Small molecules, big impact: 20 years of targeted therapy in oncology

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The identification of molecular targets and the growing knowledge of their cellular functions have led to the development of small molecule inhibitors as a major therapeutic class for cancer treatment. Both multitargeted and highly selective kinase inhibitors are used for the treatment of advanced treatment-resistant cancers, and many have also achieved regulatory approval for early clinical settings as adjuvant therapies or as first-line options for recurrent or metastatic disease. Lessons learned from the development of these agents can accelerate the development of next-generation inhibitors to optimise the therapeutic index, overcome drug resistance, and establish combination therapies. The future of small molecule inhibitors is promising as there is the potential to investigate novel difficult-to-drug targets, to apply predictive non-clinical models to select promising drug candidates for human evaluation, and to use dynamic clinical trial interventions with liquid biopsies to deliver precision medicine.

Introduction

Cancer chemotherapy uses drugs to kill cancer cells that are more primed for death than non-malignant host cells. The focus of novel drug development has shifted towards the identification and targeting of molecular drivers of cancer. There are two main approaches for targeted cancer therapy: antibodies and small molecules. Antibodies are typically characterised by high selectivity; however, their targets are often restricted to the cell surface and they require intravenous or subcutaneous dosing because of their large molecular weight. By comparison, small molecule inhibitors vary in selectivity, and by virtue of their small size, can potentially bind a wider range of extracellular and intracellular targets. To date, there are 43 small molecule inhibitors approved by the US Food and Drug Administration (FDA) for oncology indications (table). Although most of these approvals were based on the prolonged survival of patients with advanced cancer that were refractory to conventional chemotherapy, many of these drugs show superiority over cytotoxic chemotherapy, with fewer side-effects as first-line therapy in the recurrent or metastatic setting. There are also examples of small molecule inhibitors that are approved as treatment for minimal residual disease or as adjuvant therapy delivered with curative intent (appendix pp 1–4). Most approved small molecule inhibitors target intracellular kinases that regulate cell signalling through the transfer of phosphate groups to target proteins (figure 1). A broad range of targets are currently being investigated, including those involved in protein–protein interactions, cancer metabolism, and immune modulation. We review the development of multitargeted and biomarker-selected small molecule inhibitors, discuss unresolved issues, and predict future directions for this continuously evolving field.

See Online for appendix

Search strategy and selection criteria

We searched for English language publications in PubMed and references from relevant articles between Jan 1, 1990, and Dec 31, 2019, using the search terms "molecular targeted therapy", "kinase inhibitor", "cancer", "precision medicine", "personalized medicine", "clinical trials", and the names for all small molecule targeted inhibitors described in this Therapeutics paper. Abstracts and reports were included for trials that have been presented at oncology scientific meetings but have not yet been published.

Categories of small molecule inhibitors

The development of small molecule inhibitors has followed two related, yet independent paths, defined largely by target selectivity profiles. Multikinase inhibitors exert their anticancer activity by simultaneously targeting a broad spectrum of the human kinome. The use of these drugs is generally based on histological diagnosis, without the need for additional individualised patient selection. Selective small molecule inhibitors have fewer targets and, in some cases, inhibit a single component of cell signalling. Patients are often selected for treatment with these biological agents on the basis of the presence or absence of specific predictive biomarkers detected from tumour or blood sampling.

Multikinase small molecule inhibitors

Sorafenib and sunitinib are prototypic examples of multikinase small molecule inhibitors. Like most agents of this class, both drugs inhibit VEGFR1, VEGFR2, KIT, and PDGFR-α, among a wide range of other targets. Dose-limiting toxic effects are similar across this drug class and are predominantly driven by inhibition of VEGFR. Given that a wide spectrum of the kinome is potentially inhibited by these agents, development of multikinase inhibitors has been largely empirical, with some notable exceptions. Early activity was observed in renal cell carcinoma, pancreatic neuroendocrine tumours, and hepatocellular carcinoma, which ultimately led to confirmatory studies and regulatory approvals.[4,5] Subsequent generations inhibiting different profiles of kinases have further expanded the reach of this drug class to include the treatment of thyroid cancer,[6,7] soft tissue sarcoma,[8] and colorectal cancer.[9] The exact profile

of targeted kinases and the inhibitors' potency accounts for differences observed in therapeutic activity and toxicity.[10,11] Although VEGFR is the primary therapeutic target for most multikinase inhibitors, the modest activity of the single agent bevacizumab (an anti-VEGF monoclonal antibody) suggests that a simultaneous and overlapping blockade of angiogenic and non-angiogenic signalling pathways might be partially responsible for the differences observed in the anticancer activity of different multikinase inhibitors.

