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Towards a more precise future for oncology

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Summary

Prospective molecular characterization of cancer has enabled physicians to define the genomic changes of each patient's tumor in real-time and select personalized therapies based on these detailed portraits. Despite the promise of such an approach, previously unrecognized biologic and therapeutic complexity is emerging. Here, we synthesize lessons learned and discuss the steps required to extend the benefits of genome-driven oncology, including proposing strategies for improved drug design, more nuanced patient selection, and optimized use of available therapies. Finally, we suggest ways that next-generation genome-driven clinical trials can evolve to accelerate our understanding of cancer biology and improve patient outcomes.

Keywords

precision oncology; drug development; clinical trial design; genome-driven oncology

Introduction

The scope of precision oncology is rapidly expanding to address previously undruggable targets and rare genomic drivers (Hyman et al., 2017b). While only a minority of patients currently benefit from genomic matching to targeted therapies, this population continues to grow as the field advances (Hyman et al., 2017b; Schram and Hyman, 2017; Zehir et al., 2017). Herein, we propose next steps for refining drug development, patient matching to

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molecularly-guided therapies, and clinical trial design to extend the benefits of precision oncology. We focus in particular on genomically-driven drug development, which complements research on immunotherapy and other novel treatment strategies.

Developing Better Drugs

The current generation of therapies that define precision oncology have helped to elucidate many of the key characteristics of an optimal molecularly-targeted drug. Among the most important factors are its therapeutic index, target selectivity, and resistance liabilities.

Therapeutic Index

The presence of a therapeutic window to allow for optimal dosing is crucial for the success of a targeted therapy. The therapeutic index is a function of drug selectivity, characteristics of the target, and off-target toxicities. For example, the therapeutic index of EGFR inhibitors varies based on differences in selectivity between the activating mutation being targeted and wildtype EGFR. Many patients that respond well to first- and second-generation EGFR inhibitors such as erlotinib, gefitinib, and afatinib, have L858R mutations and exon 19 deletions that increase receptor dimerization and diminish ATP binding, enhancing the affinity of inhibitors compared to wildtype EGFR. By comparison, these agents have a negative therapeutic index in EGFR exon 20 insertions because inhibition against exon 20 mutants is less potent than against wildtype EGFR, limiting the tolerability of this class of agents (Beau-Faller et al., 2014; Naidoo et al., 2015; Robichaux et al., 2018; Vyse and Huang, 2019; Yun et al., 2007). Alternative irreversible inhibitors such as TAK-788 and poziotinib have been developed that have similar potency against wildtype and exon 20 mutant EGFR which may provide sufficient therapeutic index to permit anti-tumor activity (Chouitar et al., 2018; Han et al., 2017; Vyse and Huang, 2019). While this approach has for the first time unlocked clinical activity in previously refractory EGFR exon 20 mutant non-small cell lung cancers (NSCLCs), relatively narrow therapeutic indices manifest clinically as EGFR-mediated toxicities (Han et al., 2017). The challenge of developing drugs for patients with EGFR exon 20 mutations reveals that for certain mutations, substantial toxicity may derive from inhibition of the wildtype target in normal host tissues (so called on-target, off-tumor effects).

Beyond the importance of therapeutic index for individual molecularly targeted drugs, toxicity has also been the primary barrier to successfully implementing targeted therapy combinations. For example, despite very promising preclinical data suggesting concurrent MAPK and PI3K pathway inhibition prevents feedback reactivation and bypass resistance, clinical attempts to co-target these pathways have proven largely intolerable (Lopez and Banerji, 2017; Shimizu et al., 2012). Careful attention to both the individual therapeutic indices of drugs and the extent of overlapping toxicities is critical when choosing therapeutic combinations.

Target Selectivity

The development of purpose-built inhibitors that selectively and potently inhibit the target of interest has also unlocked therapeutic potential for a broader proportion of cancer patients.

Target selectivity decreases off-target toxicity and allows for more potent drug activity, thereby improving efficacy (Figure 1). Activating RET alterations including fusions are found in ~2% of lung adenocarcinoma and up to 20% of papillary thyroid cancers, while activating germline and somatic mutations are identified in the majority of medullary thyroid carcinomas (Drilon et al., 2018a; Dvorakova et al., 2008; Elisei et al., 2008; Kato et al., 2017; Moura et al., 2009; Mulligan, 2014; Stransky et al., 2014; Subbiah et al., 2018a; Subbiah et al., 2018b). Historically, multikinase inhibitors (MKI) that include some degree of RET inhibition such as lenvatinib, vandetanib, cabozatinib, and ponatinib have exhibited limited to modest clinical activity in RET altered tumors, depending on the patient population. All of these drugs exhibit more potent off-target inhibition, typically *VEGFR* (KDR), that defines their dose limiting toxicity and thus precludes maximal RET blockade (Azad et al., 2009; Drilon et al., 2018a; Drilon et al., 2016; Elisei et al., 2013; Gautschi et al., 2017; Hayman et al., 2012; Mologni et al., 2013; Subbiah et al., 2018b; Wirth et al., 2018). Conversely, selective RET inhibitors, including selpercatinib (LOXO-292) and pralsetinib (BLU-667), have been developed that permit potent and tonic target inhibition (Brandhuber BB; Subbiah et al., 2018a) and have demonstrated substantial efficacy and favorable safety profiles in comparison to MKIs (Ackermann et al., 2019; Drilon et al., 2019; Drilon et al., 2016; Drilon et al., 2018c; Gainor et al., 2019; Gautschi et al., 2017; Guo et al., 2019; Subbiah et al., 2018a; Subbiah et al., 2018b; Taylor et al., 2019; Wirth et al., 2019). Ultimately, improved understanding of the genomic drivers of individual cancers coupled with advances in structural biology have enabled the development of rational, fit-for-purpose drugs that specifically target the biomarker of interest. The creation of such selective inhibitors is critical to optimize tolerability and maximize therapeutic efficacy.

