Targeted therapy in rare cancers—adopting the orphans

Javier Munoz and Razelle Kurzrock

Abstract | Designation of a rare 'orphan' disease is usually conferred by a prevalence of one in 1,500 to 2,500 individuals. Increasingly, orphan diseases are also being defined by their molecular fingerprints. Rare diseases are uniquely challenging from a therapeutic standpoint; it is critical to modify clinical study design of treatments for orphan disorders as well as for the increasingly smaller molecular subsets within frequently occurring cancers. In spite of the immense challenges associated with developing a treatment for a rare disorder, some of the most groundbreaking therapeutic discoveries have been made in orphan malignancies. This situation may be because a limited number of driver molecular aberrations occur in rare disorders, which can be targeted by agents. Here, we describe drug-class examples of targeted therapies for orphan diseases, with particular emphasis on malignancies or tumour-prone nonmalignant conditions, as well as potential therapeutic strategies that can be adopted to treat these orphan conditions.

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Introduction

Cancer is one of the most common causes of death worldwide.[1] Treatment of metastatic disease has yielded only modest results, and most patients succumb to their disease. To a large extent, these dismal outcomes are probably because cancer consists of hundreds of molecular disease subsets, each requiring its own personalized treatment approach. Therefore, the standard paradigm of classifying patients by histology alone, and treating large unselected groups of patients with the same treatment is unlikely to dramatically improve outcomes. A new approach is emerging and entails matching molecular classification with targeted therapy. However, the challenge that arises from the molecular subclassification of malignancies is that molecularly distinct cancer subtypes may each become orphan diseases.

The terms 'rare disorder' and 'orphan disease' are often used interchangeably in the medical literature. There is no single standardized numerical cutoff that encompasses these conditions. Some definitions rest primarily on the number of patients diagnosed with a given disease, whereas others include factors such as disease severity or availability of therapy. The US Rare Disease Act of 2002 relies solely on prevalence as "rare diseases and disorders are those which affect small patient populations, typically populations smaller than 200,000 individuals (about one in 1,500 people) in the United States."[2] In Japan, a rare disease is defined as one that affects fewer than 50,000 patients, or approximately one in 2,500 people.[3] The European Commission on Public Health defines rare diseases as "life-threatening or chronically debilitating diseases that are of such low prevalence that special combined efforts are needed to address them."[4] ESMO defines rare tumours as those with an incidence of fewer than six per 100,000 persons per year.[5] The United States Orphan Drug Act defines as orphan diseases as conditions "for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will [be] recovered from sales in the United States of such drug."[6] The necessity of international networking to develop therapeutic models for orphan diseases has been emphasized.[7]

Prevalence is defined as the number of patients living with a disease at a given moment, whereas incidence is the number of new diagnoses of a particular condition in a given year. Prevalence, rather than incidence, has been used to describe the impact of orphan diseases primarily because regulatory definitions of orphan entities are based on prevalence. Nevertheless, there are limitations to such definitions; for example, prevalence is influenced by survival, which may lead to inappropriate conclusions in patients with an aggressive rare cancer who have a decreased lifespan. Based on epidemiological information, alternative definitions of rare cancers have been sought centring on incidence instead of prevalence and rare diseases have been defined in some studies as conditions with an incidence of fewer than six per 100,000 individuals per year in Europe or an incidence of fewer than 15 per 100,000 individuals per year in the USA.[8,9] A non-comprehensive list of tumour-related rare diseases is shown in Table 1, which lists the prevalence of some cancer-related orphan diseases and the molecular pathways thought to be involved in the genesis of these conditions.[10]

Competing interests
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Department of Investigational Cancer Therapeutics (Phase I Program), University of Texas, MD Anderson Cancer Center, Unit 455, 1515 Holcombe Boulevard, Houston, TX 77030-4009, USA (**J. Munoz**, **R. Kurzrock**).

Correspondence to: J. Munoz javier.munoz@me.com

Key points

- The terms 'rare disorder' and 'orphan disease' are often used interchangeably
- Dramatic success in treating some orphan cancers is owing to identifying a main driver of malignant transformation
- By contrast, slow progress has been seen in drug development for the most-common tumours
- Identification of molecular aberrations may turn common tumours into a collection of orphan diseases
- The therapeutic paradigm is changing from 'one size fits all' to personalized targeted treatment

Malignancies, adverse reactions to drugs, metabolic diseases or infections might be considered orphan diseases depending on the definition used.[11] The prevalence of orphan diseases may vary among diverse patient populations. Thus, an entity that is rare in one group of patients may be common in another, which is particularly true for genetic diseases. As an example, several paediatric malignancies are considered rare because in general fewer children develop cancer compared to adults. Some orphan diseases are hereditary; hence, the driving genetic aberrations of such disorders are present throughout the life of a particular patient, even if the associated symptoms are initially silent. General medical practitioners will not have the opportunity to diagnose or treat most orphan diseases during the length of their careers.

The definition of targeted therapy is elusive as well. A superficial definition implies that it is a therapy that is used to target a specific molecular aberration or genetic anomaly. The target or biomarker was discovered first in some cases, such as HER2 in breast cancer, whereas in others the drug was discovered before the target was defined, such as all-*trans* retinoic acid (ATRA) used for the treatment of acute promyelocytic leukaemia (APL).[12] In the latter situation, the treatment itself served as a 'clinical probe' leading to the discovery of the underlying aberration (rearrangement of the retinoic acid receptor in the case of APL). By contrast, we could use bevacizumab as an example, hailed as an agent that targets VEGF-A. To date, however, we have been unable to identify biomarkers that can be used to select a population primed for therapeutic response to anti-VEGF therapy.[13] Finally, a given 'targeted' therapeutic agent might impact multiple targets (for example, sorafenib, which is a multikinase inhibitor) instead of a single one. Hence, targeted therapy cannot always be defined as having single-target specificity.[12]

Recent discoveries have provided a plethora of breakthroughs. These range from a better understanding of the molecular underpinnings of disease, such as BRAF V600E mutations in melanoma, to newer therapeutic weapons against cancer, such as blockade of programmed death 1 (PD-1) immunotherapy or trastuzumab plus a derivative of maytansine (T-DM1) antibody-linker-chemotherapy conjugate.[14,15] The latter seems to be a three-part 'judge, jury and executioner' ensemble as this conjugate will selectively find HER2-positive malignant cells with its antibody moiety and target them for destruction by delivering its chemotherapy moiety intracellularly. In summary, targeted therapy abrogates tumour proliferation in a selected subset of patients by interfering with specific pathways driving carcinogenesis and concomitantly resulting in less damage to normal tissues.

Orphan malignancies demonstrate some of the highest response rates, primarily owing to the identification of a main driver of malignant transformation. In addition, it has been hypothesized that the limited number of underlying pathways leading to these orphan diseases makes them both rare and treatable.[16] By contrast, slow incremental progress has been demonstrated for treatment of the most common tumours, such as colon, lung and breast cancer, even though the investment in research for these diseases is many magnitudes greater than for orphan diseases.[16] This dichotomy may be owing to the possibility that multiple molecular pathways drive the development of many common cancers, making them both common and difficult to treat uniformly.[16]

Intratumour heterogeneity is another possible reason for the lower efficacy of targeted therapies for treating common solid tumours, over agents used to treat the rare haematological malignancies.[17–19] Several recent publications demonstrate coexisting diverse clones in individual tumours, including breast cancer where a continuum of genetic mutational evolution supports the need to repeat tissue biopsies at the time of disease progression, molecularly stratify heterogeneous tumours for targeted therapy trials according to new aberrations, and develop efficacious combination therapies.[19]

Despite several dramatic success stories in the treatment of orphan malignancies, the Orphan Drug Act was introduced in 1982 to attract pharmaceutical investment in drug development for rare diseases. Various incentives, such as 7 years of exclusive marketing, were offered to pharmaceutical companies as part of this act.[16] More recently, it has become increasingly evident that an optimal approach would be to stratify common tumours into molecular subsets, each of which constitutes an orphan disease. An example is *ALK*-rearranged non-small-cell lung cancer (NSCLC; seen only in 4% of the lung cancer population), which shows near-universal regression with ALK inhibitor treatment.[20] The application of such molecular pharmacogenetic approaches has tremendous potential for improving the efficacy of novel targeted agents, while diminishing cost and toxicity. However, using molecular signatures to determine treatment also requires a radical rethink of study designs if a personalized approach to cancer treatment is to be realized. Novel targeted agents have not always yielded the expected outcome in large cohorts, which might be due to multiple redundant molecular pathways and the onset of treatment resistance. Additional combinatorial trials of targeted drugs are underway to address this lack of efficacy.[21]

Targeted therapy

Some of the most remarkable oncological interventions, resulting in frequent complete or near-complete responses with prolongation of overall survival (Table 2), have occurred in orphan cancers. Examples include