In some instances, the clinical activity of these multi-targeted agents might be linked to their ability to inhibit a single kinase. Imatinib was the first approved by the US FDA small molecule inhibitor to target the BCR–ABL fusion protein, which is the pathogenic hallmark of chronic myeloid leukaemia.[12,13] Imatinib is also a potent inhibitor of KIT (among other kinases), and is approved by the US FDA, along with other multikinase inhibitors, for the treatment of gastrointestinal stromal tumours with KIT alterations.[14] Similarly, the activity of lenvatinib, cabozantinib, and vandetanib in medullary thyroid cancer is likely to be driven by inhibition of activating *RET* mutations found in most of these tumours.[6,15,16]

Selective small molecule inhibitors

A subset of cancers exhibit strong addiction to an oncogene or, conversely, unique molecular vulnerabilities that can selectively exploit pathways, such as those involved in DNA repair or apoptosis. Selective small molecule inhibitors offer the potential to potently antagonise the intended target while minimising off-target inhibition that might lead to dose reduction or to intolerable side-effects. EGFR inhibitors, such as erlotinib and gefitinib, were initially developed without individual patient selection and had modest overall efficacy in patients with non-small-cell lung cancer who were pretreated with standard cytotoxic chemotherapy.[17,18] Later, recognition that a subset of patients benefited greatly (ie, with increased overall survival) led to the identification of *EGFR* mutations as a predictive biomarker and eventual relabelling of these two agents. This finding established a new paradigm by which use of a small molecule inhibitor was predicated on the testing of stored tumour samples for the presence of a genomic biomarker.[19] The testing of novel small molecule inhibitors has evolved to include biomarker selection of patients during initial dose escalation in phase 1, first-in-human trials. This approach was used for mutant-selective *BRAF Val600Glu* kinase inhibitors for patients with melanoma, leading to global regulatory approval of these drugs (vemurafenib, dabrafenib and encorafenib) within several years of the first dosing study in humans.[20] Multiple other small molecule inhibitors targeting genomic rearrangements in *ALK* and *ROS1* (collectively found in 5% of non-small-cell lung cancer) have shown similar benefits.[21,22] In acute myeloid leukaemia, combining an FLT3 inhibitor (midostaurin) with induction chemotherapy for an *FLT3*-mutated subtype prolonged overall survival. This study was the first to show such a survival benefit in patients with acute myeloid leukaemia since the introduction of induction chemotherapy in the 1970s.[23] Several other genomically-targeted drugs have also been approved for this disease, including patients with mutations in *IDH2* (enasidenib[24]) and *IDH1* (ivosidenib[25]).

	Drug target	Protein substrate	Indications
Alectinib, brigatinib, crizotinib, ceritinib, lorlatinib	ALK	Tyrosine	Non-small-lung cell carcinoma
Venetoclax	BCL2	BCL2	Chronic myeloid leukaemia , acute myeloid leukaemia
Bosutinib, dasatinib, nilotinib, ponatinib	BCR–ABL	Tyrosine; CAMK	Chronic myeloid leukemia
Imatinib	BCR–ABL	Tyrosine; CAMK	Chronic myeloid leukemia, acute lymphoblastic leukaemia, myelodysplastic and myeloproliferative disease (with *PDGFR* gene re-arrangements)
Vemurafenib	BRAF	Serine and threonine; CAMK; NEK; TKL	Melanoma, Erdheim-Chester disease
Dabrafenib	BRAF	Serine and threonine; CAMK; NEK; TKL	Melanoma, non-small-lung cell carcinoma, anaplastic thyroid cancer
Encorafenib	BRAF	Serine and threonine; CAMK; NEK; TKL	Melanoma
Acalabrutinib	BTK	Tyrosine	Mantle cell lymphoma, chronic lymphocytic leukaemia
Ibrutinib	BTK	Tyrosine	Chronic lymphocytic leukaemia and small lymphocytic lymphoma, mantle cell lymphoma, marginal zone lymphoma, Waldenstrom macroglobulinaemia
Zanubrutinib	BTK	Tyrosine	Mantle cell lymphoma
Abemaciclib, palbociclib, ribociclib	CDK4 and CDK6	CMGC	Breast cancer
Pexidartinib	CSF1R	Tyrosine	Tenosynovial giant cell tumour
Afatinib, dacomitinib, gefitinib, osimertinib	EGFR and HER family	Tyrosine	Non-small-lung cell carcinoma
Erlotinib	EGFR and HER family	Tyrosine	Non-small-lung cell carcinoma, pancreatic cancer
Neratinib	EGFR and HER family	Tyrosine	Breast cancer
Lapatinib tosilate	EGFR and HER family	Tyrosine	Breast cancer
Gilteritinib, midostaurin	FLT3	Tyrosine	Acute myeloid leukaemia
Erdafitinib	FGFR family	Tyrosine	Urothelial cancer
Ruxolitinib phosphate	JAK family	Tyrosine	Myelofibrosis
Imatinib, sunitinib, regorafenib	KIT	Tyrosine	Gastrointestinal stromal tumours, dermatofibrosarcoma protuberans
Enasidenib, ivosidenib	IDH1 and IDH2	Tyrosine	Acute myeloid leukaemia
Binimetinib, cobimetinib, trametinib	MEK1 and MEK2	Serine and threonine; TKL	Melanoma, non-small-lung cell carcinoma, anaplastic thyroid cancer
Everolimus	mTOR	Serine and threonine	Breast cancer, neuroendocrine tumour, renal cell cancer
Temsirolimus	mTOR	Serine and threonine	Renal cell cancer
Entrectinib, larotrectinib	NTRK1, NTRK2, and NTRK3	Tyrosine	*NTRK* fusion-positive tumours
Olaparib	PARP1 and PARP2	Poly (ADP-Ribose) polymerase	Breast, ovarian, fallopian tube, and primary peritoneal cancers

