Targeted cancer therapies

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Oncology has become one of the major focus areas for pharmaceutical and biotechnology companies. In 2009, ~16,000 of the ~40,000 Phase I, II and III trials listed on ClinicalTrials.gov were related to cancer (~40%). This large interest stems from the existence of high unmet need for improved treatments of multiple types of cancer and the substantial market success of targeted cancer therapies launched in the past decade.

US oncology market growth Although the overall growth in pharmaceutical sales in the United States — the largest pharmaceutical market — has been slowing in recent years (to ~2–5% in 2008–2009; REF. 1), the oncology market continues to grow at double-digit rates. In 2009, the US sales of oncology drugs (excluding hormonal therapies and vaccines) reached US$18.5 billion, a growth of ~11% compared with 2008.

Oncology drugs can be broadly classified into two categories: traditional cytotoxic chemotherapies, such as platinum-based anticancer drugs, and molecularly targeted drugs, which generally have been developed to specifically modulate the activity of one or more proteins involved in cancer. Although the sales of both types of these drugs are expanding, the majority of sales growth is attributed to an increasing uptake of targeted cancer therapies. In 2009, US sales of targeted anticancer therapies reached $10.4 billion — an almost twofold increase since 2005 (FIG. 1a) — and their sales share increased from 46% in 2005 to 56% in 2009.

Antibodies are the market leaders Currently, there are 22 FDA-approved targeted cancer therapies, 9 of which are monoclonal antibodies (mAbs), 12 of which are small-molecule drugs and one of which is a fusion protein (see Supplementary information S1 (table)). Among these drugs, four mAbs — bevacizumab (Avastin; Roche), rituximab (Rituxan/MabThera; Biogen Idec/Roche), trastuzumab (Herceptin; Roche) and cetuximab (Erbitux; Eli Lilly/Bristol-Myers Squibb) — and one small-molecule drug — imatinib (Gleevec; Novartis) — constitute 86% of the 2009 US sales (FIG. 1b). In 2009, the small-molecule drugs constituted 23% (~$2.4 billion) of the total US sales of targeted therapies, with ~50% of those sales being derived from imatinib.

Drug combinations So far, the success of many targeted cancer therapies has been based on their efficacy when used in combination with established chemotherapies. For example, bevacizumab did not show any survival benefit as a monotherapy for patients with metastatic colorectal cancer, but provided a 2.5-month survival advantage when used in combination with the FOLFOX4 (oxaliplatin (Eloxatin; Sanofi–Aventis) plus leucovorin plus 5-fluorouracil) chemotherapy regimen[2].

The success of combining one targeted drug with chemotherapy has led to the hypothesis that efficacy could be enhanced by adding two or more targeted agents[3], especially to combat the resistance mechanisms used by cancer cells. Although such combinations have shown promising efficacy in preclinical models, the results in clinical trials so far have not been encouraging in general. For example, the CAIRO2 trial showed that addition of cetuximab to capecitabine (Xeloda; Roche), oxaliplatin and bevacizumab resulted in significantly shorter progression-free survival and inferior quality of life for first-line treatment of patients with metastatic colorectal cancer[4]. Nevertheless, with further optimization of dose regimens and greater understanding of biomarker data, it is possible that some patient subpopulations could benefit from such combinations.

Indication expansion Another factor that underlies the growth in the market for targeted cancer therapies is expansion of their indications. Most of the blockbuster drugs highlighted above were launched for a narrow indication, but were later approved for other indications. A good example is imatinib, which was first approved by the FDA in 2001 for the treatment of chronic myeloid leukaemia (CML), which is estimated to affect ~5,000 people in the United States[5]. Based on this indication alone and an annual price of ~$32,000, US sales of imatinib would have peaked at $100–150 million. However, in 2009, US sales of imatinib reached ~$1.1 billion, with worldwide sales reaching $3.95 billion. It is projected that in 2014, worldwide sales of imatinib could be more than $5 billion[6]. This growth has been mainly driven by its expansion into nine different indications (see Supplementary information S2 (table)).

Pricing The substantial market success of targeted cancer therapies so far is in part due to the pricing of such drugs at annual costs of ▸

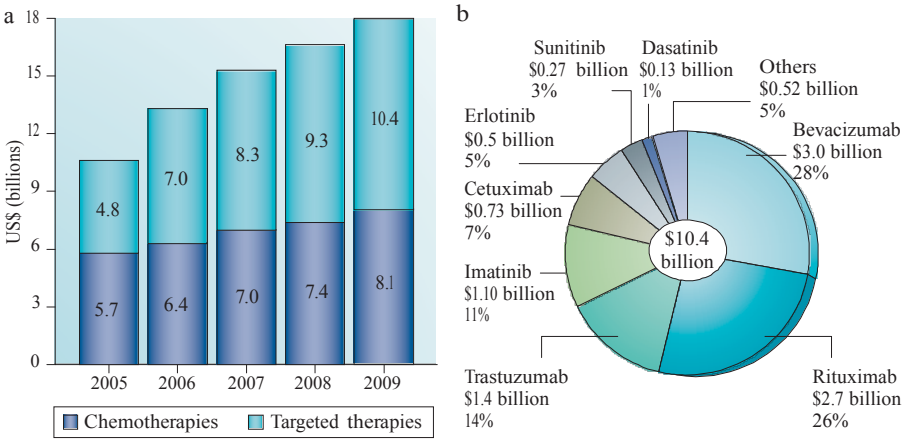

Figure 1 | **Market for targeted cancer therapies. a** | US sales of chemotherapies and targeted cancer therapies, 2005–2009. **b** | Targeted therapies share of the US market based on 2009 sales. Sources: company reports.