Table 1 | Actionable molecular aberrations in selected orphan diseases

Orphan disease	Estimated prevalence (per 100,000 people)	Aberration or target	Targeted therapy used or under evaluation
Acute promyelocytic leukaemia[10,103]	1–9	*PML–RARα* rearrangement	All-*trans* retinoic acid
Anaplastic large-cell lymphoma[10,86,107,108]	0.1	*ALK* rearrangement, CD30 expression	Crizotinib, brentuximab vedotin
Castleman's disease[10,51–54,109]	<1	Interleukin-6 overexpression	Interleukin-6 antibody, interleukin-6 receptor antibody
Chronic myeloid leukaemia[10,27–29,103]	1–9	*BCR–ABL*	Imatinib, nilotinib, dasatinib
Cowden syndrome[10,103,110]	0.45–0.5	*PTEN* mutation	Rapamycin
Dermatofibrosarcoma protuberans[10,103,111]	1–5	*COL1A1–PDGFB*	Imatinib
Ewing's sarcoma[10,61–65]	<1	*IGF1R*	IGF-1R inhibitors
Gastrointestinal stromal tumour[10,113]	13.4–15.6	*KIT* mutation	Imatinib
Hairy-cell leukaemia[10,81]	10	*BRAF* mutation	BRAF inhibitors
Hodgkin lymphoma[10,86,114]	22	CD30	Brentuximab vedotin
Hypereosinophilic syndromes[10,115]	1.5	*FIP1L1–PDGFRA*	Imatinib
Medullary thyroid carcinoma[10,104,105,116]	7	*RET* mutation	Vandetanib, cabozantinib
Melanoma[10,74–78,112]	11.7–16.4	*BRAF* mutation	Vemurafenib
Myelofibrosis with myeloid metaplasia[10,117]	2.7	*JAK* mutation	Ruxolitinib
Proteus syndrome[10,101]	<1	*AKT1*	AKT inhibitor?
Renal-cell carcinoma (papillary)[10,118,119]	<1	*MET* mutation	MET inhibitors
Systemic mastocytosis[120]	0.2	*KIT* D816V mutation	Imatinib

2-chlorodeoxyadenosine in hairy-cell leukaemia,[22] imatinib in gastrointestinal stromal tumours (GIST),[23] lenalidomide in del(5q) myelodysplastic syndrome (MDS),[24] and ATRA in APL.[25] Indeed, considering their rarity, there is a disproportionately high number of drugs approved for orphan malignancies compared with drugs for the most-common tumours.[16]

Chronic myeloid leukaemia

Chronic myeloid leukaemia (CML) undergoes clinical and genetic evolution from chronic to accelerated phase, and then to blast crisis.[26] It is likely that most malignancies go through a similar evolution, but the transitions are less clearly delineated in the clinic. In recent years, CML has been transformed from a uniformly lethal disease from which patients succumbed in a median of about 6 years, to a leukaemia with a median survival exceeding 22 years.[27]

There were four key factors that revolutionized outcome for patients with CML: first, the molecular target (BCR–ABL kinase) was identified; second, a potent BCR–ABL inhibitor (imatinib) was discovered;[28] third, imatinib was administered to patients with newly diagnosed disease, in whom it was far more effective than in individuals with blast crisis or even late chronic-phase disease; and, finally, more-powerful second-generation and third-generation BCR-ABL inhibitors were developed to overcome resistant *BCR–ABL* mutations as they emerged.[29] Therefore, dramatically changing outcomes in CML required applying matched targeted therapy to prevent transformation, not after transformation. CML may be a model for effective personalized treatment of cancer.

Although imatinib in CML is the poster child of targeted therapy with previously unprecedented success, its inhibition of the activity of the BCR-ABL tyrosine kinase is not perfect; the kinase active site gatekeeper T315I mutation results in resistance to imatinib and it has been suggested that such kinase domain mutations may already be present in more-primitive CML bone marrow cells until they consequently evolve, multiply and expand into the peripheral circulation.[30] Subsequent efforts have focused on developing second-generation tyrosine kinase inhibitors, such as dasatinib and nilotinib, to access the ATP-binding site despite the adverse structural environment produced by imatinib resistance mutations.[31] The T315I gatekeeper mutation stabilizes the hydrophobic backbone of the tyrosine kinase; Azam *et al.*[32] hypothesized that the addition of agents to destabilize the hydrophobic backbone, such as AP24163 (ARIAD, Cambridge, MA), might support the use of upfront combinatorial strategies to avert ultimate resistance. In general, combining agents at a lower dose with distinct but synergistic mechanisms might putatively increase treatment efficacy while avoiding their full-dose toxicity. As such, imatinib for treating CML is an example of targeted therapy in a haematological malignancy that illustrates the development of resistance to single agents leading to the search for newer drugs and combinatorial efforts to overcome disease progression.

With a new nosological classification of malignancies using molecular profiling, many solid tumours will be defined as 'rare'. Therefore, it will be necessary to apply matched targeted treatments to these diseases. Furthermore, if remarkably improved outcomes similar to those seen in CML are to be realized in solid tumours,

Table 2 | Impact of targeted therapies on overall survival in selected disorders

Orphan disease	Old model	Old survival	New model	New survival
Acute promyelocytic leukaemia[121,124]	Chemotherapy	19 months	All-*trans* retinoic acid	>58 months
Chronic myeloid leukaemia[27]	Chemotherapy	6 years	Imatinib	>22 years
Melanoma[123]	Dacarbazine	<10 months	Vemurafenib	16 months
Medullary thyroid cancer[104,116]	Chemotherapy	36 months	Vandetanib	Not reached
Gastrointestinal stromal tumour[124]	Chemotherapy	12–18 months	Imatinib	Close to 5 years
Relapsed Hodgkin lymphoma[125,126]	Chemotherapy	1.2 years	Brentuximab vedotin	22.4 months

it might be critical to use these therapies early in the disease course, that is, to prevent transformation (metastases) rather than to treat after metastatic evolution has been established. The analogy between chronic-phase CML and rare cancers is likely to be weak for most rare cancers; however, it is particularly relevant for some benign tumours, such as pigmented villonodular synovitis or dermatofibrosarcoma protuberans that respond to imatinib therapy.[33,34] Although the appearance of the BCR–ABL fusion protein is the pivotal event underlying CML, the transformation from chronic-phase CML to blast crisis seems to be secondary to continued BCR–ABL activity, genetic instability and additional multiple mutations.[26,35,36] A parallel example of a stable chronic condition transforming into an acute process can be seen in severe congenital neutropenia. The evolution of this condition to acute myeloid leukaemia is apparently a multistep process, including the development of additional mutations in genes such as *ZC3H18*.[37] The metastatic heterogeneous genotype that escapes current targeted therapies in solid tumours likely differs from the genotype seen during localized disease at diagnosis.

The analogy of transformation in haematological malignancies and the development of metastasis in solid tumours could be supported by the transformation of local primary extramedullary plasmacytoma into systemic multiple myeloma, progression from intramedullary to extramedullary multiple myeloma, or the transformation of localized granulocytic sarcoma to systemic acute myeloid leukaemia.[38–40] Myeloma has been recently touted as a model for studying the multistep process of metastasis,[41] and most medical oncologists would consider that there is a thin line between haematological and solid tumours when it comes to some types of lymphomas.

Acute promyelocytic leukaemia

Despite the fact that APL is a well-known entity in medicine, it is an orphan disease. Once described during the past decade as the most-aggressive and rapidly lethal form of acute myeloid leukaemia, it became one of the most-curable leukaemia subtypes.[42] APL occurs when haematopoietic progenitor cells at the promyelocyte stage are arrested during maturation secondary to a reciprocal chromosomal translocation between chromosomes 15 and 17. This translocation produces a leukaemogenic fusion protein that juxtaposes the gene encoding the retinoic acid receptor α (*RARα*) and the promyelocytic leukaemia (*PML*) gene.[42,43] The identification of a promoter of differentiation (ATRA) as a direct modulator of the PML–RARα fusion protein (Figure 1a) has vastly improved the treatment of patients with APL.[43] Furthermore, the translocation was discovered as a result of the treatment itself serving as a clinical probe. Once it became known that patients with APL responded to treatment with ATRA, scientists searched the breakpoint region for related genes, and homed in on RARα.[43,44] Further investigation confirmed the direct perturbation of RARα in APL.[43,44] Because of the *PML–RARα* translocation, RARα does not respond properly to physiological concentrations of retinoid-related proteins, hence pharmacological treatment with ATRA is needed. Subsequently, it was reported that arsenic trioxide and ATRA degrade the PML–RARα fusion protein by synergistic induction of differentiation; ATRA targets the RARα moiety, whereas arsenic trioxide targets the PML moiety of the fusion protein.[44] Furthermore, ATRA apparently activates genes coding membrane porins that augment arsenic uptake by APL cells (Figure 1a).[44] Because patients exposed to single-agent arsenic trioxide or ATRA ultimately develop resistance or recurrence, combinatorial drug use with concomitant arsenic trioxide and ATRA has been attempted with positive results and represents an example of the success of combination targeted therapy in leukemia.[44]

Castleman's disease

Castleman's disease, also known as angiofollicular lymph-node hyperplasia and giant lymph-node hyperplasia, was initially described by Benjamin Castleman in 1956 after evaluating 13 cases of mediastinal lymphadenopathy.[45] Many variants have been described since then, initially as localized processes, and subsequently as systemic or multicentric conditions.[46] The discovery of a human herpes virus associated with Kaposi sarcoma (HHV-8) led to the identification of its association with primary effusion (body-cavity-based) lymphomas[47] and with some cases of multicentric Castleman's disease. The HHV-8 genome encodes a viral analogue of human interleukin (IL)-6,[48] which stimulates angiogenesis and haematopoiesis.