(Table continues on next page)

	Drug target	Protein substrate	Indications
(Continued from previous page)			
Niraparib, rucaparib	PARP1 and PARP2	Poly (ADP-Ribose) polymerase	Ovarian, fallopian tube, and primary peritoneal cancers
Talazoparib	PARP1 and PARP2	Poly (ADP-Ribose) polymerase	Breast cancer
Alpelisib	PI3K	Phosphatidylinositol 3-kinase	Breast cancer
Copanlisib	PI3K	Phosphatidylinositol 3-kinase	Follicular lymphoma
Duvelisib, idelalisib	PI3K	Phosphatidylinositol 3-kinase	Chronic lymphocytic leukemia and small lymphocytic lymphoma, follicular lymphoma
Crizotinib, entrectinib	ROS1	Tyrosine	Non-small-lung cell carcinoma
Glasdegib, sonidegib, vismodegib	SMO	Covalent antagonist	Basal cell carcinoma, acute myeloid leukaemia
Selinexor	XPO1	Covalent antagonist	Multiple myeloma
Axitinib	VEGFR multikinase	Tyrosine; CMGC; TKL	Renal cell cancer
Cabozantinib	VEGFR multikinase	Tyrosine; CMGC; TKL	Medullary thyroid, hepatocellular carcinoma, and renal cell cancer
Lenvatinib	VEGFR multikinase	Tyrosine; CMGC; TKL	Thyroid cancer (iodine-refractory differentiated), endometrial cancer*
Pazopanib	VEGFR multikinase	Tyrosine; CMGC; TKL	Renal cell cancer, soft tissue sarcoma
Regorafenib	VEGFR multikinase	Tyrosine; CMGC; TKL	Colorectal cancer, Gastrointestinal stromal tumours, hepatocellular carcinoma
Sorafenib	VEGFR multikinase	Tyrosine; CMGC; TKL	Hepatocellular carcinoma, renal cell cancer, thyroid cancer (iodine refractory, differentiated)
Sunitinib	VEGFR multikinase	Tyrosine; CMGC; TKL	Gastrointestinal stromal tumours, pancreatic cancer, neuroendocrine tumour, and renal cell cancer
Vandetanib	VEGFR multikinase	Tyrosine; CMGC; TKL	Medullary thyroid cancer

TKL=tyrosine-kinase like. CMGC=cyclin-dependent kinases, mitogen-activated protein kinases, glycogen synthase kinases, and cyclin dependent kinase-like kinases. NTRK=neurotrophic tropomyosin-related kinase. *Accelerated approval of lenvatinib for microsatellite stable and mismatch repair proficient endometrial cancer when used in combination with pembrolizumab.

Table: **Approved small molecule inhibitors and indications**

Not all selective small molecule inhibitors require individualised patient selection. Almost all cutaneous basal-cell carcinomas are characterised by the presence of genomic alternations that activate the Hedgehog signalling pathway, which can be irreversibly blocked by SMO inhibitors.[26] Similarly, the activity of some of these inhibitors is dependent on specific signalling routes, even in the absence of genomic alterations within these pathways. For example, the JAK1 and JAK2 inhibitor, ruxolitinib phosphate, improves survival in patients with myelofibrosis, regardless of the mutational status of the *JAK2* gene.[27]

Molecular screening and evolving clinical trial frameworks

The identification of patients with rare driver mutations for proof-of-concept trials with targeted small molecule inhibitors can be challenging. The first trial of crizotinib screened more than 1500 tumour samples from patients with treatment-resistant non-small-cell lung cancer to enrol 82 patients with *ALK* rearrangements.[28] Further exacerbating this issue, patients with advanced cancers are often not well enough to wait for the results of tissue biomarker testing from trials, especially for qualifying genomic alterations of low prevalence. Additional practical considerations, such as insufficient archival tumour tissue, make sequential testing for trial eligibility inefficient and often entirely impractical.

To address these obstacles in drug development, many academic cancer centres and government-sponsored trial networks have instituted broad molecular screening programmes to screen most or all patients. These programmes typically use broad (panels of several hundred genes) multigene next-generation sequencing (NGS) of tumour-derived DNA, or sometimes DNA and RNA, from patients with advanced cancer to identify clinically actionable genomic alterations that can be matched to approved therapies or therapies under investigation.[29,30] In some parts of the world, mainly in high-income countries, NGS is increasingly reimbursed by insurance agencies or by the government as part of routine care. Despite the increased adoption of this method, the overall clinical use of this approach remains uncertain, with some critics arguing that too few patients benefit from genotype-matched treatment to justify the investment in broad multigene testing.[31,32] However, this approach can be transformative for patients with highly actionable genomic alterations, such as with *NTRK* gene rearrangements or microsatellite instability-high genomic signatures that occur at a very low frequency across many tumour types.[33,34] Small molecule TRK family inhibitors, larotrectinib and entrectinib for *NTRK*-gene fusions, and pembrolizumab for immune checkpoint inhibition of PD-1 in microsatellite instability-high or mismatch repair deficient solid tumours, are the first examples of US FDA approved tumour-agnostic treatments on the basis of a common biomarker, rather than a tumour primary site. These treatments can produce notable and long-lasting efficacy, sometimes dramatically altering the natural history of the disease. The broad distribution of *NTRK* gene fusions and microsatellite instability-high or mismatch repair deficiency across cancers means that selective testing of tumour types that are known to be specifically enriched for these alterations will invariably miss many patients who might otherwise benefit from these transformative therapies.