Resistance Liabilities

Potential mechanisms of primary and acquired resistance should be accounted for when designing drugs. Considerations include both resistance resulting from anatomic sanctuary sites with poor drug penetrance as well as resistance secondary to molecular alterations. For cancers where metastasis to the brain are common including NSCLC, breast cancer, and melanoma, ensuring that drugs targeting key genomic alterations in these cancers have adequate central nervous system (CNS) penetrance has become a key design parameter (Offin et al., 2019). While crizotinib, a first-generation ALK inhibitor, achieves a high initial rate of systemic disease control, poor brain penetration leads to as many as 60% of patients developing CNS progression while on therapy (Johung et al., 2016; Zhang et al., 2015; Zweig and Neal, 2018). Prospective evaluation of CNS penetrant next-generation ALK inhibitors have demonstrated markedly improved disease control within the brain, ultimately contributing to increased progression-free and overall survival (Camidge et al., 2018; Gadgeel et al., 2018; Peters et al., 2017; Shaw et al., 2016).

In addition to resistance liabilities dictated by anatomic drug penetrance, drug development has increasingly taken into account predicted mechanisms of on-target acquired resistance. Successive generations of ALK inhibitors, for example, have been designed specifically to maintain binding potency despite the acquisition of both individual and even compound mutations in the ALK kinase domain (Figure 2) (Crinò et al., 2016; Dagogo-Jack and Shaw, 2016; Gainor et al., 2016; Kim et al., 2016; McCusker et al., 2019; Ou et al., 2016; Shaw et

al., 2016; Shaw et al., 2014; Zhang et al., 2016). On-target resistance has similarly proven a challenge in secondary resistance to multiple other genome-directed therapies, including those targeting EGFR (Balak et al., 2006; Kobayashi et al., 2005; Kosaka et al., 2006), ROS1 (Sehgal et al., 2018), NTRK (Schram et al., 2017a), and ABL, among others (Milojkovic and Apperley, 2009). Increasing access to highly sensitive tumor- and plasma-based sequencing platforms has created a feed-forward loop whereby the specific resistance liabilities of each successive generation of targeted therapy can be identified in real-time and drive design decisions of the next-generation inhibitor.

New Frontiers for Drug Development

Whereas small molecule inhibitors have generally inhibited both wild-type and mutant proteins, newer approaches have focused on specifically suppressing the activity of aberrant molecular targets using mutant and isoform-selective inhibitors. In parallel, breakthroughs in protein engineering have revealed new classes of agents capable of expanding the therapeutic index against validated drug targets, including antibody-drug conjugate (ADC) therapies that release cytotoxic payloads at the site of disease. Finally, entirely novel approaches initially pioneered in other areas of medicine, including protein-refolders that restore the function of pathogenic oncoproteins without inhibiting wildtype proteins, are now being explored in oncology.

Isoform and Mutant-Selective Inhibitors

Recognizing that more selective therapies tend to have improved efficacy and tolerability, several strategies have been employed to more specifically and directly inhibit oncogenic drivers, including the development of isoform and mutant-selective therapies (Figure 3A). For example, the PI3K pathway is among the most commonly mutated in cancer (Thorpe et al., 2015; Zehir et al., 2017), but early efforts to target it with pan-PI3K inhibitors showed limited efficacy (Rodon et al., 2013). Isoform-selective PI3K inhibitors, by contrast, have shown improved outcomes relative to pan-PI3K and dual PI3K/mTOR inhibitors (Baselga et al., 2017; Yang et al., 2019). Moreover, isoform-specific inhibitors can be used to minimize toxicity attributable to an “off-target” isoform. Pan-FGFR inhibitors used to target FGFR2/3-altered cancers cause high rates of hyperphosphatemia, mediated predominantly by FGFR1 inhibition (Gattineni et al., 2014; Loriot et al., 2019; Nogova et al., 2017; Schram et al., 2017b; Wöhrle et al., 2011; Wu et al., 2013). Isoform-specific FGFR2 and/or FGFR3 inhibitors that spare FGFR1 are being developed to optimize tolerability and efficacy in FGFR2/3-altered tumors.

In recent years, drug selectivity has advanced beyond isoform selectivity and toward individual mutant alleles. Such selectivity allows for inhibition of the mutant oncogenic protein while sparing wild-type protein. In some cases, mutant allele selectivity may be the only way to pharmacologically inhibit an otherwise undruggable target. KRAS is among the most commonly mutated oncogenes in cancer (Mai and Lito, 2018; Ostrem et al., 2013; Zehir et al., 2017), but despite its recognition as a key oncogenic driver, it has historically be considered undruggable in part due to a lack of targetable binding pockets (Cox et al., 2014; McCormick, 2015; Stephen et al., 2014). Recently, however, improvements in small

molecule design have facilitated the development of highly selective warheads that react with the mutant cysteine of KRAS G12C, forming an irreversible bond and locking the protein in its inactive GDP-bound state (Janes et al., 2018; Lito et al., 2016; Ostrem et al., 2013; Patricelli et al., 2016). In the absence of this mutant cysteine, these covalent inhibitors do not react with wildtype KRAS and thus spare host tissues. In keeping with the hypothesized wide therapeutic index of the drug based on mutant allele selectivity, early results from phase I trials of KRAS G12C inhibitors show minimal toxicity and early signs of efficacy in KRAS G12C-mutant NSCLC (Fakih et al., 2019; Jänne PA, 2019). Moreover, as mutant allele selective approaches such as KRAS G12C inhibitors have entered the clinic, the opportunity for combinatorial therapy has emerged and may finally permit the field to deliver on the promise of co-targeting cancer dependencies.