In 1989, the systemic presentation with constitutional symptoms seen in the plasma-cell variant of Castlemans's disease was associated with an unknown factor,[49] subsequently categorized as the B-stimulatory cytokine IL-6 secreted by the diseased lymph nodes.[50] Hence, it is not surprising that anti-IL-6 and anti-IL-6 receptor antibodies (Figure 1b) were eventually used in treating this disease, with remarkable resolution of the systemic symptoms.[51–55]

Castleman's disease has been divided into subtypes, including hyaline vascular, plasma cell, HHV-8-associated and multicentric.[46] The plasma-cell variant of Castleman's disease has been associated with POEMS syndrome, an acronym for polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes.[46] On the one hand, unicentric Castleman's disease is an indolent condition and is usually treated with locoregional therapies. On

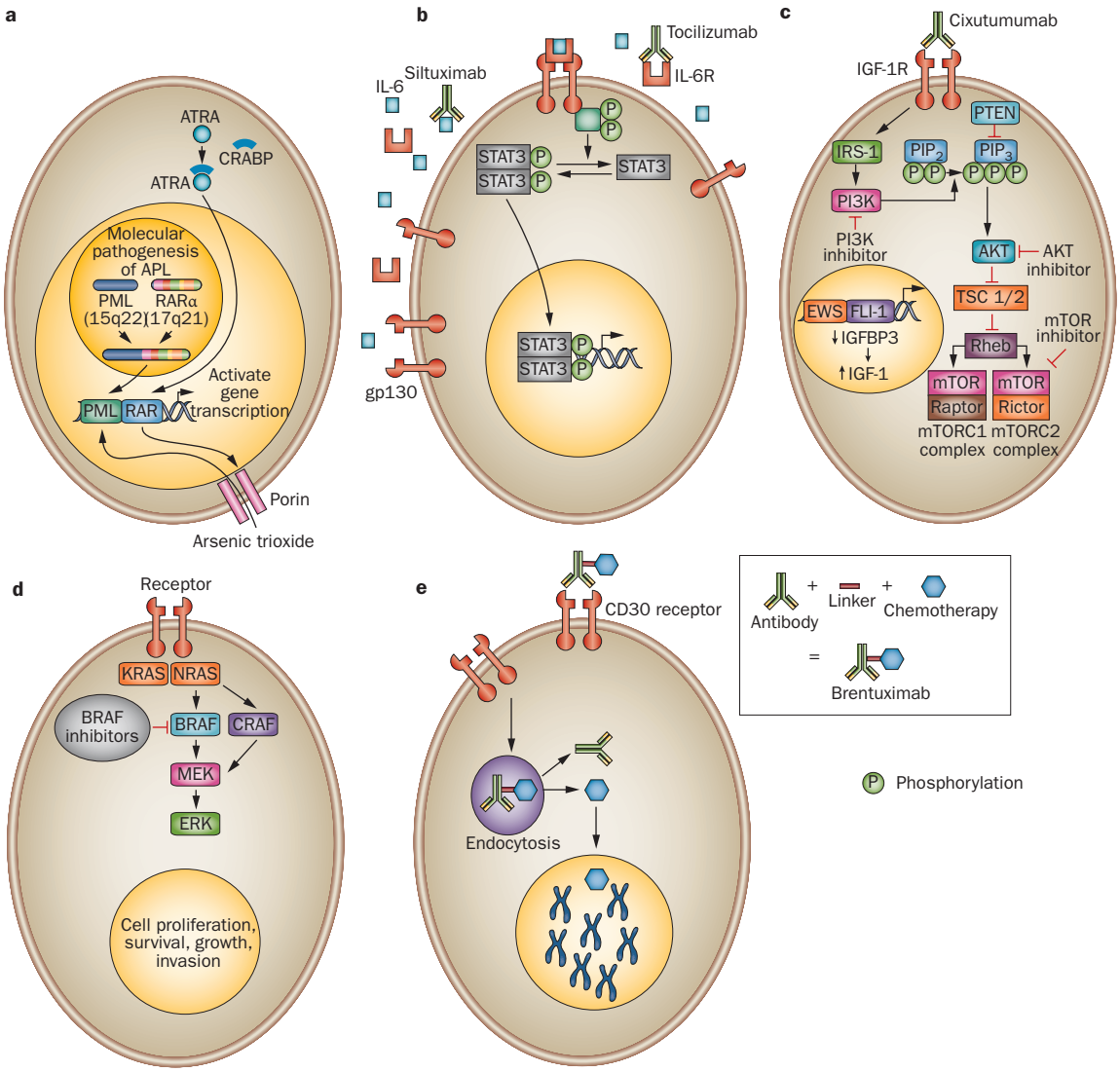

Figure 1 | Targeted therapy for orphan diseases. **a** | Mechanism of action of ATRA.[81] Inside acute promyelocytic leukaemia cells, ATRA binds to CRABP, and is transported to the nucleus, where it binds to target genes initiating transcription and promoting cell differentiation. **b** | IL-6 mechanism of action.[27] The binding of IL-6, with or without its soluble receptor (IL-6R), to gp130 activates homodimerization of gp130, which triggers STAT and JAK. Anti-IL-6 therapy results in high response rates in Castleman's disease, a disorder driven by IL-6. **c** | PI3K/AKT/mTOR signalling cascade.[39] PI3Ks are activated by various receptors. After AKT is recruited to the plasma membrane by PIP_2 and PIP_3, there is phosphorylation and activation of AKT by the mTORC2 complex, which subsequently leads to activation of multiple molecular targets by AKT, including the TSC1–TSC2 complex. These signals can be suppressed at multiple points in the pathways. **d** | The NRAS/BRAF/MEK/ERK signalling cascade regulates cellular functions such as growth, differentiation and survival.[48] In melanoma, BRAF mutations bypass activation by NRAS, subsequently causing MEK/ERK activation, favouring growth and survival instead of differentiation. Mutant NRAS, through CRAF, seems to activate MEK/ERK independently of BRAF. **e** | Brentuximab vedotin is an antibody–drug conjugate composed of an anti-CD30 antibody conjugated to a potent inhibitor of microtubule polymerization named monomethyl auristatin E.[82] After binding to CD30-positive cells, the antibody–drug conjugate is internalized, and subsequently the microtubule inhibitor drug is released, causing apoptosis. Abbreviations: ATRA, all-*trans* retinoic acid; CRABP, cellular retinoic acid binding proteins; gp, glycoprotein; IL, interleukin; PIP_2, phosphatidylinositol 3,4 bisphosphate; PIP_3, phosphatidylinositol 3,4,5 trisphosphate; STAT, signal transducers and activators of transcription.

the other hand, a diagnosis of multicentric Castleman's disease often mandates systemic therapy.[46]

The IL-6 pathway cascade is initiated when IL-6 binds to its receptor, which, in turn, causes homodimerization of gp130 and subsequent activation of the janus kinase (JAK) pathway and downstream phosphorylation of signal transducer and activator of transcription (STAT) proteins that translocate to the nucleus, producing gene transcription and cell proliferation (Figure 1b).[55] In Japan, the anti-IL-6 receptor antibody tocilizumab has demonstrated efficacy in patients with Castleman's disease and is approved for the treatment of the condition.[51] Studies of siltuximab, an antibody against the IL-6 ligand, demonstrated a similar effect with almost 80% of patients benefiting while experiencing minimal adverse effects.[52] From a molecular standpoint, in addition to increased levels of

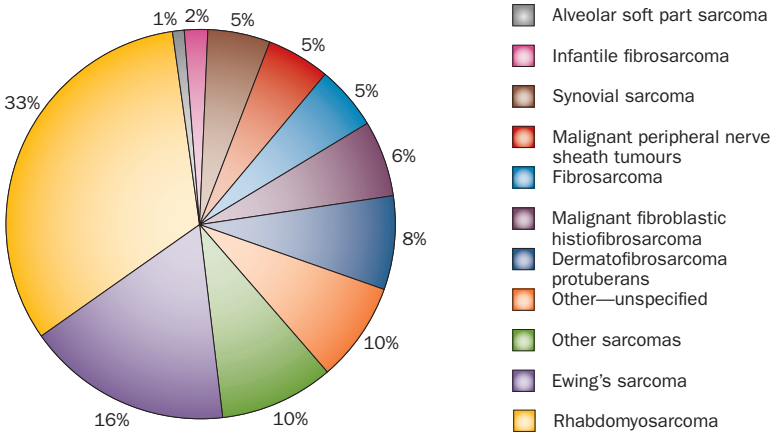

Figure 2 | Distribution of types of sarcoma in childhood. Under the broad umbrella of 'sarcoma' are multiple small subtypes of diseases, each with its own molecular profile. Permission obtained from BMJ Publishing Group Ltd © Slater, O. & Shipley, J. *J. Clin. Pathol*. **60**, 1187–1194 (2007).

IL-6, patients with Castleman's disease have upregulated VEGF (which in turn might be mediated by the RAF pathway in HHV-8–infected human cells), EGFR overexpression, and elevated IL-1b, which could potentially be used as therapeutic targets.[55] Furthermore, blocking the IL-1 receptor with an IL-1 receptor antagonist, such as the cytokine inhibitor anakinra, may be beneficial for patients with refractory Castleman's disease, perhaps because IL-1 stimulates the production of IL-6, as well as other cytokines.[54]

Ewing's sarcoma

Ewing's sarcoma is an aggressive malignancy named after the American pathologist James R. Ewing who described the first cases of it in 1921.[56] The incidence of this rare disease depends on the age of the patient, with a rate of 0.2 cases per 1,000,000 in children younger than 5 years of age to as high as 0.6 cases per 1,000,000 in adolescents aged 15–19 years; it accounts for 16% of sarcomas that occur during childhood (Figure 2).[57–59] Ewing's sarcoma is associated with fusion of the Ewing's sarcoma gene on chromosome 22 to the *FLI1* gene on chromosome 11.[56] Metastatic Ewing's sarcoma is managed with combination chemotherapy, yet its prognosis remains dismal, with a 5-year survival rate as low as 22.1% in the metastatic setting,[60] and novel targeted therapies are desperately needed.

