Added value of molecular targeted agents in oncology

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The treatment of certain cancers has been revolutionised in recent years by the introduction of novel drugs designed to target specific molecular factors implicated in tumour growth. Notable examples include trastuzumab, a humanised monoclonal antibody (mAb) against human epidermal growth factor receptor (HER)-2 in women with HER2-positive breast cancer; rituximab, an anti-CD20 mAb in patients with non-Hodgkin’s lymphoma; imatinib, a tyrosine kinase inhibitor in KIT-positive gastrointestinal stromal tumours and sunitinib, another tyrosine kinase inhibitor, in metastatic renal cell carcinoma. For regulatory reasons, new molecular targeted agents are first evaluated in advanced and metastatic disease, wherein they prolong survival. However, their most profound impact has been observed in the adjuvant setting, where they may contribute to curative therapy rather than mere palliation. Expansion in the use of molecular targeted therapies will have important cost implications for health care systems. Although expensive, on a monthly basis, molecular targeted therapies may not be more costly than treatments for other major chronic diseases, especially considering the contribution of cancer to the global disease burden, the associated socioeconomic costs and the long-term benefits of therapy. Nevertheless, the use of these agents must be optimised, in part using molecular biomarkers associated with drug response.

Key words: biomarkers, economic perspectives, targeted therapy

introduction

Each year in Europe, an estimated 3.2 million people are diagnosed with cancer (excluding nonmelanoma skin cancers) and 1.7 million people die of cancer [1]. Mortality rates associated with most cancers have decreased over the last 20 years [2–4]. According to one estimate, the age-adjusted death rate from all cancers fell between 1992 and 2002 by 12.5% in men (to 162.3/100 000) and by 8.4% (to 95.8/100 000) in women. In men, major decreases of >20% were observed in cancers of the stomach, larynx, lung, bone, testis, thyroid and Hodgkin’s lymphoma. In women, there were decreases of ≥213% in death rates due to cancers of the stomach, intestines, gall-bladder, pleura, bone, thyroid, uterus, Hodgkin’s lymphoma and breast [3]. Incremental gains in survival times have been achieved with the successive approval of new agents in metastatic cancers, including colorectal [5–7], breast [8–11] and lung cancer [12–15]. Nevertheless, conventional chemotherapy is limited both in terms of efficacy and toxicity.

In the past decade, advances in our understanding of the biology of cell signalling have led to the introduction of novel treatmentsrationally designed to target specific molecular factors implicated in tumour growth. By acting more selectively against cancer cells than healthy cells, these molecular targeted agents offer the potential for improved efficacy and less toxicity, as compared with conventional chemotherapy. Molecular targeted agents have revolutionised the management of certain molecular subsets of cancers, and have contributed to recent improvements in survival rates, in subgroups of novel nosological entities. Using trastuzumab, rituximab, imatinib and sunitinib as representative examples of different classes of molecular targeted agents, this paper discusses the impact of such agents on cancer care and the optimisation of their future use in the context of economic pressures.

added value of molecular targeted agents

The clinical development process for new antineoplastics is more complex than that for many other drug classes owing to the challenges of showing a clinical benefit across a spectrum of disease stages and lines of therapy, and in combination with various other standard-of-care chemotherapeutic, radiological and surgical treatments. New drugs are initially tested in advanced metastatic disease—initially as second-line treatment after the failure of established agents (i.e. in highly treatment-refractory populations) and later as first-line therapy in untreated patients. Drugs that show a benefit in advanced disease may then be evaluated in earlier adjuvant settings (i.e. after surgery or radiotherapy) wherein they may contribute to the prevention of disease recurrence. They may also be
used in neoadjuvant settings (i.e. before surgery), wherein they may reduce tumour size so as to allow surgery and/or improve outcomes of surgery where tumours are resectable. The major challenge is the proper identification of the subgroups of disease and patients who will truly benefit from these treatments. Other challenges in the development of new anticancer agents include the selection of optimal efficacy end points and the establishment of cost-effectiveness [16].

trastuzumab

Breast cancer accounts for ~30% of all cancer cases, and ~17% of cancer deaths, in women. Trastuzumab (Herceptin®; Roche Pharma AG, Grenzach-Wyhlen, Germany) has revolutionised the management of breast cancer since it was first approved in Europe in 2000, specifically in the subset of patients whose tumours express the human epidermal growth factor receptor (HER)-2 protein. Encoded by the HER2 oncogene, HER2 mediates numerous processes that contribute to breast cancer pathogenesis [17]. Amplification of HER2, and overexpression of the HER2 protein, occurs in 20% of breast cancers and independently predicts a worse prognosis, including shorter survival [18].