Antibody Drug Conjugates

Another approach to increasing the therapeutic index has been using antibody drug conjugates (ADCs). By directly linking a cytotoxic payload to a targeted antibody, ADCs are designed to expand the therapeutic window of traditional cytotoxic agents (Figure 3B) (Coats et al., 2019). Unfortunately, in many cases ADC toxicity has been greater than predicted for a variety of reasons, including host tissue expression of the target, non-specific cleavage of the toxin, and other less well understood mechanisms (Coats et al., 2019).

Through iterative improvement, the initial promise of this class of agents is finally beginning to deliver clinically. For example, the ADC trastuzumab deruxtecan (DS8201) is comprised of the anti-HER2 antibody trastuzumab conjugated to the cytotoxic topoisomerase I inhibitor, deruxtecan. This agent has shown unprecedented activity in HER2-driven cancers including HER2-amplified breast and gastric cancer (Modi et al., 2019; Shitara et al., 2019), in addition to promising activity in HER2-low breast cancer (Doi et al., 2017), a population for which HER2-targeted therapy has been largely ineffective (Modi et al., 2019; Shitara et al., 2019; Tamura et al., 2019). Identifying tumor-specific targets optimal for ADC development and optimizing the safety of these engineered drugs will be key to their further development and utilization.

Allosteric Inhibitors

Traditionally, the majority of small molecule inhibitors have targeted the ATP binding site. More recently, structure-based drug design, computational chemistry with dynamic simulation, and advances in high-throughput drug screening approaches have collectively enabled the development of non-ATP competitive inhibitors that engage novel allosteric sites. These allosteric inhibitors may overcome on-target resistance mediated by mutations in the active site of validated targets as well as facilitating inhibition of previously undruggable proteins. For example, the use of imatinib to target BCR-ABL fusion-positive CML was one of the first successes of precision medicine, often credited as launching the field (Longo, 2017). A series of successive generations of ATP-competitive ABL inhibitors followed, permitting salvage of an increasing variety of active site resistance mutations (O'Hare et al., 2007; O'Hare et al., 2009). However, these resistance mutations can become polyclonal and even develop *in cis*, limiting the effectiveness of kinase domain inhibitors (Deininger et al., 2016; Shah et al., 2002). For this reason, developing an orthogonal

approach for inhibiting ABL through an allosteric mechanism not impacted by the acquisition of active site mutations is appealing. One such inhibitor, asciminib (ABL001), has already entered the clinic and demonstrated proof-of-concept in CML patients heavily pretreated with ATP-competitive inhibitors and harboring recalcitrant resistance mechanisms (Hughes et al., 2019; Wylie et al., 2017). Another approach being actively explored is the combination of selective ATP-competitive and allosteric inhibitors with non-overlapping resistance liabilities, which may collectively delay or even entirely forestall the development of acquired resistance.

Allosteric inhibitors may also enable therapy directed at previously undruggable targets. For example, the phosphatase SHP2, in conjunction with SOS1, plays an important role in enabling nucleotide exchange, allowing RAS to cycle between its inactive GDP-bound and its activated GTP-bound states (Chan and Feng, 2007; Grossmann et al., 2010; Lu et al., 2019; Mai and Lito, 2018; Mainardi et al., 2018; Matozaki et al., 2009; Nichols et al., 2018; Ostman et al., 2006; Ruess et al., 2018). Phosphatases had not previously been considered attractive drug targets, but allosteric inhibitors are in development that alter SHP2's conformation and abrogate its activity, leading to inhibition of MAPK-driven tumors in preclinical models and prompting several ongoing clinical trials (Frankson et al., 2017; Mai and Lito, 2018).

Proteolysis Targeting Chimeras (PROTACS)

Another emerging approach to targeting key cancer dependencies relies on protein degraders, referred to by a variety of terms including Proteolysis Targeting Chimeras (PROTACS) and "molecular glues", among other names. This heterogeneous group of therapies generally involve the use of a bifunctional molecule that brings the intended target into the proximity of a ubiquitin ligase, ultimately leading to the target's degradation (Figure 3C). The application of this technology to cancer therapeutics is still in its infancy, but is potentially multifaceted. Like allosteric inhibitors of key oncogenes, this technique may degrade key cancer dependencies even in the setting of resistance mutations that otherwise render existing therapeutics inactive. Perhaps most exciting is the ability this technology possesses to engage proteins without catalytic sites, those that lack traditional deep binding pockets required of kinase inhibitors, or otherwise difficult to drug transcription factors. Many key drivers of cancer, including transcription factors, cannot be targeted by currently available therapeutics, either because they are not expressed on the cell surface and therefore are inaccessible to antibodies or because they lack a binding pocket to which a small molecule inhibitor can attach. PROTACs may overcome these challenges and exploit the endogenous protein degradation machinery of the cell by simultaneously binding a target and the E3 ubiquitin ligase, promoting protein degradation (Chamberlain and Hamann, 2019; Schapira et al., 2019). ARV-110 is the first such drug to enter phase I clinical trials and links the E3 ubiquitin ligase with the androgen receptor in patients with prostate cancer (NCT03888612). This novel approach to decrease cellular protein levels may make it possible to effectively target numerous previously undruggable targets.

Protein Refolders

Small molecules are being developed to restore the natural function of mutant proteins by molding protein conformation to re-enable lost activity (Figure 3D). This strategy has already proven successful in the treatment of cystic fibrosis, a non-oncologic hereditary disease characterized by excessive mucus production due to mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) protein. By re-enabling CFTR to reach the cell surface and function similarly to wildtype protein, protein refolders diminish the clinical sequelae of cystic fibrosis (Middleton et al., 2019). The application of protein refolders to cancer is currently being explored and represents a novel means of targeting mutant tumor suppressors. Loss-of-function mutations in the tumor suppressor TP53 are the most common mutations in cancer (Zehir et al., 2017). However, there are currently no therapies approved that specifically target TP53-altered cancers. Efforts are underway to develop small molecules that restore the activity of mutant TP53 through protein refolding (Blandino and Di Agostino, 2018; Bykov et al., 2002). In addition to expanding the number of possible drug targets, this approach provides the additional benefit of being mutant specific, thereby decreasing toxicity.

