopic dermatitis; Dermatologic drugs; Hair growth stimulants; Inflammatory bowel disease; Psoriatic arthritis; Systemic lupus erythematosus
ARQ-252; SHR-0302	JAK1	Arcutis; JiangsuHengrui (Originator); Reistone Biopharma	Dermatologic drugs; Eczema; Hair growth stimulants; Inflammatory bowel disease; Rheumatoid arthritis; Autoimmune diseases
Deuterated ruxolitinib	JAK1/2	Concert Pharmaceuticals (Originator)	Hair growth stimulants
Gusacitinib	JAK1/2/3; SYK; TYK2	AsanaBioSciences; Endo (Originator)	Atopic dermatitis; Eczema; Hematopoiesis disorders; Leukemia; Lymphocytic leukemia; Non-Hodgkin's lymphoma; Rheumatoid arthritis; Solid tumors; Autoimmune diseases
Cerdulatinib	JAK; SYK	Dermavant Sciences; NicOx; Portola Pharmaceuticals (Originator)	dermatologic drugs; Hematological cancer; Non-Hodgkin's lymphoma; Rheumatoid arthritis
Gandotinib	JAK2	Lilly	Hematopoietic disorders

PI3Kβ、PI3Kδ 3种分型, 它是一种异源二聚体酶, 含有1个调节亚基p85和1个催化亚基p110。调节亚基被激活后可以将催化亚基富集到细胞膜然后磷酸化其底物, 在非活化状态下催化亚基的酶活性受到抑制。IB也是异源二聚体酶, 只有PI3Kγ一种分型, 主要在免疫和造血细胞中表达。I型PI3K的PIP2磷酸化生成PIP3, 然后进行信号转导。II型没有调节亚基, 只存在1个可以与磷酸化的适配器蛋白作用的催化亚基。III型PI3K也是异型二聚体酶, 同样含有两个亚基: 调节亚基P150和催化亚基Vps34, 其底物为PI, 磷酸化后生成PIP, 参与调控细胞内的运输和自噬[71]。在FDA批准上市的药物中以PI3K为靶点的只有alpelisib (乳腺癌)[72]、copanlisib (复发滤泡淋巴瘤)[73]和idelalisib (慢性粒细胞白血病)[74] 3个药物, 但是处于临床试验的药物中则有16个, 涉及的适应证为炎症、肿瘤、免疫性疾病等 (表7)。

Table 7 PI3K inhibitors, their protein kinase targets, and therapeutic indications