Trastuzumab ORR, is a humanised immunoglobulin G1-kappa monoclonal antibody (mAb) against the extracellular domain of HER2 [19]. Currently, trastuzumab is approved for the treatment of patients with metastatic HER2-positive breast cancer, either as monotherapy or in combination therapy (under particular conditions) and in the adjuvant setting for early HER2-positive breast cancer following surgery, chemotherapy or radiotherapy. Trastuzumab is also approved for use in combination therapy for HER2-positive metastatic adenocarcinoma of the stomach or gastro-oesophageal junction [20].

Trastuzumab prolongs overall survival (OS) when added to standard chemotherapy in patients with metastatic HER2-positive breast cancer [11,21–24]. For example, in a major phase III trial involving 469 randomised patients, the addition of trastuzumab to standard first-line chemotherapy (doxorubicin or epirubicin plus either cyclophosphamide or paclitaxel) significantly improved the time to progression (TTP; 7.4 versus 4.6 months; \( P < 0.001 \)), the OS (median 25.1 versus 20.3 months; \( P = 0.01 \)) and other outcomes versus chemotherapy alone [11]. On subgroup analysis, significant benefits in objective response rate (ORR) and TTP (though not OS) were seen in comparison with both the anthracycline/ cyclophosphamide and paclitaxel chemotherapy regimens (Table 1). The addition of trastuzumab to doctaxel also improves ORR, TTP and OS over monotherapy with docetaxel alone [21, 22]. Combination therapy with trastuzumub plus doctaxel was similarly effective with or without the addition of carboplatin [24], while the addition of carboplatin improved the efficacy of trastuzumab plus paclitaxel [23] (Table 1). According to observational data, the use of trastuzumab has reversed the worse prognosis associated with HER2-positive status in women with breast cancer. In a multivariate retrospective analysis, trastuzumab recipients with HER2-positive disease \((n = 191)\) had a 44% reduction in the risk of death versus women with HER2-negative disease \((n = 1782; \ P < 0.0001)\) [25].

The benefit of trastuzumab as adjuvant therapy following surgery in operable early breast cancer has been established by several major studies [26–30]. Pooled analysis of two large trials involving 3351 women with surgically removed HER2-positive node-positive or high-risk node-negative breast cancer showed that the addition of 1 year of trastuzumab therapy to chemotherapy with paclitaxel, doxorubicin and cyclophosphamide halved the rate of disease recurrence over a 2-year follow-up, as compared with chemotherapy alone [hazard ratio (HR) 0.48; \( P < 0.0001 \)] [26]. Trastuzumab also reduced the risk of distant metastasis by 33% (\( P < 0.0001 \)) and death by 33% compared with standard chemotherapy (\( P = 0.015 \)). After this finding was reported, patients who had been randomly allocated to the non-trastuzumab arm and who were <6 months from completing chemotherapy were eligible to receive trastuzumab. Taking this crossover into account, the benefit of trastuzumab persisted at 4 years, with an HR of 0.49 (\( P < 0.0001 \)) for disease-free survival and 0.63 (\( P = 0.0004 \)) for OS among trastuzumab recipients versus the non-trastuzumab arm [27]. Similarly, in the Herceptin Adjuvant (HERA) study, the addition of 1 year of trastuzumab therapy after standard neoadjuvant or adjuvant chemotherapy with doxorubicin and cyclophosphamide followed by docetaxel in 3401 women reduced the 2-year risk of death by 34\% \( (P = 0.015) \) [28]. Indeed, adjuvant use of trastuzumab has consistently reduced the overall mortality risk by approximately a third over follow-up periods of 2–5 years, as compared with the use of standard chemotherapy regimens [26–29] (Figure 1).

Current guidelines recommend that trastuzumab should be considered for use within adjuvant systemic therapy (where appropriate) for women with node-positive HER2-positive primary breast cancer, as well for those with metastatic disease [31, 32]. Modelling data based on the results of the HERA study suggest that from 2005 to 2015, the adjuvant use of trastuzumab will result in an annual reduction of 2.5% in the number of women with breast cancer who develop metastases, corresponding to 27 727 patients, in five European countries alone [33].