For most small molecule inhibitors approved for tumour-specific use in a biomarker-defined population, there is ongoing uncertainty as to whether patients whose cancers are outside of the approved indications, but have the same biomarkers, will benefit. For example, BRAF-inhibitor therapy (eg, vemurafenib, dabrafenib, encorafenib) is highly effective in melanoma with the *BRAF Val600Glu* mutation, but minimally active as

a monotherapy for colorectal cancer with the same genomic alteration.[35] In addition, the SHIVA randomised trial[36] failed to show a benefit across different cancer types for various biomarker-directed small molecule inhibitor therapies compared with treatment of physician's choice; however, concerns have been raised about the biological relevance of the qualifying biomarkers and access to best-in-class targeted drug therapies for this study. Several national and international precision medicine platforms have been launched to further explore a biomarker-based, histology-agnostic strategy (appendix pp 5–11).[37–54] The so-called basket trials are one popular approach to establish the efficacy of a specific drug in all tumour types with a shared mutation.[29] These types of trials have provided important efficacy signals in tumour subpopulations that are genomically well-defined, such as neratinib in *ERBB2* mutant, non-amplified cancers;[55] vemurafenib in *BRAF Val600Glu* mutant non-small-cell lung cancer,[56] Erdheim-Chester disease and Langerhans cell histiocytosis,[57] and malignant gliomas;[58] dabrafenib and trametinib in anaplastic thyroid cancers[59] and biliary cancers with the *BRAF Val600Glu* mutation;[60] and capivasertib in oestrogen-receptor-positive breast and gynaecological cancers with the *AKT1 Glu17Lys* mutation.[61]

Lessons learned from small molecule inhibitors in precision medicine

There are several lessons learned from biomarker-based development of small molecule targeted inhibitor therapy (panel). The therapeutic index of a drug, defined as its efficacy to toxicity ratio, is an important consideration when trying to improve upon existing small molecule inhibitors in drug development. For tumours that have oncogene addiction (whereby tumour cells are highly dependent, or addicted, to a specific oncogenic pathway for their growth and survival), such as *BRAF Val600Glu*-mutant melanoma or *ERBB2*-amplified breast cancer, increased target inhibition and selectivity led to improved antitumour efficacy and a wider therapeutic index because of the low or absent expression of intended targets in normal tissues. By comparison, in situations of narrow therapeutic index where the drug target is widely expressed (eg, MEK1, MEK2, and EGFR), potent antitumour activity is offset by severe side-effects. However, in the case of small molecule inhibitors against EGFR, increased selectivity for mutant isotypes compared with wild type have improved long-term tolerability and simultaneously permit greater inhibition of the EGFR signalling pathway in tumours.[62,63] Identification of tumour-specific vulnerabilities, including PARP family member inhibition in germline *BRCA1* and *BRCA2* mutant cancers of the ovaries, breast, and pancreas,[64–66] can provide opportunities for synthetic lethality, whereby the concurrent perturbation of two genes or proteins leads to enhanced cell death that is not seen when either is targeted alone. More potent pathway suppression with combination therapy, such as the use of dual BRAF and MEK blockade in melanoma with the *BRAF Val600Glu* mutation, or combined BRAF, MEK, and EGFR blockade in colorectal cancer with the *BRAF Val600Glu* mutation, can also produce a more lasting