Drug (Code) name	Target	Organization	Therapeutic indication
Launched			
Alpelisib	PI3Kα	Novartis	Breast cancer
Copanlisib	PI3K	Bayer	Relapsed follicular lymphoma
Idelalisib	PI3K; P110	Gilead	Chronic lymphocytic leukemia; Follicular lymphoma; Small lymphocytic lymphoma
Phase III			
Rigosertib	CDK1; PI3K; STPK13	Onconova	Head and neck cancer; Blood cancer; Hematopoietic disorder; Lymphocytic leukemia; Lymphoma; Myelodysplastic syndrome; Myeloid leukemia; Ovarian cancer; Pancreatic cancer; Solid tumor
Enzastaurin	PI3K; PKCβ; AKT	Lilly	Breast cancer; Colorectal cancer; Glioblastoma multiforme; Multiple myeloma; Neurologic cancer; Non-Hodgkin's lymphoma; Non-small cell lung cancer; Oncolytic drugs; Ovarian cancer; Pancreatic cancer; Prostate cancer; Pulmonary hypertension; Renal cancer; Solid tumors
Phase II			
Paxalisib	mTOR; PI3K; KTA	Genentech (Originator); Kazia Therapeutics; Novogen (Kazia Therapeutics)	Breast cancer therapy; Glioblastoma multiforme; Neurologic cancer; Oncolytic drugs
NSC-350625; ONC-201; ONC201/TIC10; OP-10; TIC-10	ERK; PI3K; AKT	ChemDiv (Originator); Harvard Medical School (Originator); Ohara Pharmaceutical; Oncoceutics; Pennsylvania State University (Originator); University of Pennsylvania (Originator); Wayne State University (Originator)	Brain cancer; Breast cancer; Colorectal cancer; Endocrine cancer; Female reproductive system cancer; Glioblastoma multiforme; Lymphocytic leukemia; Multiple myeloma; Myelodysplastic syndrome; Myeloid leukemia; Neurologic cancer; Non-Hodgkin's lymphoma; Oncolytic drugs; Solid tumors; Ovarian cancer; Sarcoma
Fimepinostat	HDAC1/2/3/6/10; PI3Kα/β/δ	Curis (Originator); National Cancer Institute (NCI)	Cancer of unspecified body location/system; Endocrine cancer; Lymphoma; Solid tumors; Multiple myeloma; Neurologic cancer; Non-Hodgkin's lymphoma
Perifosine	PI3K; AKT	AEterna Zentaris (Originator); Asta Medica (Originator); Handok; Hikma; Keryx; M.D. Anderson Cancer Center; Memorial Sloan-Kettering Cancer Center; National Cancer Institute (NCI); Nippon Kayaku; University of Chicago; Yakult Honsha	Brain cancer; Breast cancer; Colorectal cancer; Digestive/Gastrointestinal cancer; Ovarian cancer; Head and neck cancer; Leukemia; Lymphoma; Melanoma; Multiple myeloma; Neurologic cancer; Non-Hodgkin's lymphoma; Non-small cell lung cancer; Oncolytic drugs; Pancreatic cancer; Prostate cancer; Renal cancer; Respiratory/Thoracic cancer; Sarcoma; Solid tumors
Buparlisib	PI3Kα/β/δ/γ	Adlai Nortye; Dana-Farber Cancer Institute; Hospices Civilsde Lyon Memorial Sloan-Kettering Cancer Center; Novartis (Originator); Prince of Songkla University (PSU); University of Kansas; Yonsei University	Bladder cancer; Breast cancer; Colorectal cancer; Digestive/Gastrointestinal cancer; Endocrine cancer; Female reproductive system cancer; Glioblastoma multiforme; Head and neck cancer; Hematopoiesis disorders; Liver cancer; Lymphocytic Leukemia; Melanoma; Non-Hodgkin's lymphoma; Non-small cell lung cancer; Oncolytic drugs; Ovarian cancer; Pancreatic cancer; Prostate cancer; Respiratory/Thoracic cancer
Leniolisib	PI3Kδ	Novartis (Originator); Pharming	Immunological genetic disorders
Parsaclisib	PI3Kδ	Incyte (Originator); Innovent Biologics	Breast cancer; Lymphoma; Hematopoiesis disorders; Non-Hodgkin's lymphoma; Rheumatoid arthritis; Solid tumors; Systemic lupus erythematosus; Autoimmune diseases
IPI-549	PI3Kγ	Infinity Pharmaceuticals (Originator)	Bladder cancer therapy; Breast cancer; Melanoma; Head and neck cancer; Non-small cell lung cancer; Ovarian cancer; Renal cancer; Solid tumors
Tenalisib	PI3Kδ/γ	Incozen; Rhizen Pharmaceuticals (Originator)	Hematological cancer; Lymphocytic leukemia; Lymphoma; Non-Hodgkin's lymphoma
Seletalisib	PI3Kδ	UCB (Originator)	Antipsoriatics; Disorders; Immunological genetic immunomodulators
AMG-319	PI3Kδ	Amgen (Originator); Cancer Research UK	Head and neck cancer; Hematological cancer; Solid tumors
Serabelisib	PI3Kα	Intellikine (Millennium Pharmaceuticals); Millennium Pharmaceuticals (Originator); Petra Pharma	Breast cancer; Digestive/Gastrointestinal cancer; Female reproductive system cancer; Non-small cell lung cancer; Renal cancer; Solid tumors
Dezapelisib	PI3Kδ	Incyte (Originator)	Lymphoma; Non-Hodgkin's lymphoma
Nemiralisib	PI3Kδ	Glaxo Smith Kline (Originator)	Asthma; Chronic obstructive pulmonary diseases (COPD); Immunological genetic disorders; Respiratory disorders (not specified)

4.7 细胞周期蛋白依赖性激酶 (CDK4/6)

CDK4/6是细胞周期蛋白依赖性激酶 (cyclin dependent kinase) 家族成员, 该家族一共有13个, CDK1～13[75]。细胞周期蛋白依赖性激酶是一类丝氨酸/苏氨酸激酶。CDK通过与其对应的细胞周期蛋白结合, 能够在细胞周期调控、转录、代谢等各个阶段发挥作用[76]。在细胞周期的4个分期里, CDK4/6主要负责G1-S期的调控。CDK4和CDK6有71%的氨基酸序列同源性, 都能与cyclin D结合成复合物进而促使抑癌基因Rb磷酸化, 使得转录因子E2F从Rb-E2F脱离出来, 激活一系列基因使细胞进入S期开始的DNA复制[77]。CDK4/6的抑制剂在抗肿瘤方面作用机制主要有3方面: ① 抑制肿瘤细胞恶性增殖, 恢复正常细胞周期; ② 触发免疫机制; ③ 改变癌细胞微环境[78]。FDA批准的ribociclib (乳腺癌)[79]、abemaciclib (乳腺癌)[80]和palbociclib (乳腺癌)[81] 3个药物对CDK4/6都具有很高的选择性, 适应证都是乳腺癌。但处于临床的几个药物则不再是单纯地作用于CDK4/6, 对家族的其他成员也有一定的作用 (表8)。