Improved Patient Selection

Along with optimizing the drugs brought to clinic, genome-driven oncology is evolving to improve patient selection for clinical trials. This refined patient matching is enabled by our growing understanding of the interaction between specific molecular alterations and the histologic and broader genomic context of the tumor as well as our improved ability to recognize oncogenic drivers among a much larger number of variants of unknown significance in individual tumors.

Histology Matters (Sometimes)

There is increasing recognition of the value of histology agnostic molecularly-matched therapies. This is exemplified by TRK inhibitors, which exhibit potent antitumor activity in TRK-fusion positive cancers regardless of tumor histology (Cocco et al., 2018; Doebele et al., 2020; Drilon et al., 2018b; Liu et al., 2018). The success of these drugs led to TRK selective therapies being the first molecularly targeted treatments approved by regulatory agencies for use across all solid tumors.

While TRK inhibition drives tumor-agnostic efficacy, the activity of most targeted therapies is conditioned by the tumor histology. For example, combination BRAF and MEK inhibition has become standard first-line therapy for BRAF V600E-mutant melanoma and non-small cell lung cancers, but is only minimally active in colorectal cancer (Corcoran et al., 2015; Dummer et al., 2018a; Dummer et al., 2018b; Planchard et al., 2016). Similarly, HER2-mutant tumors treated with the pan-HER kinase inhibitor neratinib demonstrate marked differences in sensitivity based on tumor lineage with higher response rates among patients with breast, cervical, and biliary cancers (Hyman et al., 2018). The importance of histology also holds true for certain targetable germline alterations. In a retrospective analysis of BRCA-mutant patients, tumor lineage was the most important predictor of benefit from PARP inhibition (Jonsson et al., 2019). Basket studies exploring the efficacy of targeted

therapy across histologies are useful in identifying the characteristics of patients most likely to benefit from a given therapy and serve as an initial step in developing genomically-targeted treatments in the appropriate histologic context.

Genomic Context Matters

While most targeted therapies are designed to inhibit a single driver mutation, co-alterations may impact the efficacy of these therapies (Huang et al., 2020). For example, in patients with HER2-mutant metastatic breast cancer, concurrent mutations in HER2 or HER3 have been associated with a decreased likelihood of response to neratinib (Smyth et al., 2019). Similarly, in patients with AKT1 E17K mutations treated with a pan-AKT inhibitor, those with concurrent alterations in the PI3K pathway had shorter progression free survival (PFS) than those without these co-mutations (Hyman et al., 2017a). In patients with EGFR-mutant NSCLC, *MET* and *ERBB2* amplification have been reported to cause primary resistance to third-generation EGFR inhibitors, including osimertinib (Ortiz-Cuaran et al., 2016). While co-mutations in alternative drivers are associated with decreased likelihood of response to targeted therapies, they do not eliminate the possibility of responses in some patients. Furthermore, it is not always possible to predict whether a co-mutation is a second driver or merely a passenger mutation. Therefore, further research is needed to determine optimal matching of patients to drugs informed by the co-mutational context.

Features of the targeted mutation itself, including whether it represents a truncal or branch alteration, may also affect the likelihood of response to therapy. For example, the relatively large proportion of sub-clonal PIK3CA mutations may add to the complexity of PIK3CA inhibition (Amirouchene-Angelozzi, et al., 2017; McGranahan, et al., 2015). While high variant allele frequency may provide supportive evidence for the driver status of an alteration (Spurr, et al., 2018), patients with low allele frequency alterations have also responded to targeted therapies (Shin, et al., 2017). Optimal thresholds for defining targetable amplifications are also still under investigation and may vary based on the gene and therapeutic agent (Lai, et al., 2019).

Zygosity has also emerged as another potential mediator of responsiveness to targeted therapies. In patients with AKT1 E17K mutations treated with AZD5363, mutant allele imbalance most often caused by loss of WT AKT1 resulted in a prolonged PFS compared to patients with heterozygous AKT1 E17K tumors (Hyman et al., 2017a). Similarly, in patients with BRAF V600-mutant melanoma, loss of the wild-type allele resulted in improved PFS compared to patients whose tumors were heterozygous at this allele. Interestingly, patients with genomic gains of mutant BRAF V600 did not demonstrate improved outcomes compared to those with heterozygous BRAF V600, implying that loss of the wild-type allele may be more important than the dose of mutant oncogene in sensitizing to targeted therapy (Bielski et al., 2018). By contrast, the zygosity of BRCA1/2 mutations did not mediate responsiveness to PARP inhibition in a retrospective analysis of BRCA-mutant patients, suggesting that the implications of zygosity for responsiveness may vary depending on the biomarker being targeted and the affected tumor lineage (Jonsson et al., 2019).

Triaging Variants of Unknown Significance

A critical component of precision oncology is identifying which patients harbor druggable targets. A major challenge has been characterizing which variants of unknown significance (VUSs) found by broad next-generation sequencing actually drive tumor growth. Computational analyses of population-scale genomic data have identified novel “hotspot” mutations that are altered more frequently in cancer than would be predicted in the absence of selection. This positive selection suggests that hotspot mutations may be oncogenic and functionally important (Chang et al., 2018; Koyama et al., 2019). As proof-of-principle, several patients with VUSs in targets for which investigational therapies existed were enrolled on relevant therapies and benefited clinically based solely on the knowledge that their mutation was a hotspot (Chang et al., 2018). While not every hotspot is functional (Buisson et al., 2019), such computational weight of evidence is an important tool for identifying still occult driver mutations. Numerous additional methods are aiding in further characterizing variants of unknown significance, including saturation mutagenesis in genes of interest (Findlay et al., 2014) and multiplexed functional assays (Gasperini et al., 2016).