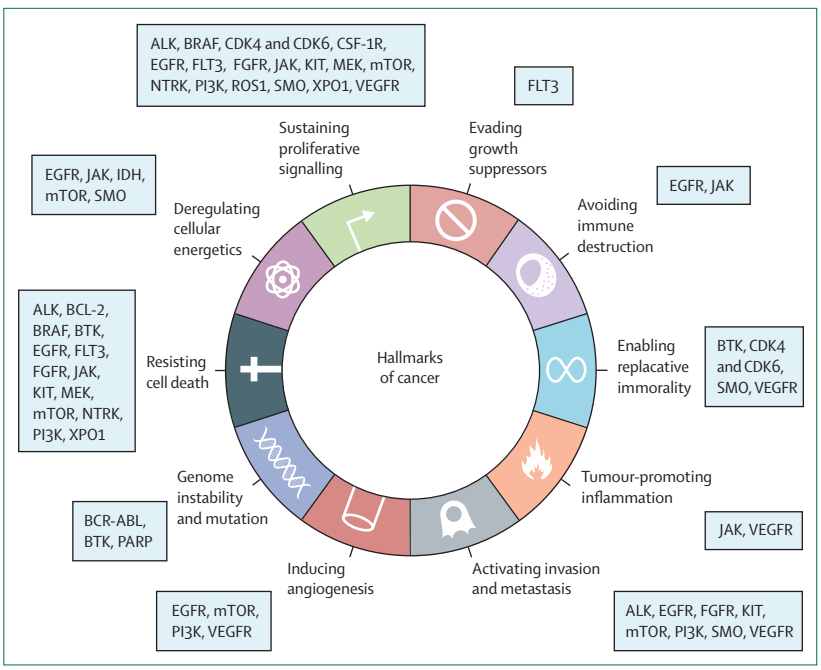

***Figure 1*: Targets of approved small molecule inhibitors**
Targets are mapped to the hallmarks of cancer[1] as annotated by the Cancer Gene Census[2] on the COSMIC website.[3] The hallmarks of cancer are currently not annotated for CSF-1R, IDH, MEK, NTRK, PARP, and SMO in the Cancer Gene Census. These annotations have been added by the authors.

***Panel:* Lessons learned from small molecule inhibitors in precision medicine**

- Degree of target inhibition correlates with efficacy; strategies to increase target inhibition include:
  - More potent inhibitors (excluding targets with narrow therapeutic index)
  - Highly selective inhibitors (minimise so-called off-target toxicity)
  - Combination targeted therapy (more complete pathway inhibition)
  - Mutant selective inhibitors (broaden therapeutic index)
- Identification of tumour-specific vulnerabilities provide opportunities for synthetic lethality
- Small molecule inhibitors with fewer resistance liabilities generally achieve more durable benefit
- Penetrance into sanctuary sites (CNS)
- Early use of next-generation small molecule inhibitors is associated with better outcomes than sequential use of first and subsequent generation agents
- Abrupt treatment discontinuation of small molecule inhibitor in oncogene-addicted cancers after progression might lead to disease flare

response.[67–69] Understanding the mechanisms behind emerging resistance to treatments can lead to improved next-generation inhibitors with fewer resistance liabilities. For example, approximately a third of patients with *ALK* rearranged non-small-cell lung cancer that is treated with crizotinib acquire secondary resistance mutations (ie, resistance that occurs after exposure to the drug despite initial sensitivity) in the ALK tyrosine kinase domain. Second-generation inhibitors, such as ceritinib,[22] alectinib,[70] and brigatinib,[71] are efficacious after crizotinib-driven resistance, including for patients with gatekeeper *Leu1196Met* and *Gly1269Ala* mutations in *ALK*. Lorlatinib is a third-generation inhibitor against all known ALK-inhibitor mutations arising from resistance, including the highly resistant *Gly1202Arg* mutation, and is approved for patients with disease progression after treatment with one or more ALK inhibitors.[72] Similar insights into the structural mechanisms by which second-site mutations (eg, *ROS1 Gly2032Arg*, *TRKA Gly595Arg* or *Gly667Cys*, *TRKC Gly623Arg* or *Gly696Cys*, and *BTK Cys481Ser*) drive target-mediated resistance to early compounds have enabled the development of next-generation ROS, TRK, and BTK inhibitors with improved activity.[34,73,74] Next-generation small molecule inhibitors designed to penetrate sanctuary sites responsible for disease progression, specifically the CNS, have also been an important development for the treatment of *ALK* rearranged, *EGFR* mutant, and *ROS1* rearranged non-small-cell lung cancer. For these tumours, the CNS is a frequent site of metastasis during therapy with earlier-generation small molecule inhibitors, but next-generation agents with markedly improved CNS penetration are effective at prolonging survival.

Through the successive development of better small molecule inhibitors for cancer, the scientific community has also learned important lessons about their optimal use. Treatment with more potent and broadly penetrant next-generation small molecule inhibitors in early lines of therapy can delay the onset of treatment resistance, even when compared with serial use of first and second-generation inhibitors.[63,75] Abrupt discontinuation of an oncogene-directed small molecule inhibitor after the onset of progression might lead to a disease flare because of differences in the growth kinetics of responsive and resistant tumour subclones. Treatment beyond radiographical progression, including radiation to localised sites of oligoprogression (progression at one or a limited number of disease sites) with continued targeted therapy, can be considered for selected patients. Similarly, after intervening with non-cross resistant drug treatments that have non-overlapping mechanisms of action, such as chemotherapy and immunotherapy, additional treatment with the same oncogene-directed small molecule inhibitor might induce an objective response such as tumor shrinkage or stabilization; however, these responses are typically short lived.[76,77]

Unresolved issues in the development of targeted inhibitors

Undefined and difficult-to-drug targets

Despite the existence of over 500 protein kinases, fewer than 5% have been successfully targeted by approved drugs, and most of these compounds are tyrosine kinase inhibitors. Current estimates are that approximately 40% of patients with cancer have at least one alteration in the genes targeted by these US FDA approved drugs.[78] The remaining kinases might be undefined and have yet unknown functions in cancer, or are difficult to drug because of structural challenges, including large and flat protein–protein interaction interfaces or the absence of deep protein binding pockets.[79] Drug discovery efforts are ongoing, with new therapeutic targets from the human kinome continuing to be investigated, and novel anticancer agents directed against these targets being actively developed. These efforts are accelerated to some extent by worldwide molecular profiling initiatives that uncover alterations in genes that encode various protein kinases in the biological samples of patients with cancer. Using a chemical proteomics approach, the systematic characterisation of cellular targets of 243 kinase inhibitors by Klaeger and colleagues[80] adds valuable information to these efforts. This large repository of data provides opportunities for drug repurposing, as well as the identification and validation of potential novel kinases as therapeutic targets.