Several monoclonal antibodies directed against the human insulin-like growth factor-I receptor (IGF-1R; Figure 1c), have demonstrated remarkable antitumour activity in patients with Ewing's sarcoma enrolled on clinical trials.[61–64] Morphoproteomic analysis suggests that the mTOR and MAPK pathways may be involved in the resistance to IGF-1R inhibitors.[65] An example of this is shown by upregulated mTOR in the tumour tissue of a patient whose disease progressed after initial response to single agent IGF-1R antibody, but responded to a combination of IGF-1R antibody and mTOR inhibitor.[65] In a different patient, upregulated mTOR was detected in primary tumour tissue prior to treatment and an initial combination of IGF-1R and mTOR inhibition produced a response; on disease progression, ERK was upregulated (MAPK pathway) in the patient's resistant tumour.[65]

The development of IGF-1R antagonists in cancer was intuitive, as insulin is a growth factor with critical metabolic and mitogenic potential, both at the receptor and post-receptor levels.[66] The mechanism for mediating response in Ewing's sarcoma remains unclear, though it is known that EWS–FLI-1 inhibits transcription of *IGFBP3* (which codes for insulin-like growth factor-binding protein 3), hence raising IGF-1 levels.[61] From a pharmacodynamic standpoint, IGFBP3 and IGF-1 were selected as biomarkers for treatment with IGF-1R antibodies based on the hypothesis that blocking IGF-1R might modify IGFBP3 or IGF-1 levels. Naing *et al.*[64] documented a significant overall time-dependent response in mean IGF-1 levels for all patients in a dose expansion cohort of the IGF-1R antibody cixutumumab, and the same findings were seen with regards to IGFBP3. This finding suggests that upregulated IGF-1 and IGFBP3 was related to IGF blockade. No association was found between response to cixutumumab, type of tumour, or the change in IGFBP3 or IGF-1 levels.[64] Unfortunately, development of IGF-1R inhibitors in Ewing's sarcoma has stalled, mainly because of the difficulty inherent in designing registration trials in a subset of patients with a rare disease. Strategies that could be used in such cases would be to incorporate treatment of IGF-1R inhibitors early in the course of the disease to determine if response rates are higher than in heavily pretreated patients. Alternatively, deep sequencing could be exploited to better understand the molecular signatures of responders, and these signatures could then be used to select responsive patients for directed treatment.

Imatinib-resistant GIST

GIST, as its name implies, usually develops in the gastrointestinal tract and is associated most commonly with a *KIT* or *PDGFRA* gene mutation. These tumours are notoriously resistant to chemotherapy and radiotherapy. Although surgery is the standard of care for the management of local GIST, resection is often not curative. The advent of imatinib, an inhibitor of KIT and PDGFR, revolutionized the treatment of GIST, with a clinical benefit rate (complete response, partial response, and prolonged stable disease) exceeding 80% in the metastatic setting, and a median survival of 57 months.[67]

The model of GIST helps delineate the potential and limitations of using targeted therapies to treat solid cancers. A high percentage of patients with GIST had disease progression after cessation of 2-year maintenance imatinib therapy after surgery, despite neoadjuvant and adjuvant efforts to control disease recurrence.[68] As an example, Wang *et al.*[68] found that seven of 11 patients with primary GIST had disease progression despite approximately 2 months of neoadjuvant imatinib and 2 years of adjuvant imatinib treatment; six of those seven patients had halted imatinib treatment prior to disease progression. The administration of more-prolonged adjuvant imatinib in patients with high-risk GIST, for as long as 3 years, seems to improve recurrence-free and overall

survival.[69] Recently, a concomitant activating mutation was detected in *KRAS* (5%) or *BRAF* (2%) genes.[70] *BRAF* mutation was also screened for in 321 patients with GIST, and the *BRAF* V600E mutation was detected in nine (13%) of 70 patients with GIST who were wild-type for *KIT* or *PDGFRA* mutations.[70,71] It has been suggested that activation of the KRAS/BRAF pathway (Figure 1d) could explain the mechanism of primary resistance to imatinib in a subset of patients with GIST, despite harbouring KIT-sensitive mutations.[72,73] With the discovery of aberrations in *KIT*, *PDGFRA* and, more recently, *BRAF* and *KRAS*, GIST serves as a model demonstrating that resistance emerges as a result of a combination of mutations that make effective single-agent therapy challenging.

Malignant melanoma

In 2011, the US FDA approved vemurafenib tablets for the treatment of patients with unresectable or metastatic melanoma with the *BRAF* V600E mutation.[74] FDA approval was mainly based on the results of an international randomized, open-label trial in patients with previously untreated metastatic or unresectable melanoma with a *BRAF* V600E mutation.[75] In the trial, 675 patients were randomly assigned to oral vemurafenib or intravenous dacarbazine until disease progression or unacceptable toxicity occurred. Overall survival was significantly improved in patients receiving vemurafenib compared with those receiving dacarbazine; the overall response rate (complete plus partial response) was 48.4% versus 5.5% in the vemurafenib versus dacarbazine arms, respectively.[75]

Of interest, *BRAF* mutations[76–78] have been identified in many other malignancies, including papillary thyroid cancer,[79] colorectal cancer,[80] and hairy-cell leukaemia,[81] another orphan disease. Studies are ongoing to determine the impact of histology on response rates to vemurafenib in patients with these malignancies and mutations. To date, it seems that patients with colorectal cancer and *BRAF* mutations have lower rates of response than patients with melanoma and *BRAF* mutations.[82] It remains unclear if this is due to histology or to other factors, such as frequent co-activation of the PI3K/AKT/mTOR pathway in colorectal cancer or perhaps due to CRAF activation (Figure 1d).[76] Prahallad *et al.*[82] suggested that patients with colon cancer and a *BRAF* V600E mutation may benefit from dual BRAF and EGFR inhibition. Theoretically, BRAF inhibition might trigger EGFR feedback activation in colon cancer, a phenomenon that might not be seen in melanoma patients who generally express low levels of EGFR. In human colon cancer cells, the EGFR antibody, cetuximab, and the EGFR inhibitors, gefitinib or erlotinib, showed potent synergy with the BRAF inhibitor, vemurafenib, both *in vitro* and *in vivo*.[82] Other tumours, such as hairy-cell leukaemia, have been reported to respond to BRAF inhibition.[83]

CD30 positive ALCL

In 2011, the US FDA granted accelerated approval for brentuximab vedotin (an anti-CD30 antibody) for systemic anaplastic large-cell lymphoma (ALCL) after failure of at least one prior multiagent chemotherapy regimen,

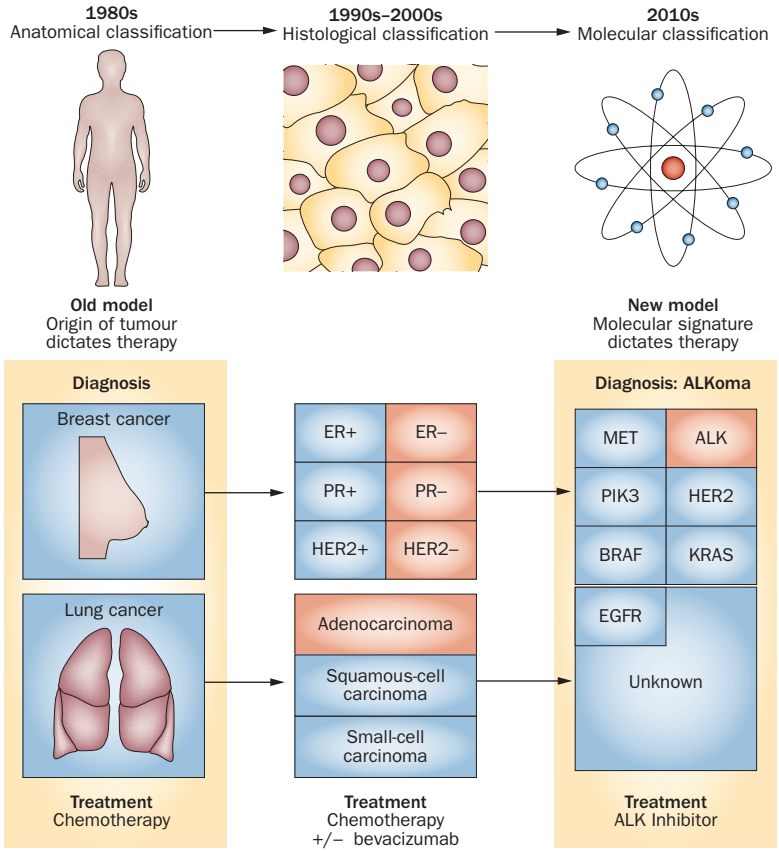

Figure 3 | Cancer in the molecular era. There has been an evolution of cancer classification over time. Although no single stratification model is perfect, a molecular classification trumps an anatomical one regarding therapeutic personalization of medicine.

and for Hodgkin lymphoma after failure of autologous stem-cell transplant or after failure of at least two prior multiagent chemotherapy regimens in patients who are not transplant candidates.[84] The accelerated approval for the systemic ALCL indication was based on a single-arm multicentre clinical trial that enrolled 58 patients who had CD30-positive systemic ALCL and had previously received frontline multiagent chemotherapy regimens. The primary efficacy end point in the systemic ALCL trial, objective response rate, was 86% with a median duration of 12.6 months, while the complete remission rate was 57% with a median duration of 13.2 months.[85]

Brentuximab vedotin is a novel antibody–drug conjugate that comprises the anti-CD30 antibody cAC10 chemically conjugated to monomethyl auristatin E, a potent synthetic analogue of the microtubule polymerization inhibitor agent dolastatin (Figure 1e).[86] When brentuximab vedotin binds to CD30, the receptors are internalized by endocytosis followed by the intracellular release of an auristatin E, which results in targeted tumour cell death (Figure 1e) in a manner similar to other antibody–drug conjugate agents.[15] Of interest, CD30 overexpression is known to occur in a small fraction of solid malignancies, including germ-cell tumours.[87] Studies to evaluate the efficacy of brentuximab vedotin in these populations are ongoing.