Optimizing the use of current and future drugs

To maximize the benefit of genome-driven oncology, it is essential to optimize the use of existing therapies. Giving novel therapies at the most appropriate time within a patients’ treatment course may enhance outcomes. Rational sequencing of treatments and the development of synergistic and tolerable combinations are two mechanisms by which physicians can improve patient outcomes using existing tools.

Timing Therapies to Minimize Resistance

Novel therapies are typically tested in patients with disease that has received maximum benefit from existing standard treatments. However, the experience with EGFR and ALK inhibitors suggests that outcomes may be improved with earlier application of our best drugs, prior to the development of resistance. Over 50% of EGFR-mutant NSCLC patients treated with first- and second-generation EGFR tyrosine kinase inhibitors (TKIs) acquire EGFR T790M mutations (Oxnard et al., 2011; Yu et al., 2013). Osimertinib was developed to overcome the T790M mutation and was initially studied in patients who had progressed on prior TKIs (Mok et al., 2017). More recent evidence demonstrates that when patients receive osimertinib as first-line therapy, effectively preventing T790M-mediated resistance, overall survival is significantly increased compared to patients treated with first-generation EGFR-TKIs (Ramalingam et al., 2020). Drug development paradigms should therefore encourage the testing of later generation inhibitors upfront.

Adjuvant and Neoadjuvant Therapy

The majority of genome-driven therapy is administered to patients with recurrent or metastatic cancer where the goal is to prolong life without the expectation of cure. Conversely, the greatest opportunity for targeted therapy may instead be in patients with earlier stage disease where effective therapies have the potential to increase cure rates. In patients with HER2-positive breast cancer, the addition of the HER2 monoclonal antibody trastuzumab to chemotherapy resulted in a substantial increase in 10-year survival (Perez et

al., 2014). Adjuvant targeted therapy is also standard of care for patients with stage 3 BRAF V600E-mutant melanoma and KIT-expressing gastrointestinal stromal tumors greater than 3 centimeters in size based on phase 3 trials that demonstrated disease-free survival benefits (Dematteo et al., 2009; Long et al., 2017). For targeted therapies with a high response rate, neoadjuvant therapy can be utilized to convert unresectable tumors to surgically resectable disease, thereby providing an opportunity for cure. For example, although larotrectinib was developed for advanced TRK fusion-positive cancers unresponsive to standard treatments, neoadjuvant larotrectinib has been successfully used in pediatric sarcoma patients to shrink tumors and allow for complete resections (Drilon et al., 2018b; DuBois et al., 2018). While further research is needed to define when such a neoadjuvant approach is appropriate, it is clear that earlier use of effective drugs may dramatically improve prognosis in a subset of patients.

Rational Combinations

Combination therapy can be utilized to increase efficacy, decrease toxicity, and/or prevent the emergence of resistance. In BRAF V600-mutant melanoma, the combination of BRAF and MEK inhibition results in prolonged survival and decreased cutaneous toxicity (squamous-cell carcinomas and keratoacanthomas) compared to BRAF inhibition alone (Kopetz et al., 2019; Long et al., 2014; Robert et al., 2015). This improved toxicity profile is made possible by the unique properties of BRAF inhibitors which target the BRAF V600 monomer in cancer cells, but paradoxically transactivate the wildtype kinase in host tissues, creating a therapeutic index (Su et al., 2012). In colon cancers harboring BRAF V600 mutations, however, RAF inhibition causes rapid feedback activation through EGFR and triple therapy with BRAF, MEK, and EGFR inhibition is required to achieve a meaningful clinical benefit (Kopetz et al., 2019). Thus, the most effective combinations may depend not only on the genomic biomarker of interest but also on the tumor type being treated.

In addition to preventing primary resistance, rational combinations can effectively treat secondary resistance. Off-target resistance has been increasingly reported as post-progression biopsies become commonplace. When the acquired alteration is itself targetable, sequencing data provides the opportunity for rational therapeutic combinations that simultaneously target the primary and acquired drivers (Cocco et al., 2019; Sequist et al., 2019). In the TATTON trial, patients with EGFR-mutant NSCLC with acquired MET amplifications were treated with osimertinib in combination with the MET inhibitor savolitinib. Savolitinib was able to restore sensitivity to osimertinib and was associated with radiographic responses (Sequist et al., 2019). Importantly, the clinical and therapeutic relevance of MET copy number gains and amplification likely depends on the technique used to measure this and standard definitions must be adopted and relevant thresholds defined in order to optimize this biomarker for clinical use (Lai, et al., 2019).

Next-generation Clinical Studies

Another frontier in advancing precision oncology involves novel clinical trial designs that assign therapies based on an individual patients' tumor genomics or adapt therapy based on prognostic biomarkers. Historically clinical trials enrolled patients with a specific cancer

type and stage of disease and offered patients either predetermined therapy or randomization to one of several study arms. As understanding of biomarkers for responsiveness and resistance to therapy has grown, so too have the list of strategies used to investigate treatment. We must continue to refine clinical trial designs to more precisely match individual patients to appropriate treatments.

Genomic Matching: Beyond the Basket Trial

Clinical trials utilizing genomic biomarkers were initially carried out in single tumor types. For example, an investigation of PARP inhibitors in heavily pre-treated prostate cancer patients demonstrated efficacy in individuals with alterations in the DNA damage repair genes *BRCA1/2* and *ATM* (Mateo, et al., 2015). Recently, basket trials that enroll patients with a biomarker regardless of tumor type have become more widespread (Tao et al., 2018). This design allows for the investigation of rare genomic alterations and inclusion of rare tumor types that could not be practically studied in a more traditional model. Umbrella and platform studies are also emerging whereby patients with a particular tumor type are enrolled to treatment arms based on their underlying genomic profile (West, 2017). Platform studies build in the potential for iteration and addition of novel therapies as these become available (Adaptive Platform Trials Coalition, 2019).