Beyond the kinome, many molecular targets with proven roles in cancer have been difficult to drug. Venetoclax is a potent and selective inhibitor of the anti-apoptotic protein BCL-2 by disrupting its protein–protein interaction with the proapoptotic protein BIM. In early clinical development, venetoclax was so potent that it led to severe tumour lysis syndrome in some patients with chronic lymphocytic leukaemia.[81] After modifying the dosing and schedule, venetoclax was found to be safe and highly effective as a single therapy for chronic lymphocytic leukaemia,[82] or in combination with anti-CD20 monoclonal antibodies for initial treatment or refractory disease.[83] This inhibitor is also approved in acute myeloid leukaemia[84] and is being investigated in several other haematological malignancies, including non-Hodgkin lymphoma[85] and multiple myeloma,[86] as well as in solid tumours, such as breast cancer.[87]

Restoring the functions of a tumour suppressor gene is more challenging than to inhibit the actions of an oncogene. The tumour suppressor TP53 is the most commonly altered transcription factor in cancer, leading to the dysregulation of a broad range of cellular functions. The targeting of TP53 with drugs is challenging, mainly because of its nuclear location and its multienzyme assembly with many cofactors to form a transcription complex. Attempts include small molecule inhibitors against MDM2 that directly block the function of this TP53 regulatory protein or prevent its interaction with TP53.[88] Whereas some oncogenes and their primary and

acquired mutant variants have been successfully targeted with first-generation and next-generation small molecule inhibitors, the targeting with drugs for other oncogenes has not been straightforward. The RAS oncogene family represents highly sought after targets in oncology because of their high prevalence of mutations in many solid tumours, but have been widely deemed undruggable because of an absence of binding pockets on their protein surface. Similarly, the transcription factor MYC is known to be a crucial driver of the pathophysiology of several aggressive non-Hodgkin lymphomas, including Burkitt lymphoma and diffuse large B-cell lymphoma; yet, targeting MYC has thus far proven to be elusive.[89] However, there are emerging activities, such as efforts to find binding pockets in mutated forms of *TP53* and *KRAS* that would be suitable for specific covalent inhibitors to bind to the mutant proteins.

Target selectivity versus promiscuity

Among protein kinase inhibitors, the drug developmental strategy is seemingly split between highly selective agents with antitumour activity against oncogene-addicted tumours versus multikinase inhibitors with regulatory approvals across a broad spectrum of malignancies. Selective inhibitors have the advantage of reduced off-target effects that might lead to undesirable toxicities. Conversely, in malignancies with broader dependencies (eg, angiogenesis), the blockade of such complex networks might require concurrent inhibition of several targets through multikinase inhibitors or combination therapy. Beyond the kinase of interest, such as with VEGFR2 in angiogenesis, additional molecular targets that are inhibited at approved drug doses might also be relevant for biological activity.[90] For example, ibrutinib is now approved for patients who have had postallogeneic transplantation for the treatment of chronic graft-versus-host disease. The drug's efficacy in this population is thought to be based on an off-target effect of ibrutinib on ITK leading to inhibition of T-helper-2 lymphocytes and an increased number of regulatory T cells.[91] Off-target effects in preclinical studies have been shown to promote cancer cell killing in some cases, highlighting the importance to thoroughly characterise the mechanisms of action of cancer drugs before clinical testing.[92]