5 总结与展望

近几十年来小分子激酶抑制剂作为一个极具潜力的靶点, 一直被研究者青睐, 从2001年到2020年4月累计有59个药物经FDA批准上市, 发展势头强劲, 这些药物的出现彻底改变了癌症的治疗方式, 为医生和患者提供了更多的治疗方案。但是相较于研究发现的518个激酶这个基数, 目前小分子激酶抑制剂数量还是很少的, 其发展仍处于起步阶段。同时现在所开发的药物还集中在EGFRs、FGFRs、VEGFRs、JAK、PI3K和CDK等小部分激酶靶点, 对其他激酶成员发掘不够, 而且现有药物都具有较大的相似性, 绝大多数是对已知药物进行优化改造而成, 在骨架结构和作用机制方面缺乏创新性, 需要探索的空间还很大。

由于早期对于激酶的研究主要是基于酪氨酸激酶及其在肿瘤学中的作用展开的, 所以早期的上市药物以及目前处于临床试验的药物, 它们的适应证主要都集中在不同类型的癌症, 没有能够很好地将该领域的研究成果运用到其他疾病领域。不过近几年有一个比较好的现象就是开始有一些药物慢慢扩散到其他疾病领域且有加强的趋势, 例如现在上市的药物中有适应证为炎症、退行性疾病相关药物了。在临床试验的药物更是向炎症、退行性疾病、自身免疫病、中枢神经系统疾病、糖尿病、心血管疾病等除肿瘤以外的适应证不断扩散和尝试, 不断地向其他疾病领域突破有利于激酶价值潜力的最大程度挖掘, 前景值得期待。

耐药性是目前在TKI类药物临床应用道路上比较大的阻碍。TKI类药物的耐药性主要分为原发性耐药和获得性耐药。对TKI天然不敏感的称之为原发性耐药; 获得性耐药则是指起初有效使用一段时间之后出现的耐药性。以EGFR抑制剂在非小细胞肺癌中的运用为例, 使用EGFR-TKIs治疗一般有效持续9～13个月就会出现获得性耐药, 从而限制了其临床运用和获益的持续性, 而T790M突变是NSCLC患者最常见的获得性耐药机制[82,83]。奥希替尼 (osimertinib) 作为克服EGFR T790M突变的抑制剂于2015年被FDA获批用于临床, 然而其又会发生靶点继发性的C797S突变, 诱导其耐药。因此, 仍需要研发下一代的可以克服

Table 8 CDK4/6 inhibitors, their protein kinase targets, and therapeutic indications

Drug (Code) name	Target	Organization	Therapeutic indication
Launched			
Ribociclib	CDK4/6	Novartis	Breast cancer
Abemaciclib	CDK4/6	Lilly	Breast cancer
Palbociclib	CDK4/6	Park Davis	Breast cancer; ER^+ and $HER2^+$
Phase II			
Milciclib	CDK1/2/4/5/7; TRKANTRK1; Wee1/2	Johns Hopkins University; Nerviano Medical Sciences (Originator); Pfizer (Originator); TGen Research Institute; Tiziana Life Sciences	Breast cancer; Liver cancer; Oncolytic drugs; Respiratory/ Thoracic cancer; Solid tumors
(*R*)-Roscovitin; Seliciclib	CDK1/2/5/7/9	CNRS (Originator); Cyclacel; Institute of Cancer Research (ICR) (Originator); ManRos Therapeutics	Breast cancer; Cystic fibrosis; Head and neck cancer; Lymphocytic leukemia; Lymphoma; Multiple myeloma; NSCLC; Oncolytic drugs; Ovarian cancer; Rheumatoid arthritis; Solid tumors
Alvocidib; Flavopiridol	BIRC5; CDK1/2/4/6/7/9	Aventis Pharma (Sanofi); Mayo Clinic; Memorial Sloan-Kettering Cancer Center; National Cancer Institute (NCI); National Cancer Institute (US) (National Cancer Institute (NCI)); Sanofi (Originator); Sumitomo Dainippon Pharma; Tolero Pharmaceuticals; Sanofi-aventis (Sanofi)	Breast cancer; Cancer of unspecified body location/system; Colorectal cancer; Gastric cancer; Head and neck cancer; Hematological cancer; Leukemia; Liver cancer; Lung cancer; Lymphocytic leukemia; Melanoma; Multiple myeloma; Myelodysplastic syndrome; Myeloid leukemia; Non-Hodgkin's lymphoma; Oncolytic drugs; Ovarian cancer; Pancreatic cancer; Prostate cancer; Renal cancer; Sarcoma; Solid tumors

EGFR C797S突变的抑制剂。事实上, 很大部分的耐药问题都是由于靶点突变造成的, 但却远不止这么简单, 比如它还与肿瘤的异质性有很大的关系[84], 所以探明耐药机制以及采取何种措施解决小分子抑制剂类药物的耐药问题是目前摆在研究者们面前的一大挑战。

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