Master protocols such as NCI-MATCH allow patients across disease types to be treated with a number of genomically-matched therapies. NCI-MATCH demonstrated the feasibility of this approach on a large scale and highlighted the high number of patients interested in genomically-directed trials, however, accrual was initially lower than predicted. This was due to several factors including the frequency of actionability, the availability of approved drugs for identified alterations making patients ineligible, the turn-around-time for genomic sequencing, and need for sufficient tissue. Rapid molecular profiling, tumor sequencing earlier in a patient's disease course, and education regarding acceptable tissue samples will be critical for future large-scale precision oncology initiatives (Flaherty et al., 2020).

Innovative trial designs have allowed for more efficient testing of biomarker-driven hypotheses. Building on these principles, future clinical trial designs will continue to assign patients to treatments based on ever more specific and individualized factors, such as mechanisms of acquired resistance to prior therapy. In the ORCHARD trial (Osimertinib Resistance Cohorts Addressing 1L Relapse Drivers), patients with EGFR-mutant NSCLC who have progressed on first-generation TKIs undergo pretreatment biopsies and are stratified to osimertinib in combination with another agent based on the mechanism of acquired resistance (or lack thereof) (NCT 03944772). This trial design allows for streamlined testing of multiple rational combination therapies.

Adaptation of therapy based on dynamic tumor monitoring

Collection of cell-free DNA (cfDNA) shed from tumors is emerging as a means to dynamically monitor response to therapy or tumor recurrence after definitive treatment and can be used for risk stratification and potentially adapting therapy in creative clinical trial designs. In a trial of AKT-mutant tumors treated with an AKT inhibitor, a cfDNA decline of 50% at day 21 was associated with improved PFS (Hyman et al., 2017a). Similarly, a

retrospective analysis of patients with breast cancer treated with combined therapy consisting of the CDK4/6 inhibitor palbociclib with the selective estrogen receptor degrader fulvestrant demonstrated that patients with a cfDNA decline on treatment had prolonged (O'Leary et al., 2018). In women with early stage breast cancer, the detection of cfDNA after initial treatment is also associated with increased risk of recurrence (Garcia-Murillas et al., 2019). Thus, cfDNA may have utility as a predictive and prognostic marker to study treatment de-escalation in low-risk patients and/or intensification in high-risk patients on treatment or after definitive surgery. In an ongoing study of patients with solid tumors demonstrating microsatellite instability, patients with detectable cfDNA after definitive treatment are randomized to either placebo or treatment intensification with adjuvant pembrolizumab to determine whether treating microscopic disease with immunotherapy prolongs survival (NCT 03832569). The success of such trials utilizing cfDNA may change the way we monitor cancer and redefine disease persistence and recurrence.

Capitalizing on Real World Data

As precision oncology turns its attention to the many rare genomic alterations that drive cancer, obtaining reliable information on individual genomic phenotypes will increasingly depend on collecting real world data (RWD) from patients treated on and off trials (AACR Project GENIE Consortium, 2017; Armenia et al., 2018; Chang et al., 2018; Dickson et al., 2020; Hyman et al., 2017b). Several initiatives have been launched with the aim of capturing RWD. The American Association for Cancer Research (AACR) has created Project GENIE (Genomics Evidence Neoplasia Information Exchange), which serves as a clinical and genomic data repository, collating information from across multiple centers nationally (AACR Project GENIE Consortium, 2017). GENIE has already been used to characterize the natural history of AKT1 E17K-mutant, estrogen receptor positive breast cancer. American Society of Clinical Oncology (ASCO) has launched CancerLinQ (Cancer Learning Intelligence Network for Quality), which uses the electronic health records of participating institutions to explore issues such as optimal drug sequencing and the impact of comorbid conditions on treatment toxicity (Rubinstein and Warner, 2018). Similarly, various industry partners are creating platforms for assembling data from the electronic medical records of patients treated in both academic and community forums, allowing for large-scale retrospective investigations of outcomes data (Khozin et al., 2019; Moser et al., 2020; Parikh et al., 2019).

Regulatory agencies have recognized the importance of collecting information on patients treated outside of clinical trials. As clinical trials have increasingly focused on rare genomic alterations and diseases, regulatory agencies have acknowledged that large randomized controlled trials may not be feasible in all circumstances and single-arm studies that demonstrate unequivocal efficacy may be sufficient for drug approval. In this circumstance, evaluating RWD post-approval is critical to confirm improvement in patient outcomes. The FDA's Real World Evidence program was created following a congressional mandate as part of the 21st Century Cures Act passed in 2016. The program has focused on using RWD not only for post-approval investigations, but also to accelerate the expansion of drug approvals for new indications (U.S. Food and Drug Administration, 2018). The approval of palbociclib, a CDK4/6 inhibitor, was recently expanded from women with HER2-negative

metastatic breast cancer to also include male breast cancer based in part on RWD (Wedam et al., 2019). As RWD increasingly supplements clinical trial data, standardization of data collection and usage will be critical.

Conclusion

Tumor molecular profiling has enabled the development of highly successful targeted therapies that have benefitted countless patients. Yet molecularly-directed studies have also underscored the complexity of predicting which patients will respond to therapy. Factors ranging from co-alterations in the tumor itself to lineage specificity alter patients' likelihood of responding to today's treatments. Moreover, many genomic drivers remain "undruggable" or are ineffectively targeted due to poor tolerability of current therapies. To realize the promise of genome-directed therapy, we must learn from prior successes and failures to optimize drug design, develop innovative new therapeutic approaches, and refine how patients are matched to treatment.