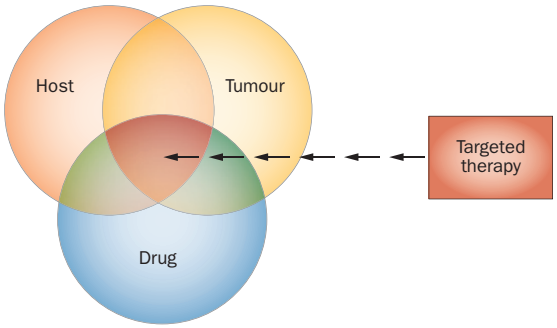

Figure 4 | The elusive equation of targeted therapy: 'the right patient, the right disease, the right drug' in a Venn diagram. Expressing a target in a tumour cell is no guarantee of efficacy after exposure to matched therapy owing to the intricacies secondary to multiple variables in the host, the drugs used, and the tumour itself; hence, true matched targeted therapy has to go through a rather small window of opportunity during drug development.

Deconstructing lung cancer

Randomized studies enrolling patients from the entire lung cancer population in an unselected fashion are likely to yield clinically insignificant or minimally significant results, as the subsets of patients with dramatic responses are diluted by the larger group of non-responders. Historically, lung cancer treatment is a good example of the inherent problems associated with an all-inclusive therapeutic approach (Figure 3). Treatment with the EGFR inhibitor gefitinib, for example, produced responses in 8.9% of all enrolled patients with advanced NSCLC. However, no survival advantage was seen after analysing patients who were not selected by EGFR status, even though some patients had remarkable responses.[88] Subsequently, it was demonstrated that gefitinib is active in patients with NSCLC with a mutated *EGFR* gene.[89–91]

Aberrations in the *IGF1R* gene, the *EML4–ALK* translocation, and aberrations in the HER2, RAS/RAF/MEK and PI3K/AKT/mTOR pathways, have also been identified as potential targets in lung cancer.[92,93] Once again, the largest therapeutic advances may be achieved in the smallest subsets of patients. The EML4–ALK fusion tyrosine kinase, an oncoprotein found in only 4% of patients with NSCLC,[93] defined one orphan disease that was uncovered following deconstruction of a heterogeneous family, and that previously had been grouped under the umbrella of lung cancer, based on organ of origin.

In 2011, the US FDA approved crizotinib to treat patients with late-stage (locally advanced or metastatic) NSCLC with an *ALK* gene rearrangement.[93] The safety and efficacy of crizotinib was established in two multicentre, single-arm studies enrolling a total of 255 patients with late-stage *ALK*-positive NSCLC. In one study, the objective response rate was 50%, with a median response duration of 42 weeks. In the other, the objective response rate was 61%, with a median response duration of 48 weeks.[94]

These data demonstrate that to launch a decisive molecular attack against cancer, a paradigm shift in therapeutic development towards smaller targeted trials dependent upon discrete anomalies in individual cancers is necessary (Figure 3). Nonetheless, it is important to mention that the current genetic-profiling platforms that are available in the clinic do not reveal large numbers of targetable aberrations in lung, colon or breast cancers.[92] Whether or not technology will show the promise of molecular dissection of diseases and targeted therapy still remains to be seen.

Del(5q) myelodysplastic syndrome

Lenalidomide, a second-generation immunomodulatory drug, has found a niche in treating del(5q) MDS,[24] an aberration present in 10% of patients with MDS.[95] Lenalidomide also has activity in patients with low-risk disease and anaemia, whereas hypomethylating agents, such as 5-azacitidine and decitabine, have a role in high-risk MDS.[96] In patients with del(5q) MDS, lenalidomide suppresses abnormal clonal expansion by inhibiting M-phase inducer phosphatase 3 and protein phosphatase 2A, resulting in lenalidomide-specific apoptosis.[97,98] Lenalidomide regulates other critical pathways, including regulators of the cytoskeleton and tumour-suppressor genes, encoded for within the del(5q) region, which may account for some of its direct antitumour and immunomodulatory properties.[97,98]

A randomized phase III study of lenalidomide versus placebo in red blood cell transfusion-dependent patients with low-risk or intermediate-risk MDS and del(5q) showed that more patients in the lenalidomide groups achieved transfusion independence (primary end point) compared with placebo (56.1% and 42.6%; $P<0.001$), while also attaining high cytogenetic response rates of 50.0% (lenalidomide 10 mg) versus 25.0% (lenalidomide 5 mg; $P=0.066$). For the lenalidomide groups combined, 3-year overall survival was 56.5%. Lenalidomide is beneficial and has an acceptable safety profile in this selected population of patients with del(5q), and is yet another example of clinical success in a small, well-defined subset of patients with a given disease.[99]

Proteus syndrome

Proteus syndrome presents as overgrowth of skin, connective tissue, and other tissues.[100] Patients with this syndrome are prone to developing tumours, including monomorphic adenomas of the parotid glands, bilateral ovarian cystadenomas, and meningiomas.[100] This syndrome has been recently associated with activation of the PI3K/AKT pathway; 26 of 29 patients with Proteus syndrome had somatic activating mutations in the *AKT1* oncogene, which might explain the process of vastly deregulated cell proliferation seen in these patients.[101] Cell lines from patients with Proteus syndrome demonstrated mixtures of mutant alleles (approximately 1–50%), supporting the hypothesis that this clinical entity is caused by somatic mosaicism due to an aberration that is lethal in the non-mosaic state.[101] Whether or not AKT inhibitors will reverse this syndrome is of interest.

Lymphangioleiomyomatosis

Lymphangioleiomyomatosis (LAM) is a rare condition of unknown aetiology that results in smooth muscle proliferation; sporadic LAM affects approximately one in 500,000 adult women in Europe.[102,103] Its clinical constellation of signs and symptoms are in part secondary to obstruction of small airways, blood vessels and lymphatic vessels. Lymphadenopathy and cystic lymphatic masses, named lymphangioleiomyomas, are also seen.[102] LAM can be sporadic or associated with tuberous sclerosis complex.[102] Sporadic LAM is putatively associated with loss of heterozygosity in the region of *TSC2* (chromosome 16p13), whereas tuberous sclerosis complex is an autosomal dominant disorder resulting from a germline mutation in *TSC1* or *TSC2* genes.[102] These genes encode tumour suppressors that regulate the mTOR pathway; hence, mTOR-based therapy has been used in patients with LAM with encouraging results.[102]

A cautionary note regarding adoption

As a major counterpoint to the theory that a single or limited number of pathways can lead to the development of orphan cancers, some rare cancers (such as glioblastoma) demonstrate abundant intertumour heterogeneity at the molecular level,[17,18] suggesting that rare cancers can also be driven by multiple alternative pathways. By the same token, some common cancers (such as oestrogen receptor-positive breast cancer) seem to be driven by a single dominant pathway and are highly treatable when this pathway is targeted, at least initially until other pathways predominate and resistance develops.[17–19] Moreover, molecular analysis performed at the time of the original pathological diagnosis, when a curative approach is frequently sought, might not be adequate in the metastatic setting, as there is a proven molecular evolution of malignancies, and heterogeneity even among disparate metastatic sites.[18,19]

Somatic mutations in specific genes are associated with therapeutic responses to targeted agents; however, most patients eventually develop therapy resistance. After therapy resistance has developed the same treatment approach is not curative, probably because advanced-stage disease harbours resistant clones driven by alternative aberrations.[19] Identifying second-line novel agents or combination regimens able to overcome acquired resistance to first-line targeted drugs will have the utmost importance in the years to come. Furthermore, some diseases respond to a targeted agent regardless of the presence of the targeted aberration. For instance, sporadic medullary thyroid cancer often harbours a *RET* mutation, but this disease responds to RET kinase inhibitors even in the absence of this mutation.[104,105] It is possible that these patients bear an as yet undefined aberration in the RET pathway. However, excluding them from treatment on the assumption that they would not respond would have eliminated the chance to discover that their tumours are indeed sensitive to RET inhibitors. Such observations demonstrate the difficulty of designing clinical trials in oncology. On the one hand, molecularly stratified trials, using currently available technology, still miss targets for drug development. On the other hand, continuing to perform non-stratified trials would likely yield much lower response rates, and hopefully further advances in molecular techniques will diminish or perhaps eliminate misses in molecularly stratified trials.

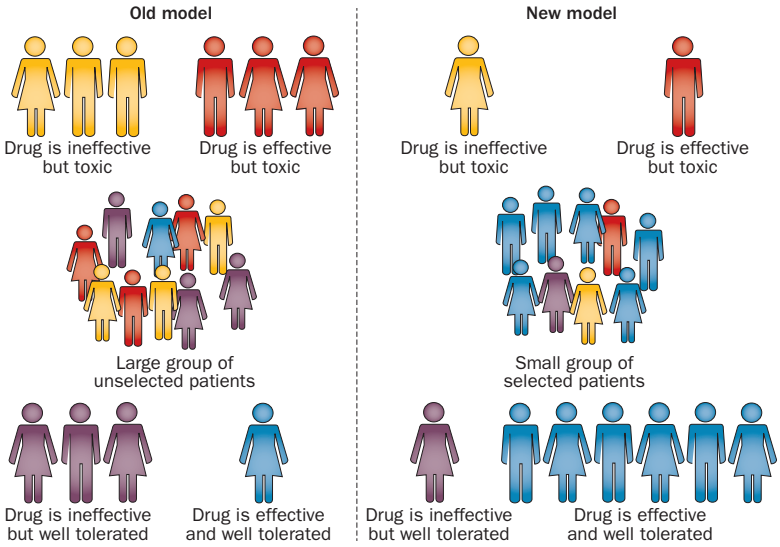

Figure 5 | Large clinical trials with unselected patients may yield modest results compared to trials enrolling a small selected population using targeted treatment matched to specific molecular abnormalities.