Recent trials have confirmed earlier evidence that trastuzumab also confers benefit when added to neoadjuvant chemotherapy regimens, i.e. those used before surgery in women with early operable breast cancer. In the Neoadjuvant Herceptintrial, women with HER2-positive locally advanced or inflammatory breast cancer treated with a neoadjuvant regimen of doxorubicin, paclitaxel, cyclophosphamide, methotrexate and fluorouracil were randomly assigned to receive 1 year of additional neoadjuvant and adjuvant trastuzumab \((n = 117)\) or no trastuzumab \((n = 118)\). Trastuzumab significantly improved the primary end point of 3-year event-free survival (71% versus 56%; HR 0.59; \( P = 0.013 \)), representing a 41% reduction in risk of recurrence, progression or death. However, it did not significantly reduce 3-year OS [34]. Current guidelines for the management of locally advanced breast cancer recommend that trastuzumab should be added to primary neoadjuvant therapy in patients with HER2-positive tumours before surgery, although concomitant use of trastuzumab and anthracyclines should be
Table 1. Efficacy rates in randomised phase II/III studies of trastuzumab used first line in patients with HER2-positive metastatic breast cancer

<table>
<thead>
<tr>
<th>Trial reference</th>
<th>Regimen</th>
<th>No. of patients</th>
<th>ORR (%)</th>
<th>Median PFS/TTP (months)</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slamon et al. [11]</td>
<td>Doxorubicin/epirubicin + cyclophosphamide(^a)</td>
<td>138</td>
<td>42</td>
<td>TTP: 6.1</td>
<td>21.4</td>
</tr>
<tr>
<td></td>
<td>Doxorubicin/epirubicin + cyclophosphamide + trastuzumab(^b)</td>
<td>143</td>
<td>56 (P &lt; 0.02)</td>
<td>TTP: 7.8 (P &lt; 0.001)</td>
<td>26.8</td>
</tr>
<tr>
<td></td>
<td>Paclitaxel(^a)</td>
<td>96</td>
<td>17</td>
<td>TTP: 3.0</td>
<td>18.4</td>
</tr>
<tr>
<td></td>
<td>Paclitaxel + trastuzumab(^b)</td>
<td>92</td>
<td>41 (P &lt; 0.001)</td>
<td>TTP: 6.9 (P &lt; 0.001)</td>
<td>22.1</td>
</tr>
<tr>
<td>Marty et al. [22]</td>
<td>Docetaxel</td>
<td>94</td>
<td>42</td>
<td>TTP: 6.1</td>
<td>22.7</td>
</tr>
<tr>
<td></td>
<td>Docetaxel + trastuzumab</td>
<td>92</td>
<td>61 (P &lt; 0.001)</td>
<td>TTP: 11.7 (P &lt; 0.001)</td>
<td>31.2 (P &lt; 0.05)</td>
</tr>
<tr>
<td>Robert et al. [23]</td>
<td>Paclitaxel + trastuzumab</td>
<td>98</td>
<td>36</td>
<td>PFS: 7.1</td>
<td>32.2</td>
</tr>
<tr>
<td></td>
<td>Paclitaxel + carboplatin + trastuzumab</td>
<td>98</td>
<td>52 (P &lt; 0.05)</td>
<td>PFS: 10.7 (P &lt; 0.05)</td>
<td>35.7</td>
</tr>
<tr>
<td>Pegram et al. [24]</td>
<td>Docetaxel + trastuzumab</td>
<td>131</td>
<td>73</td>
<td>TTP: 11.1</td>
<td>36.4</td>
</tr>
<tr>
<td></td>
<td>Docetaxel + carboplatin + trastuzumab</td>
<td>131</td>
<td>73</td>
<td>TTP: 10.4</td>
<td>36.5</td>
</tr>
</tbody>
</table>

\(^a\)Patients who had not previously received an anthracycline.
\(^b\)Patients who had previously received an anthracycline.
HER2, human epidermal growth factor receptor-2; ORR, objective response rate; PFS, progression-free survival; TTP, time to progression; OS, overall survival.

<table>
<thead>
<tr>
<th>Trial/regimen</th>
<th>Overall survival benefit</th>
<th>Median follow-up, years</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HERA</td>
<td>Chemo (\rightarrow) tras</td>
<td>2</td>
<td>(P = 0.015)</td>
</tr>
<tr>
<td>B31/N9831</td>
<td>AC (\rightarrow) paclitaxel + tras</td>
<td>2.9</td>
<td>(P = 0.0004)</td>
</tr>
<tr>
<td>BCIRG 006</td>
<td>AC (\rightarrow) docetaxel + tras</td>
<td>5.4</td>
<td>(P &lt; 0.001)</td>
</tr>
<tr>
<td>BCIRG 006</td>
<td>Docetaxel + carboplatin (\rightarrow) tras</td>
<td>5.4</td>
<td>(P &lt; 0.038)</td>
</tr>
</tbody>
</table>

\(0\) Favours trastuzumab, \(1\) Favours no trastuzumab, \(2\) followed by

Figure 1. Reduction in mortality risk in studies of trastuzumab as adjuvant therapy in women with breast cancer [26–29].

limited to clinical trials. Neoadjuvant therapy should be followed by surgery, radiotherapy and (where appropriate) postoperative systemic adjuvant treatment [35].