Development of next generation drugs

Although the perspectives of target selectivity versus promiscuity is under debate, there is an urgency to articulate a guidance for the clinical development of next-generation inhibitors as opposed to so-called me-too inhibitors. Me-too compounds have pharmacological properties and intended indications similar to established drugs, but with minimal incremental therapeutic advantages. By contrast, next-generation compounds aim to optimise existing agents to deliver improved clinical outcomes. The production of successive iterations of EGFR inhibitors for the treatment of non-small-cell lung cancer offers many informative lessons. First-generation compounds, such as gefitinib and erlotinib, are 4-anilinoquinazoline derivatives that compete with ATP to bind to EGFR, preventing receptor activation and subsequent signal transduction. Second-generation inhibitors, including afatinib, dacomitinib, and neratinib, have a higher potency for inhibiting EGFR and other HER family members compared with first-generation inhibitors, and irreversibly bind and target the receptors for degradation. However, these compounds also inhibit wild type EGFR more effectively than first-generation inhibitors, resulting in higher incidence of skin and gastrointestinal toxicity. Third-generation inhibitors (eg, pyrimidine-based osimertinib) have improved CNS penetration and have a broader coverage for mutated versions of EGFR, with selectivity for both EGFR sensitising and *EGFR Thr790Met* resistance mutations. Fourth-generation inhibitors targeting tertiary resistance mutations (ie, mutations that are resistant to third-generation EGFR inhbitors including osimertinib) such as *EGFR Cys797Ser* are being investigated, with allosteric inhibitors and protein degraders in development.[93] Next-generation selective kinase inhibitors that target molecular alterations in genes other than EGFR have already entered the clinic and include gene rearrangements (eg, *TRK*[73] and *RET*[94–97]) and copy number variations (*MET*[94]) with higher potency and greater specificity than first-generation compounds, or point mutations that were previously undruggable (*KRAS Gly12Cys*[95,96]). In haematological malignancies, inhibitors of PI3K-δ, or PI3K-δ and PI3K-γ, such as idelalisib[97] and duvelisib,[98] have proven to be efficacious compounds for patients with relapsed or refractory chronic lymphocytic leukaemia and follicular lymphoma; however, both drugs can lead to immune-mediated adverse events that have made them more difficult to integrate into early lines of therapy. A new PI3K-δ inhibitor called umbralisib is now in late-stage development, and although its early efficacy is similar to compounds that have already been approved, this drug has a different safety profile, which could lead to more widespread adoption once approved.[99] Taken together, the desirable characteristics of next-generation compounds that justify further development include: a superior therapeutic index leading to a better safety profile, an improved pharmacological profile, access to brain metastases or other sanctuary sites (eg, spinal cord and testis), reversal of primary or acquired resistance, mutant selectivity, and activity against coexisting mutations that might yield additional therapeutic benefit.

Combination therapy

The objective of delivering anticancer drugs in combination is to increase and prolong the therapeutic benefits of a single therapy through improved mechanisms of action and by reversal of primary and acquired resistance. Despite numerous efforts invested in the combinatorial development of small molecule targeted inhibitors, there have been relatively few successful examples approved

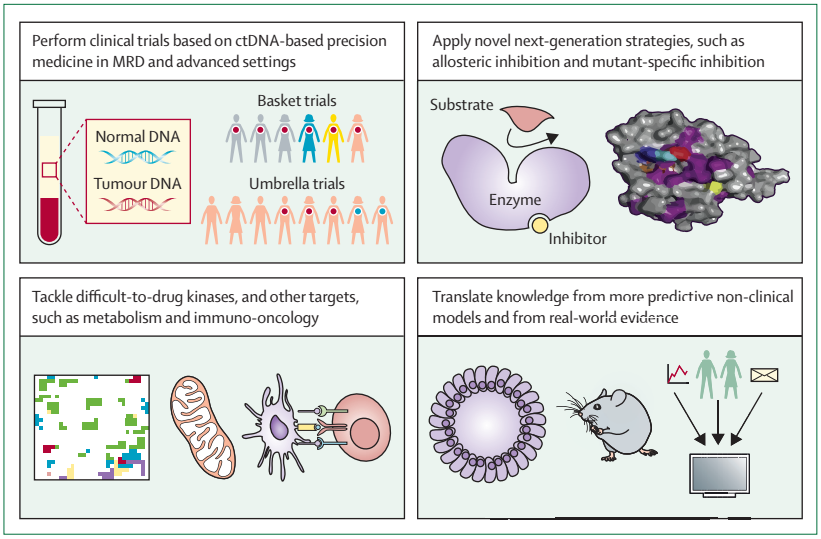

Figure 2: **Future directions for small molecule targeted inhibitors**
ctDNA=circulating tumour DNA. MRD=minimal residual disease.

for clinical use. One such example includes targeted drug combinations involving the vertical blockade of BRAF and MEK in the mitogen-activated protein kinase (MAPK) pathway (eg, dabrafenib and trametinib, vemurafenib and cobimetinib, and encorafenib and binimetinib) for the treatment of advanced melanoma with the *BRAF Val600Glu* mutation. The therapeutic index of the BRAF and MEK inhibitor combination is superior to its individual components because the addition of a MEK inhibitor might reduce some of the toxicity induced by MAPK pathway activation because of BRAF inhibition.[67,68] Another successful small molecule combination is ibrutinib with venetoclax, which had been shown to have complementary mechanisms preclinically for the treatment of chronic lymphocytic leukaemia[100] and was shown in two phase 2 studies published in 2019 to be highly effective and well tolerated (registration studies now underway).[101,102] Also, use of next-generation compounds with favourable safety profiles might facilitate combinatorial strategies, such as a recent study that showed for first time the feasibility of a dual blockade of the B-cell receptor in relapsed and refractory chronic lymphocytic leukaemia or mantle cell lymphoma with umbralisib plus ibrutinib.[103] CDK4 and CDK6 inhibition and endocrine therapy for the treatment of oestrogen-receptor-positive breast cancer is also an example of well tolerated drug classes that can be successfully combined.[104] Additional combination therapies that are approved for the treatment of various malignancies are discussed in greater detail in the Therapeutics series paper dedicated to this topic (unpublished).