In a perfect world, all patients with newly diagnosed cancer or recent development of metastatic disease will have their tumour tissue analysed for molecular aberrations. When economic resources are limited, at the very least patients with dramatic responses to therapy should have their tumour tissue thoroughly screened for mutations and aberrations.

The observation that targeted drugs have found a niche in orphan malignancies is based on clinical experience. Nevertheless, translational and pharmacological challenges and limitations remain. First, this paradigm may not be applicable to all orphan tumours (at least not with available current drugs). Second, malignancies—orphan or not—might be completely reclassified in the near future as we unveil their molecular makeup. Third, narrowing of the targets in orphan diseases is simultaneously a blessing and a curse as the cost-effectiveness of developing novel drugs for a relatively small subset of patients might not appeal to pharmaceutical companies. Fourth, the anatomy of haematological and solid tumours may also be a factor. Bulky drug molecules, such as some antibodies and nanoparticles, might have limited capacity to penetrate some solid tumours and new targeted drugs should probably be categorized according to molecular mass to address drug delivery issues. Nevertheless, bulky drug molecules might still be able to deliver a lethal strike on malignant blood cells in some haematological disorders.

In the clinic, we have repeatedly observed that having a particular target in a tumour does not guarantee efficacy when challenged by a targeted drug. This is a proof of concept that multiple other factors, known and

unknown, compose the equation that decides the fate of a given drug in a given patient (Figure 4). A greater therapeutic challenge will encompass normal host variables (immune system, and BMI), tumour variables (molecular aberrations, histology, and anatomical location) and drug variables (molecule size, mechanism of action, delivery method, and synergy). The failure to acknowledge all the components of the new paradigm of targeted therapy will have the heaviest toll on our patients.

Conclusions

Much can be learned from patients with orphan diseases, some of whom have experienced remarkable responses to single-agent therapies. First, these responders can be exploited to identify the molecular aberrations that define the disease, as occurred in APL. Second, it seems increasingly unlikely that common cancers, which seem to arise as a result of multiple diverse aberrations, will have high response rates to any one therapy. Malignancies that seem to be similar under the light microscope, a wonderful basic tool discovered in 1590, are completely different entities when examined under the 'molecular microscope'. Furthermore, randomized trials in unselected patients are likely to repeatedly select for the drug that impacts the most-common target, and result in the abandonment of good drugs that impact less-frequent aberrations (Figure 5).

Although cancer is one of the most-common diseases, overcoming it requires designing studies that will select small subgroups of appropriate patients. As the expected revenue in a particular disease (such as in a subtype of melanoma) might be low for pharmaceutical companies, a new molecular approach with no anatomical limitations, such as in *BRAF*-positive tumours, should be instituted to fuel drug development. Combination trials might also reach out to more patients as more pathways will be affected. As an additional strategy to meet the challenges outlined in the present article, adaptive trials—introducing flexibility by permitting modifications during the study founded on information available from the trial itself—might be able to attract patients and the pharmaceutical industry.[106]

Since common cancers seem to have heterogenic molecular drivers, many of which may constitute fewer than 2% to approximately 10% of the patient population, single diagnostic molecular assays are unlikely to be cost effective or yield adequate information and will exhaust tissue samples. Multi-assay platforms that include both common and rare aberrations in an individual type of cancer will need to be performed at presentation and relapse to define an accurate molecular diagnosis suitable to the era of matched targeted therapy. Finally, the emerging paradigm of personalized molecular profile-based therapy in cancer may be applicable to other diseases.

Review criteria

The PubMed database was searched using the terms "orphan", "drug", "cancer", or "targeted therapy", and searches were performed from January 2012 to June 2012. Articles published only in English were considered.

1. Stewart, D. J., Whitney, S. N. & Kurzrock, R. Equipoise lost: ethics, costs, and the regulation of cancer clinical research. *J. Clin. Oncol*. **28**, 2925–2935 (2010).
2. Griggs, R. C. *et al.* Clinical research for rare disease: opportunities, challenges, and solutions. *Mol. Genet. Metab.* **96**, 20–26 (2009).
3. Shah, R. R. in Fabry Disease: Perspectives from 5 Years of FOS (eds Mehta, A., Beck, M. & Sunder-Plassmann, G.) Ch. 11 (Oxford PharmaGenesis, Oxford, 2006).
4. European Commission. *Useful Information on Rare Diseases from an EU Perspective* [online], http://ec.europa.eu/health/ph_information/documents/ev20040705_rd05_en.pdf (2012).
5. Pentheroudakis, G. *et al.* Heterogeneity in cancer guidelines: should we eradicate or tolerate? *Ann. Oncol*. **19**, 2067–2078 (2008).
6. Orphan Drug Act. No. 97–414 Pub. L (1983).
7. Aymé, S. & Schmidtke, J. Networking for rare diseases: a necessity for Europe. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz* **50**, 1477–1483 (2007).
8. Gatta, G. *et al.* Rare cancers are not so rare: the rare cancer burden in Europe. *Eur. J. Cancer* **47**, 2493–2511 (2011).
9. Greenlee, R. T. *et al.* The occurrence of rare cancers in U. S. adults, 1995–2004. *Public Health Rep*. **125**, 28–43 (2010).
10. Orphanet. *Prevalence of rare diseases: Bibliographic data* [online], http://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.pdf (2012).
11. van de Laar, F. A., Bor, H. & van de Lisdonk, E. H. Prevalence of zebras in general practice: data from the Continuous Morbidity Registration Nijmegen. *Eur. J. Gen. Pract*. **14** (Suppl, 1), 44–46 (2008).
12. Sledge, G. W. Jr. What is targeted therapy? *J. Clin. Oncol*. **23**, 1614–1615 (2005).
13. Van Cutsem, E. *et al.* Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a biomarker evaluation from the AVAGAST randomized phase III trial. *J. Clin. Oncol*. **30**, 2119–2127 (2012).
14. Topalian, S. L. *et al.* Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N. Engl. J. Med*. **366**, 2443–2454 (2012).
15. Burris, H. A. 3rd, Tibbitts, J., Holden, S. N. & Lewis Phillips, G. D. Trastuzumab emtansine (T-DM1): a novel agent for targeting HER2+ breast cancer. *Clin. Breast Cancer* **11**, 275–282 (2011).
16. Braiteh, F. & Kurzrock, R. Uncommon tumors and exceptional therapies: paradox or paradigm? *Mol. Cancer Ther*. **6**, 1175–1179 (2007).
17. Snuderl, M. *et al.* Mosaic amplification of multiple receptor tyrosine kinase genes in glioblastoma. *Cancer Cell* **20**, 810–817 (2011).
18. Gerlinger, M. *et al.* Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. *N. Engl. J. Med*. **366**, 883–892 (2012).
19. Shah, S. P. *et al.* The clonal and mutational evolution spectrum of primary triple-negative breast cancers. *Nature* **486**, 395–399 (2012).
20. Choi, Y. L. *et al.* EML4-ALK mutations in lung cancer that confer resistance to ALK inhibitors. *N. Engl. J. Med*. **363**, 1734–1739 (2010).
21. Moulder, S. *et al.* Responses to liposomal doxorubicin, bevacizumab, and temsirolimus in metaplastic carcinoma of the breast: biologic rationale and implications for stem-cell research in breast cancer. *J. Clin. Oncol*. **29**, e572–e575 (2011).
22. Robak, T., Krykowski, E., Blasinska-Morawiec, M. & Urbanska-Rys, H. Treatment of patients with hairy cell leukemia with 2-chloro-2'-deoxyadenosine (2-CdA). *Arch. Immunol. Ther. Exp. (Warsz)* **42**, 25–29 (1994).
23. Demetri, G. D. *et al.* Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N. Engl. J. Med.* **347**, 472–480 (2002).
24. Giagounidis, A. A. *et al.* Prognosis of patients with del(5q) MDS and complex karyotype and the possible role of lenalidomide in this patient subgroup. *Ann. Hematol*. **84**, 569–571 (2005).
25. Ohno, R. *et al.* Leukaemia Study Group of the Ministry of Health and Welfare. Multi-institutional study of all-*trans*-retinoic acid as a differentiation therapy of refractory acute promyelocytic leukemia. *Leukemia* **7**, 1722–1727 (1993).
26. Hehlmann, R. How I treat CML blast crisis. *Blood* **120**, 737–747 (2012).
27. Huang, X., Cortes, J. & Kantarjian, H. Estimations of the increasing prevalence and plateau prevalence of chronic myeloid leukemia in the era of tyrosine kinase inhibitor therapy. *Cancer* **118**, 3123–3127 (2012).
28. Druker, B. J. *et al.* Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. *N. Engl. J. Med*. **344**, 1038–1042 (2001).