The use of trastuzumab according to HER2 status is a good example of how molecular targeted therapy should be directed by the presence of the target, and of the challenges therein. The two main methods used for HER2 testing are immunohistochemistry (IHC), which measures overexpression of the HER2 protein, and fluorescence in-situ hybridization (FISH), which detects amplification of the HER2 gene. Both tests determine HER2 status according to the cell characteristics of slide-mounted tumour samples, and both have relative advantages and disadvantages [18, 36, 37]. IHC was the assay used in the phase III trials of trastuzumab and it remains the most widely used technique to determine HER2 status. IHC is relatively inexpensive to carry out and uses standard microscopes. However, its accuracy is variable, depending on such factors as the storage, preparation and fixation of the sample and the type of assay antibody used. Moreover, the semi-quantitative scoring system (0 to +3, according to the degree of cell staining) complicates the interpretation of the results. Two IHC tests are approved for use: the HercepTest assay, which uses a rabbit polyclonal antibody (A0485), and the Ventana Pathway assay, which uses a mouse mAb (CB11). Particular problems with HER2 testing occurred in 2003, when batches of the A0485 antibody with a 50% reduction in the normal antibody concentration gave rise to an increased risk of false-negative results. In the same year, problems with the Ventana test led to an increased risk of false-positive results. The FISH assay is less affected by tissue preparation methods and hence gives more reproducible results. The assay has an internal control (which reduces the likelihood of false-negative
results) and a more objective scoring system. However, the FISH test is more expensive and time consuming than IHC, involves a special fluorescent microscope and requires careful scoring to avoid misinterpretation [18]. Two new test methods—chromogenic in situ hybridisation and silver in situ hybridisation—have recently been developed to combine the advantages of the IHC and FISH [18, 38] tests.

Although tests for biomarkers such as HER2 represent an important advance in cancer care, the validity of their results should not be taken for granted. In 2003, batches of the A0485 antibody with a 50% reduction in the normal antibody concentration gave rise to an increased risk of false-negative results, while problems with the Ventana test led to an increased risk of false-positive results. In Canada, a $17.5 million settlement was reached following a legal class action brought against one regional health care provider after almost 400 of 1000 estrogen receptor tests carried out in breast cancer patients from 1997 to 2005 proved to be incorrect [39, 40]. Physicians and laboratories must be aware of these and other potential sources of error in HER2 tests and should compare tissue sample results with control cases in order to validate their readings. USA guidelines recommend that each year laboratories should ensure that positive and negative HER2 categories by each test are 95% concordant with an alternative validated method or the same validated method [36]. Laboratories should also be vigilant with regard to changes made by manufacturers to the formulation of antibodies or other testing materials.

Guidelines for breast cancer management and HER2 testing in Europe and the United States do not favour one HER2 test over another [31, 32, 36]. Rather, recommendations stress the importance of cross-validation of tests, the use of standardised methods and interpretative criteria and the implementation of other quality assurance measures [36]. A clear positive result by either method will prompt the patient to be offered trastuzumab therapy, while an equivocal result with one test can be followed by the use of the other. However, the optimal approach for testing HER2 remains controversial, with some experts favouring the routine use of FISH [37].

Disease progression following trastuzumab therapy can result from various mechanisms of drug resistance in tumour cells [41]. The role of continued trastuzumab therapy, in combination with other agents, is the subject of ongoing research. Newer molecular targeted agents are also in development for first- or second-line therapy in patients with breast cancer [41]. These agents include lapatinib, a tyrosine kinase inhibitor of HER2 and endothelial growth factor receptor (EGFR) activation. In a phase III trial, lapatinib halved the risk of disease progression in women with HER2-positive advanced breast cancer that had progressed after treatment with regimens that included trastuzumab plus an anthracycline and a taxane [9].

**Rituximab**

Rituximab (MabThera®, Roche Pharma AG, Grenzach-Wyhlen, Germany) was the first molecular targeted agent developed for use in oncology. Rituximab cyclophosphamide is a chimeric (murine–human) mAb directed against the CD20 antigen [42]. CD20 is a specific B lymphocyte antigen with attractive properties for a therapeutic target: it is expressed in >95% of lymphoma cells; it is not expressed on stem cells or B progenitor cells and it does not show modulation, internalisation or shedding when bound by an antibody [43, 44]. Rituximab has transformed strategies for the treatment of haematological malignancies. It is currently approved in Europe for initial and maintenance therapy in non-Hodgkin’s lymphoma (NHL) and (in combination with chemotherapy) in CD20-positive diffuse large B-cell NHL and chronic lymphocytic leukaemia (CLL) [45].