Many clinical trials evaluating targeted combinatorial blockade of the PI3K-AKT-mTOR and MAPK pathways to overcome the extensive crosstalk between these two key signalling cascades have failed.[105] Overlapping toxic effects including fatigue, skin, mucosal, and gastrointestinal adverse events have limited the horizontal inhibition of these two pathways using different drug doses and schedules. Other vertical combinations with multiple inhibitors of the same pathway, such as PI3K and mTOR inhibitors,[106,107] or EGFR and MEK inhibitors,[108,109] have been challenging to administer. Mitigation approaches that can deliver these agents preferentially to tumour cells, or alternative administration schedules that can effectively investigate these pathways without causing prohibitive toxicity, are needed for continued attempts to develop PI3K-MAPK inhibitor combinations. Another challenge in this area is the identification of biomarker strategies to enable patient selection on the basis of sensitivity and resistance to the combinations of molecularly targeted agents, which might coincide with, or differ from, those biomarkers specific to the individual drugs. Lastly, the financial burden associated with combination therapy is not trivial, especially when the cost of a single targeted therapy might already be unaffordable. Use of more than one drug for the treatment of all patients with an approved indication should be justified, as this practice might substantially raise the cost of the regimen.

Future directions

Over the next decade, small molecule targeted inhibitors will undoubtedly continue to play an important role in oncology, and tangible solutions to some of the current unresolved issues are being addressed (figure 2). With advances in molecular biology, and medicinal and computational chemistry, steps are already being made to develop compounds for difficult-to-drug targets (ie, oncogenes and tumour suppressor genes), with mutant-selective inhibitors leading the way as prime examples that have already progressed to phase 1 clinical trial testing. For instance, there are at least three *KRAS Gly12Cys* specific inhibitors (AMG510 [NCT03600883], MRTX849 [NCT03785249], and JNJ-74699157 [NCT04006301]) under development, with early promising signs of antitumour activity.[95] Allosteric inhibitors represent a class of small molecule inhibitors that structurally and functionally complement ATP-competitive kinase inhibitors by binding to an alternative site and inducing an inactive kinase conformation. Improvements in molecular modelling of dynamic interactions have been increasingly used to identify novel and selective allosteric binding pockets.[110] Asciminib is an allosteric inhibitor that has a high affinity for the BCR–ABL1 myristoyl pocket,[111] and phase 2 trials evaluating its combination with catalytic site ABL1 kinase inhibitors (NCT03906292), as well as comparative phase 3 trials against conventional standard of care (NCT03106779) for patients with chronic myeloid leukaemia, are ongoing. Allosteric inhibition of validated targets in solid tumours such as ALK, EGFR, and KIT, might offer similarly transformative benefits and could potentially be combined with ATP-competitive inhibitors. Several small molecule inhibitors target cellular metabolic vulnerabilities, including inhibitors of fatty acid synthase, nicotinamide

phosphoribosyltransferase, isocitrate dehydrogenase, glutaminase, and polyamine and arginine metabolism. Small molecule immuno-oncology inhibitors, such as antagonists to HPK1, adenosine receptors, toll-like receptors, and chemokine receptors, are actively being pursued by pharmaceutical and academic groups. In addition to these new classes of compounds, novel vulnerabilities might arise as therapeutic opportunities following the development of resistance to small molecule inhibitors, such as *MET* amplification targeting in non-small-cell lung cancers with *EGFR* mutations after EGFR inhibitor treatment, ERK inhibition after dual BRAF and MEK blockade in melanoma, and interrogation of AURKA or AURKB,[112,113] CDK7,[114] CDK2,[115] and TTK[116] post CDK4 and CDK6 inhibition in breast cancer. Increasing recognition of intratumoral heterogeneity, in which different spatial regions of a primary tumour or metastases in distinct anatomical sites have different resistance mutations,[117] might inform adaptive trial designs that include sequential targeting with small molecule inhibitors.[118]

Besides the emergence of new drugs and new targets, the development of small molecule targeted inhibitors is accelerated by rapid technological progress, such as the use of non-invasive liquid biopsies to enable tumour genomic profiling in a dynamic manner over time. Genotyping of circulating tumour DNA (ctDNA) is already being investigated in a clinical trial setting to try and direct patients towards specific targeted inhibitors (eg, the B-FAST study in non-small-cell lung cancer [NCT03178552]), and includes so-called umbrella trial designs that assign different treatments to patients with the same histology, but with different genomic drivers. Furthermore, the detection of ctDNA persistence after radiographical response to small molecule targeted treatment with inhibitors might provide an opportunity to test sequential or combination therapies, such as in immunotherapy, to improve the rate of long-term disease control for patients with advanced cancer. Moving forward, liquid biopsy should also be used in the setting of molecular residual disease where the detection of ctDNA after definitive therapy might pose opportunities for interception studies with small molecule inhibitors. This method could potentially increase the proportion of patients with molecular residual disease who can be cured with the use of ctDNA clearance as a surrogate endpoint for long-term disease control. From the non-clinical perspective, there is a need for predictive models that can efficiently and reliably test new compounds and combinations with genomically and functionally oriented assays to prioritise the most promising drugs for entry into clinical trials. Finally, innovative clinical trial designs that take advantage of laboratory findings and track evidence from real-world settings are essential to expedite the delivery of small molecules to patients.

Contributions

All authors reviewed the literature; wrote, edited, and proofread the manuscript; and approved the final text.

Declaration of interests

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