29. Cornelison, A. M., Kantarjian, H., Cortes, J. & Jabbour, E. Outcome of treatment of chronic myeloid leukemia with second-generation tyrosine kinase inhibitors after imatinib failure. *Clin. Lymphoma Myeloma Leuk*. **11** (Suppl. 1), S101–S110 (2011).
30. Razga, F. *et al.* Analysis of mutations in the BCR-ABL1 kinase domain, using direct sequencing: detection of the T315I mutation in bone marrow CD34$^+$ cells of a patient with chronic myelogenous leukemia 6 months prior to its emergence in peripheral blood. *Mol. Diagn. Ther*. **16**, 163–166 (2012).
31. Levinson, N. M. & Boxer, S. G. Structural and spectroscopic analysis of the kinase inhibitor bosutinib and an isomer of bosutinib binding to the Abl tyrosine kinase domain. *PLoS ONE* **7**, e29828 (2012).
32. Azam, M. *et al.* AP24163 inhibits the gatekeeper mutant of BCR-ABL and suppresses *in vitro* resistance. *Chem. Biol. Drug Des*. **75**, 223–227 (2010).
33. Cassier, P. A. *et al.* Efficacy of imatinib mesylate for the treatment of locally advanced and/or metastatic tenosynovial giant cell tumor/pigmented villonodular synovitis. *Cancer* **118**, 1649–1655 (2012).
34. Stacchiotti, S. *et al.* Dermatofibrosarcoma protuberans-derived fibrosarcoma: clinical history, biological profile and sensitivity to imatinib. *Int. J. Cancer* **129**, 1761–1772 (2011).
35. Zhao. L. J. *et al.* Functional features of RUNX1 mutants in acute transformation of chronic myeloid leukemia and their contribution to inducing murine fullblown leukemia. *Blood* **119**, 2873–2882 (2012).
36. Nacheva, E. P. *et al.* Deletions of immunoglobulin heavy chain and T cell receptor gene regions are uniquely associated with lymphoid blast transformation of chronic myeloid leukemia. *BMC Genomics* **11**, 41 (2010).
37. Beekman, R. *et al.* Sequential gain of mutations in severe congenital neutropenia progressing to acute myeloid leukemia. *Blood* **119**, 5071–5077 (2012).
38. Bink, K. *et al.* Primary extramedullary plasmacytoma: similarities with and differences from multiple myeloma revealed by interphase cytogenetics. *Haematologica* **93**, 623–626 (2008).
39. Sheth, N., Yeung, J. & Chang, H. p53 nuclear accumulation is associated with extramedullary progression of multiple myeloma. *Leuk. Res*. **33**, 1357–1360 (2009).
40. Lee, S. G. *et al.* Preceding orbital granulocytic sarcoma in an adult patient with acute myelogenous leukemia with t(8;21): a case study and review of the literature. *Cancer Genet. Cytogenet*. **185**, 51–54 (2008).
41. Ghobrial, I. M. Myeloma as a model for the process of metastasis: implications for therapy. *Blood* **120**, 20–30 (2012).
42. Wang, Z. Y. & Chen, Z. Acute promyelocytic leukemia: from highly fatal to highly curable. *Blood* **111**, 2505–2515 (2008).
43. Kamimura, T., Miyamoto, T., Harada, M. & Akashi, K. Advances in therapies for acute promyelocytic leukemia. *Cancer Sci*. **102**, 1929–1937 (2011).
44. Hu, J. *et al.* Long-term efficacy and safety of all-trans retinoic acid/arsenic trioxide-based therapy in newly diagnosed acute promyelocytic leukemia. *Proc. Natl Acad. Sci. USA* **106**, 3342–3347 (2009).
45. Castleman, B., Iverson, L. & Menendez, V. P. Localized mediastinal lymph node hyperplasia resembling thymoma. *Cancer* **9**, 822–830 (1956).
46. Cronin, D. M. & Warnke, R. A. Castleman disease: an update on classification and the spectrum of associated lesions. *Adv. Anat. Pathol*. **16**, 236–246 (2009).
47. Cesarman, E., Chang, Y., Moore, P. S. & Knowles, D. M. Kaposi's sarcoma-associated herpesvirus-like DNA sequences in AIDS-related body-cavity-based lymphomas. *N. Engl. J. Med*. **332**, 1186–1191 (1995).
48. Neipel, F. *et al.* Human herpesvirus 8 encodes a homolog of interleukin-6. *J. Virol*. **71**, 839–842 (1997).
49. Yabuhara, A. *et al.* Giant lymph node hyperplasia (Castleman's disease) with spontaneous production of high levels of B-cell differentiation factor activity. *Cancer* **63**, 260–265 (1989).
50. Beck, J. T. *et al.* Brief report: alleviation of systemic manifestations of Castleman's disease by monoclonal anti-interleukin-6 antibody. *N. Engl. J. Med*. **330**, 602–605 (1994).
51. Nishimoto, N. *et al.* Mechanisms and pathologic significances in increase in serum interleukin-6 (IL-6) and soluble IL-6 receptor after administration of an anti-IL-6 receptor antibody, tocilizumab, in patients with rheumatoid arthritis and Castleman disease. *Blood* **112**, 3959–3964 (2008).
52. Van Rhee, F. *et al.* Siltuximab, a novel anti–nterleukin-6 monoclonal antibody, for Castleman's disease. *J. Clin. Oncol*. **28**, 3701–3708 (2010).
53. Ahmed, B. *et al.* Cutaneous castleman's disease responds to anti interleukin-6 treatment. *Mol. Cancer Ther*. **6**, 2386–2390 (2007).
54. El-Osta, H., Janku, F. & Kurzrock, R. Successful treatment of Castleman's disease with interleukin-1 receptor antagonist (Anakinra). *Mol. Cancer Ther*. **9**, 1485–1488 (2010).
55. El-Osta, H. E. & Kurzrock, R. Castleman's disease: from basic mechanisms to molecular therapeutics. *Oncologist* **16**, 497–511 (2011).
56. Cripe, T. P. Ewing sarcoma: an eponym window to history. *Sarcoma* **2011**, 457532 (2011).
57. Slater, O. & Shipley, J. Clinical relevance of molecular genetics to paediatric sarcomas. *J. Clin. Pathol*. **60**, 1187–1194 (2007).
58. National Cancer Institute. *Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975–1995* [online], http://seer.cancer.gov/publications/childhood/ (1999).
59. Stiller, C. A., Allen, M. B. & Eatock, E. M. Childhood Cancer in Britain: The National Registry of Childhood Tumours and Incidence Rates 1978–1987. *Eur. J. Cancer* **31A**, 2028–2034 (1995).
60. Paulino, A. C., Mai, W. Y. & The, B. S. Radiotherapy in metastatic Ewing sarcoma. *Am. J. Clin. Oncol*. http://dx.doi.org/10.1097/COC.0b013e3182467ede.
61. Huang, H. J. *et al.* R1507, an anti-insulin-like growth factor-1 receptor (IGF-1R) antibody, and EWS/FLI-1 siRNA in Ewing's sarcoma: convergence at the IGF/IGFR/Akt axis. *PLoS ONE* **6**, e26060 (2011).
62. Kurzrock, R. *et al.* A phase I study of weekly R1507, a human monoclonal antibody insulin-like growth factor-I receptor antagonist, in patients with advanced solid tumors. *Clin. Cancer Res*. **16**, 2458–2465 (2010).
63. Tolcher, A. W. *et al.* Phase I, pharmacokinetic, and pharmacodynamic study of AMG 479, a fully human monoclonal antibody to insulin-like growth factor receptor 1. *J. Clin. Oncol*. **27**, 5800–5807 (2009).
64. Naing, A. *et al.* Phase I trial of cixutumumab combined with temsirolimus in patients with advanced cancer. *Clin. Cancer Res*. **17**, 6052–6060 (2011).
65. Subbiah, V. *et al.* Targeted morphoproteomic profiling of Ewing's sarcoma treated with insulin-like growth factor 1 receptor (IGF1R) inhibitors: response/resistance signatures. *PLoS ONE* **6**, e18424 (2011).
66. Suh, S. & Kim, K. W. Diabetes and cancer: is diabetes causally related to cancer? *Diabetes Metab. J*. **35**, 193–198 (2011).
67. Ksienski, D. Imatinib mesylate: past successes and future challenges in the treatment of gastrointestinal stromal tumors. *Clin. Med. Insights Oncol*. **5**, 365–379 (2011).
68. Wang, D. *et al.* Phase II trial of neoadjuvant/adjuvant imatinib mesylate for advanced primary and metastatic/recurrent operable gastrointestinal stromal tumors: long-term follow-up results of Radiation Therapy Oncology Group 0132. *Ann. Surg. Oncol*. **19**, 1074–1080 (2012).
69. Joensuu, H. *et al.* One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: a randomized trial. *JAMA* **307**, 1265–1272 (2012).
70. Miranda, C. *et al.* KRAS and BRAF mutations predict primary resistance to imatinib in gastrointestinal stromal tumors (GIST). *Clin. Cancer Res*. **18**, 1769–1776 (2012).
71. Hostein, I. *et al.* BRAF mutation status in gastrointestinal stromal tumors. *Am. J. Clin. Pathol*. **133**, 141–148 (2010).
72. Croom, K. F. & Perry, C. M. Imatinib mesylate: in the treatment of gastrointestinal stromal tumours. *Drugs* **63**, 513–522 (2003).
73. Blay, J. Y. A decade of tyrosine kinase inhibitor therapy: historical and current perspectives on targeted therapy for GIST. *Cancer Treat. Rev*. **37**, 373–384 (2011).
74. Flaherty, K. T., Yasothan, U. & Kirkpatrick, P. Vemurafenib. *Nat. Rev. Drug Discov*. **10**, 811–812 (2011).
75. Chapman, P. B. *et al.* Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N. Engl. J. Med*. **364**, 2507–2516 (2011).
76. Huang, P. & Marais, R. Cancer: Melanoma troops massed. *Nature* **459**, 336–337 (2009).
77. Luke, J. J. & Hodi, F. S. Vemurafenib and BRAF inhibition: a new class of treatment for metastatic melanoma. *Clin. Cancer Res*. **18**, 9–14 (2012).
78. Curtin, J. A. *et al.* Distinct sets of genetic alterations in melanoma. *N. Engl. J. Med*. **353**, 2135–2147 (2005).
79. Bhaijee, F. & Nikiforov, Y. E. Molecular analysis of thyroid tumors. *Endocr. Pathol*. **22**, 126–133 (2011).
80. Spindler, K. L., Pallisgaard, N., Vogelius, I. & Jakobsen, A. Quantitative cell-free DNA, KRAS, and BRAF mutations in plasma from patients with metastatic colorectal cancer during treatment with cetuximab and irinotecan. *Clin. Cancer Res*. **18**, 1177–1185 (2012).
81. Tiacci, E. *et al.* BRAF mutations in hairy-cell leukemia. *N. Engl. J. Med*. **364**, 2305–2315 (2011).
82. Prahallad, A. *et al.* Unresponsiveness of colon cancer to BRAF(V600E) inhibition through feedback activation of EGFR. *Nature* **483**, 100–103 (2012).
83. Dietrich, S. *et al.* BRAF inhibition in refractory hairy-cell leukemia. *N. Engl. J. Med*. **366**, 2038–2040 (2012).
84. Younes, A. CD30-targeted antibody therapy. *Curr. Opin. Oncol*. **23**, 587–593 (2011).
85. Pro, B. *et al.* Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: results of a phase II study. *J. Clin. Oncol*. **30**, 2190–2196 (2012).