► $50,000–100,000 per patient. This makes a drug that treats 10,000–20,000 patients a blockbuster. Although this market success has fuelled further innovation in targeted cancer therapies, it has also created challenges for patients, private payers and governments. In the United States, private payers and Medicare are required by law to cover drugs that are approved by the FDA for cancer-related indications, and current legislation does not allow Medicare to use any of the existing methods to limit the price of cancer drugs[7]. However, as Medicare comes under increasing budgetary pressures, it seems likely that it could take measures to limit spending on cancer therapies.

Future prospects

Despite the availability of improved drugs, including targeted cancer therapies, cancer is still one of the leading causes of mortality worldwide. Cancer is estimated to have accounted for 7.9 million deaths (around 13% of all deaths) in 2007, and ~1.4 million new cancer cases and ~566,000 deaths from cancer occurred in the United States in 2008 (REFS 5,8).

Additionally, for indications for which targeted therapies have been successful, the high mutation potential of cancer cells means that patients may relapse following initial treatment success, which creates a need for new targeted agents that could be used as later lines of therapy. An example is the development of dasatinib (Sprycel; Bristol-Myers Squibb) and nilotinib (Tasigna; Novartis) for patients with CML who have relapsed or are refractory to treatment with imatinib[6].

At present, the pipeline of targeted cancer drugs includes a few hundred new small molecules and mAbs. Among these are agents that modulate novel targets, such as heat-shock protein, 90 kDa, MET and poly (ADP-ribose) polymerase 1, and next-generation agents for established targets such as human epidermal growth factor receptor 2 (HER2; also known as ERBB2) and the epidermal growth factor receptor (TABLE 1). The large number of anticancer drug candidates currently in clinical trials suggests that the market is likely to be increasingly crowded in the future. The challenge will be to determine the right drug combinations or lines of therapy for different types of cancers. In this respect, advances such as recent data showing that patients with colorectal cancer with *KRAS* mutations do not benefit from treatment with cetuximab[9], are setting the stage for increased use of molecular diagnostics that could help oncologists choose the most effective treatment options for their patients.

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Competing interests statement
The author declares no competing financial interests.

SUPPLEMENTARY INFORMATION
see online article: S1 (table) | S2 (table)
All links are active in the online pdf

Table 1 | **Selected targeted cancer therapies in advanced clinical development**

Drug candidate	company	Major indication(s)	Target(s)	stage
Antibodies				
Denosumab	Amgen	Bone metastases	RANK ligand	BLA submitted
Ipilimumab	Bristol-Myers Squibb	Melanoma	CTLA4	Phase III
Tremelimumab	Pfizer/ Debiopharm	Melanoma	CTLA4	Phase III
Zalutumumab	Genmab	Head and neck cancer	EGFR	Phase III
Pertuzumab	Genentech	Breast cancer	HER2	Phase III
Trastuzumab-DM1	Genentech/ Immunogen	Breast cancer	HER2	Phase III
Small molecules				
Omacetaxine	ChemGenex	CML with T315I BCR–ABL mutation	MCL1	NDA submitted
BSI-201	Sanofi–Aventis	Triple-negative breast cancer	PARP1	Phase III
ZD6474	AstraZeneca	Failure of previous EGFR therapy	EGFR	Phase III
Tanespimycin	Bristol-Myers Squibb	Multiple myeloma, GIST	HSP90	Phase III
IPI-504	Infinity	GIST	HSP90	Phase III
Ridaforolimus	Ariad/Merck	Sarcoma	mTOR	Phase III
XL184	Exelixis	Medullary thyroid cancer	MET, VEGFR2, RET	Phase III

BLA, biologic license application; CML, chronic myeloid leukaemia; CTLA4, cytotoxic T-lymphocyte protein 4; EGFR, epidermal growth factor receptor; GIST, gastrointestinal stromal tumour; HER2, human epidermal growth factor receptor 2 (also known as ERBB2); HSP90, heat-shock protein, 90 kDa; IGFR1, insulin-like growth factor receptor 1; MCL1, myeloid cell leukaemia sequence 1; mTOR, mammalian target of rapamycin; NDA, new drug application; NSCLC, non-small cell lung cancer; PARP1, poly (ADP-ribose) polymerase 1. Sources: company reports, ClinicalTrials.gov, American Society of Clinical Oncology, American Society of Hematology.