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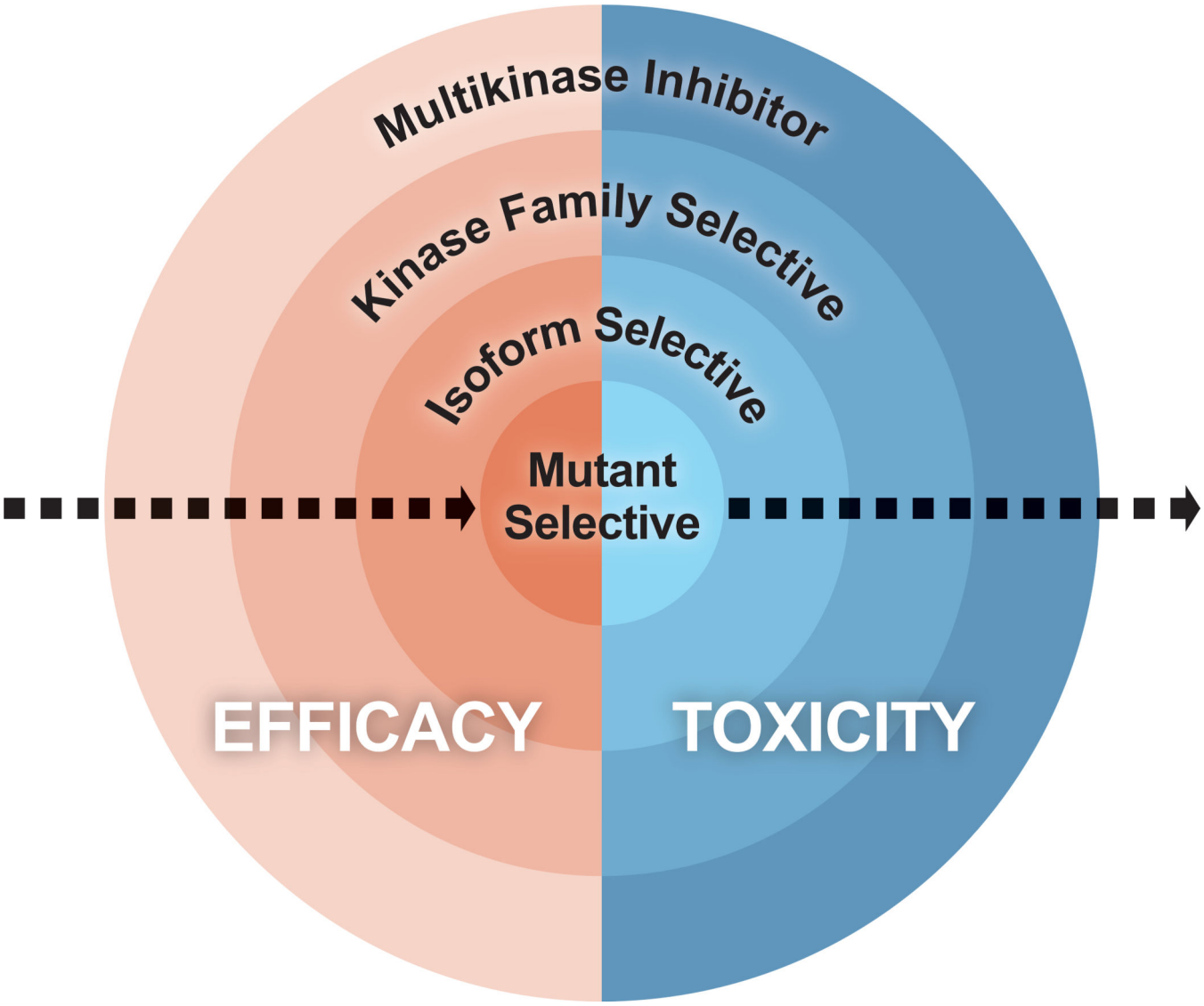

Figure 1. Relationship between efficacy and toxicity of different drug classes.

In general, efficacy increases and toxicity decreases as kinase inhibitors become more specific for the mutated protein being targeted.