86. Foyil, K. V. & Bartlett, N. L. Brentuximab vedotin for the treatment of CD30$^+$ lymphomas. *Immunotherapy* **3**, 475–485 (2011).
87. Younes, A., Yasothan, U. & Kirkpatrick, P. Brentuximab vedotin. *Nat. Rev. Drug Discov*. **11**, 19–20 (2012).
88. Kris, M. G. *et al.* Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer: a randomized trial. *JAMA* **290**, 2149–2158 (2003).
89. Thatcher, N. *et al.* Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). *Lancet* **366**, 1527–1537 (2005).
90. Han, S. W. *et al.* Predictive and prognostic impact of epidermal growth factor receptor mutation in non-small-cell lung cancer patients treated with gefitinib. *J. Clin. Oncol*. **23**, 2493–2501 (2005).
91. Lynch, T. J. *et al.* Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N. Engl. J. Med*. **350**, 2129–2139 (2004).
92. ASCO. ASCO's Blueprint for Transforming Clinical and Translational Cancer Research. Cancer in the Molecular Era: Identifying the Drivers of Lung Cancer [online], http://www.asco.org/ascov2/department%20content/cancer%20policy%20and%20clinical%20affairs/downloads/blueprint.pdf (2012).
93. Tiseo, M. *et al.* Anaplastic lymphoma kinase as a new target for the treatment of non-small-cell lung cancer. *Expert Rev. Anticancer Ther*. **11**, 1677–1687 (2011).
94. Gandhi, L. & Jänne, P. A. Crizotinib for ALK-rearranged non-small cell lung cancer: a new targeted therapy for a new target. *Clin. Cancer Res*. **18**, 3737–3742 (2012).
95. Kantarjian, H. *et al.* The heterogeneous prognosis of patients with myelodysplastic syndrome and chromosome 5 abnormalities: how does it relate to the original lenalidomide experience in MDS? *Cancer* **115**, 5202–5209 (2009).
96. Garcia-Manero, G. Myelodysplastic syndromes: update on diagnosis, risk-stratification, and management. *Am. J. Hematol*. **86**, 490–498 (2011).
97. Komrokji, R. S., Lancet, J. E. & List, A. F. Lenalidomide in myelodysplastic syndromes: an erythropoiesis-stimulating agent or more? *Curr. Hematol. Malig. Rep*. **5**, 9–14 (2010).
98. Heise, C., Carter, T., Schafer, P. & Chopra, R. Pleiotropic mechanisms of action of lenalidomide efficacy in del(5q) myelodysplastic syndromes. *Expert Rev. Anticancer Ther*. **10**, 1663–1672 (2010).
99. Fenaux, P. *et al.* A randomized phase 3 study of lenalidomide versus placebo in RBC transfusion-dependent patients with low-/intermediate-1-risk myelodysplastic syndromes with del5q. *Blood* **118**, 3765–3776 (2011).
100. Biesecker, L. The challenges of Proteus syndrome: diagnosis and management. *Eur. J. Hum. Genet*. **14**, 1151–1157 (2006).
101. Lindhurst, M. J. *et al.* A mosaic activating mutation in AKT1 associated with the Proteus syndrome. *N. Engl. J. Med*. **365**, 611–619 (2011).
102. Piha-Paul, S. A., Hong, D. S. & Kurzrock, R. Response of lymphangioleiomyomatosis to a mammalian target of rapamycin inhibitor (temsirolimus) -based treatment. *J. Clin. Oncol*. **29**, e333–e335 (2011).
103. Orphanet. The portal for rare diseases and orphan drugs [online], www.orpha.net (2012).
104. Wells, S. A. Jr *et al.* Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. *J. Clin. Oncol*. **30**, 134–141 (2012).
105. Kurzrock, R. *et al.* Activity of XL184 (cabozantinib), an oral tyrosine kinase inhibitor, in patients with medullary thyroid cancer. *J. Clin. Oncol*. **29**, 2660–2666 (2011).
106. López, M. F., Dupuy, J. F. & Gonzalez, C. V. Effectiveness of adaptive designs for phase II cancer trials. *Contemp. Clin. Trials* **33**, 223–227 (2012).
107. de Jong, D. *et al.* Anaplastic large-cell lymphoma in women with breast implants. *JAMA* **300**, 2030–2035 (2008).
108. Gambacorti-Passerini, C., Messa, C. & Pogliani, E. M. Crizotinib in anaplastic large-cell lymphoma. *N. Engl. J. Med*. **364**, 775–776 (2011).
109. Dégot, T., Métivier, A. C., Casnedi, S., Chenard, M. P. & Kessler, R. Thoracic manifestations of Castleman's disease [French]. *Rev. Pneumol. Clin*. **65**, 101–107 (2009).
110. Squarize, C. H., Castilho, R. M. & Gutkind, J. S. Chemoprevention and treatment of experimental Cowden's disease by mTOR inhibition with rapamycin. *Cancer Res*. **68**, 7066–7072 (2008).
111. Llombart, B. *et al.* Dermatofibrosarcoma protuberans: a clinicopathological, immunohistochemical, genetic (COL1A1-PDGFB), and therapeutic study of low-grade versus high-grade (fibrosarcomatous) tumors. *J. Am. Acad. Dermatol*. **65**, 564–575 (2011).
112. Risberg, K., Fodstad, O. & Andersson, Y. Immunotoxins: a promising treatment modality for metastatic melanoma? *Ochsner J*. **10**, 193–199 (2010).
113. Chan, K. H. *et al.* Gastrointestinal stromal tumors in a cohort of Chinese patients in Hong Kong. *World J. Gastroenterol*. **12**, 2223–2228 (2006).
114. Dahlgren, J., Klein, J. & Takhar, H. Cluster of Hodgkin's lymphoma in residents near a nonoperational petroleum refinery. *Toxicol. Ind. Health* **24**, 683–692 (2008).
115. Helbig, G. *et al.* Durable remission after treatment with very low doses of imatinib for FIP1L1-PDGFRα-positive chronic eosinophilic leukaemia. *Cancer Chemother. Pharmacol*. **67**, 967–969 (2011).
116. Deshpande, H., Marler, V. & Sosa, J. A. Clinical utility of vandetanib in the treatment of patients with advanced medullary thyroid cancer. *Onco. Targets Ther*. **4**, 209–215 (2011).
117. Stein, B. L., Crispino, J. D. & Moliterno, A. R. Janus kinase inhibitors: an update on the progress and promise of targeted therapy in the myeloproliferative neoplasms. *Curr. Opin. Oncol*. **23**, 609–616 (2011).
118. Vidal, M., Wells, S., Ryan, A. & Cagan, R. ZD6474 suppresses oncogenic RET isoforms in a *Drosophila* model for type 2 multiple endocrine neoplasia syndromes and papillary thyroid carcinoma. *Cancer Res*. **65**, 3538–3541 (2005).
119. Salvi, A. *et al.* Germline and somatic c-met mutations in multifocal/bilateral and sporadic papillary renal carcinomas of selected patients. *Int. J. Oncol*. **33**, 271–276 (2008).
120. Shah, N. P. *et al.* Dasatinib (BMS-354825) inhibits KITD816V, an imatinib resistant activating mutation that triggers neoplastic growth in most patients with systemic mastocytosis. *Blood* **108**, 286–291 (2006).
121. Soignet, S., Fleischauer, A., Polyak, T., Heller, G. & Warrell, R. P. Jr. All-trans retinoic acid significantly increases 5-year survival in patients with acute promyelocytic leukemia: long-term follow-up of the New York study. *Cancer Chemother. Pharmacol*. **40** (Suppl.), S25–S29 (1997).
122. Adamson, P. C. All-*trans*-retinoic acid pharmacology and its impact on the treatment of acute promyelocytic leukemia. *Oncologist* **1**, 305–314 (1996).
123. Ascierto, P. A. *et al.* The role of BRAF V600 mutation in melanoma. *J. Transl. Med*. **10**, 85 (2012).
124. Blay, J. Y., Le Cesne, A., Cassier, P. A. & Ray-Coquard, I. L. Gastrointestinal stromal tumors (GIST): a rare entity, a tumor model for personalized therapy, and yet ten different molecular subtypes. *Discov. Med*. **13**, 357–367 (2012).
125. Younes, A. *et al.* Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. *J. Clin. Oncol*. **30**, 2183–2189 (2012).
126. Foyil, K. V. & Bartlett, N. L. Anti-CD30 antibodies for Hodgkin lymphoma. *Curr. Hematol. Malig. Rep*. **5**, 140–147 (2010).

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