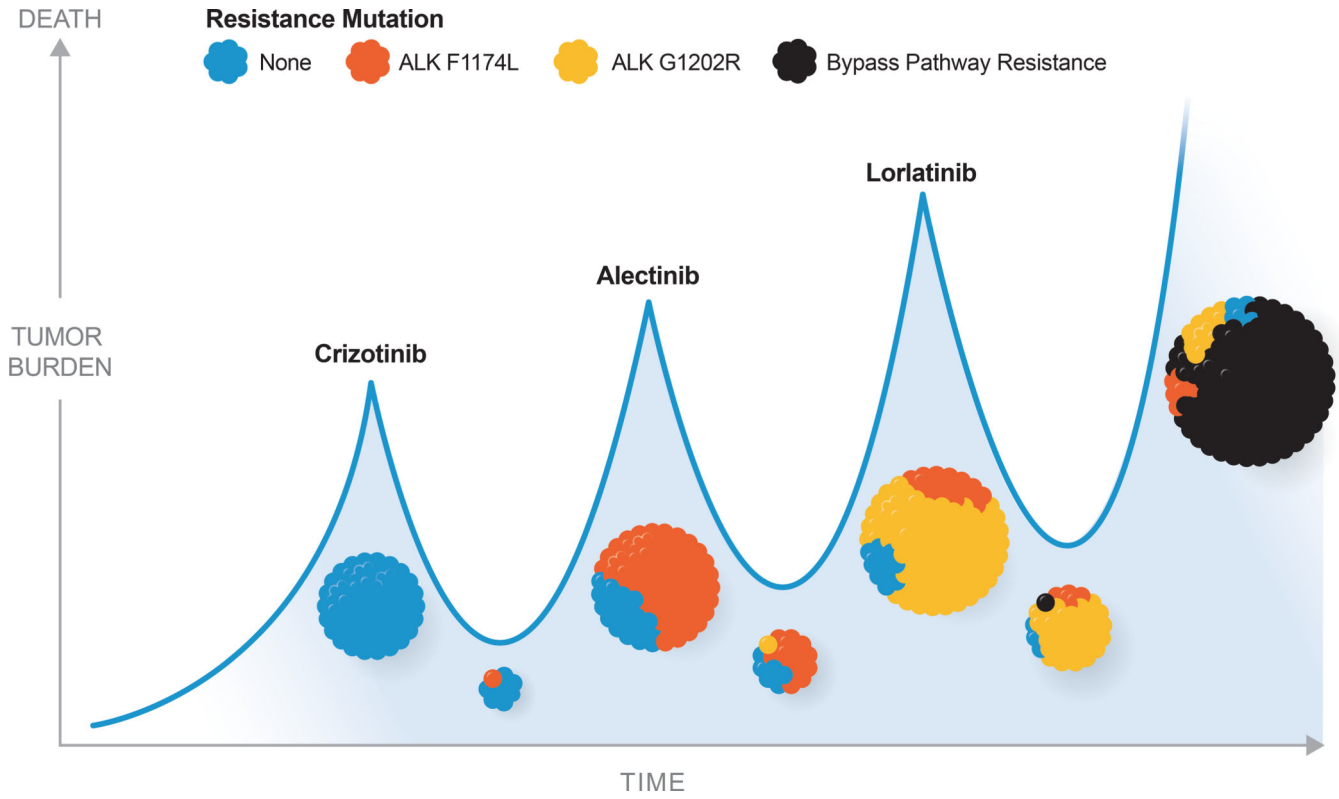

Figure 2. Schematic of ALK fusion-positive non-small cell lung cancer over time with exposure to sequential therapy.

Mutations in the ALK kinase domain that impair drug binding lead to acquired resistance in ALK fusion-positive NSCLC. Successive generations of ALK inhibitors have been designed to combat this on-target resistance and can be rationally sequenced in clinical practice to restore tumor control until a yet undruggable resistance mechanism emerges.

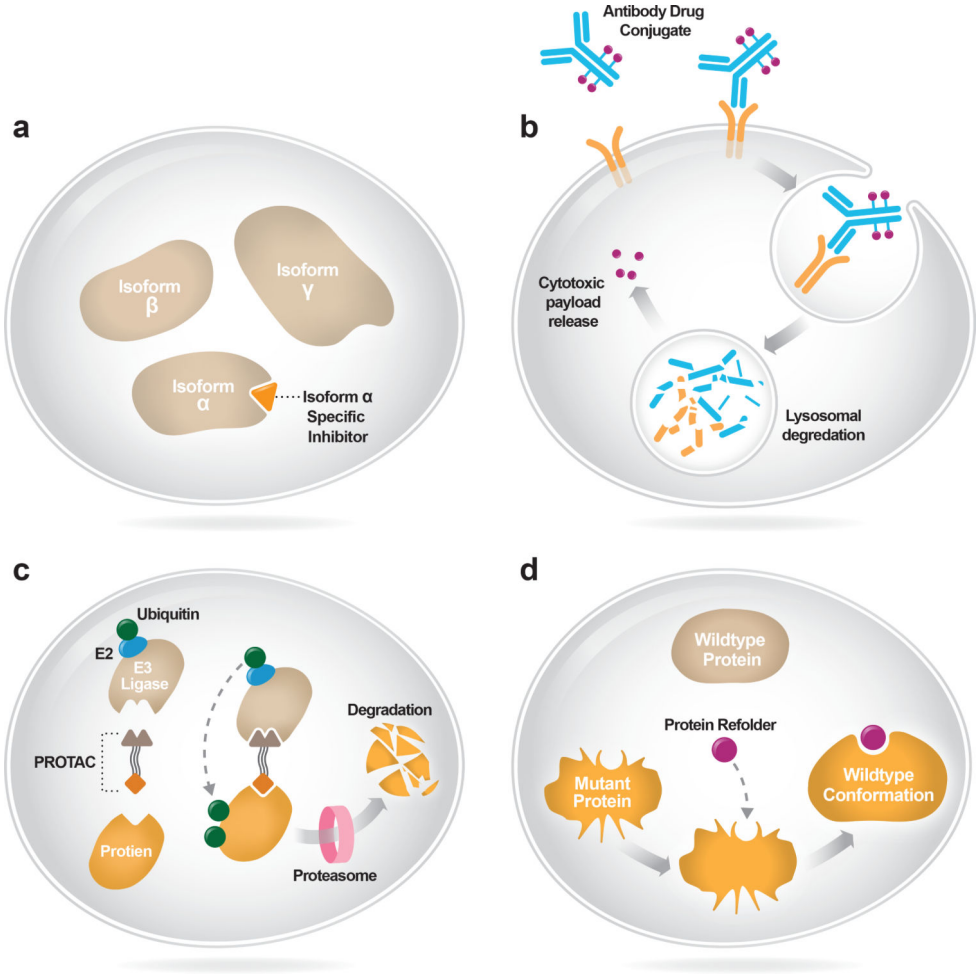

Figure 3A-D. New frontiers for drug development.

(A) Isoform-selective inhibitors bind to an individual protein isoform within the cell. (B) Antibody drug conjugates bind to cell surface antigens and are internalized into the cell where they release a cytotoxic payload to induce cell death. (C) Proteolysis Targeting Chimeras (PROTACs) bind both mutant proteins and E3 ubiquitin ligase, facilitating proteasomal degradation of the target. (D) Protein refolders enable mutant proteins to regain wildtype conformation and activity.