NHL accounts for ~3% of all cancers and a similar proportion of cancer deaths [1]. Rituximab was first approved in Europe in 1998 for use in the treatment of relapsed low-grade or follicular NHL [42]. Subsequently, the addition of rituximab to the standard CVP regimen (cyclophosphamide, vincristine, and prednisone) in a total of 321 previously untreated patients with stage III–IV follicular lymphoma significantly improved the 4-year OS rate (83% versus 77% with CVP alone; P = 0.029) and substantially prolonged the TTP and time to treatment failure [46, 47]. Subsequent studies in patients with advanced follicular lymphoma have confirmed the efficacy of rituximab when added to front-line chemotherapy with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) [48], mitoxantrone, chlorambucil and prednisolone followed by interferon [49] and cyclophosphamide, adriamycin, etoposide and prednisolone, followed by interferon [50] (Table 2).

Rituximab was subsequently evaluated in the maintenance therapy for NHL. The European Organisation for Research and Treatment of Cancer (EORTC) 20981 trial evaluated the benefit of adding rituximab to initial therapy with the standard CHOP regimen (i.e. R-CHOP) in patients with relapsed/resistant follicular lymphoma [51]. Patients who achieved remission or partial remission on either initial regimen were re-randomised to receive maintenance rituximab or observation. Initial therapy with R-CHOP produced significantly longer median progression-free survival (PFS) than did CHOP (33.1% versus 20.2%, respectively; HR 0.65; P < 0.001). Moreover, compared with observation alone, maintenance therapy with rituximab substantially improved 3-year PFS (51.5 versus 14.9 months, respectively; HR 0.40; P < 0.001) and 3-year OS (85% versus 77%; HR 0.52; P = 0.011). Observational data from the Surveillance, Epidemiology and End Results programme in the United States support an effect of rituximab on the natural history of NHL in routine clinical practice. Thus, the introduction of rituximab in 1997 coincided with the reversal of the 1.6% annual increase in mortality between 1991 and 1997 into a 2.8% annual decrease between 1997 and 2003 [52, 53] (Figure 2).

Initial treatment with R-CHOP also significantly improves outcomes in patients with diffuse large B-cell lymphoma (DLBCL), as compared with CHOP. Ten-year follow-up data from the randomised Groupe d’Etude des Lymphomes d’Adulte LNH98.5 study, involving 399 elderly patients with DLBCL, revealed that median OS was 37 months in those who received CHOP and 7 years 9 months in those who received R-
CHOP. Ten-year survival rates were 28% and 43%, respectively ($P < 0.001$) [54].

In France, the use of rituximab in first-line and maintenance treatment of follicular lymphoma (and for the initial treatment of DLBCL) was assigned the highest level of the Commission d’Évaluation des Médicaments, which evaluates every new treatment relative to existing therapies and assigns it an Improvement of Medical Benefit assessment level for the purpose of reimbursement pricing.

Rituximab was the first agent to significantly improve survival in CLL. The international randomised phase III CLL8 trial compared outcomes in treatment-naive patients with CD20-positive CLL randomly allocated to first-line treatment with fludarabine plus cyclophosphamide, with or without rituximab ($n = 817$). Patients who received rituximab showed a 19-month gain in median PFS (32.8 versus 51.8 months; $P < 0.001$; HR 0.56) and a significantly higher survival rate at 37.7 months follow-up (84.1% versus 79.0%; $P = 0.01$) [55].

**imatinib mesylate**

Before the introduction of imatinib (Glivec®; Novartis Pharma GmbH, Nuremberg, Germany) in 2001, the management of gastrointestinal stromal tumours (GISTs) was restricted to surgery and adjuvant treatments of limited effectiveness. Recurrence was usual and prognosis was poor among high-risk patients [56–59]. A breakthrough came in the late 1990s with the identification of mutations in the gene encoding KIT tyrosine kinase, a cell surface transmembrane receptor expressed by GISTs [60]. Mutations in the KIT gene (mainly in exons 9 and 11) are found in ~90% of GISTs [61]. These mutations result in constitutive activation of KIT signalling and uncontrolled cell proliferation and are central to the pathogenesis of most GISTs [60]. Other mutations, most notably in platelet-derived growth factor receptor (PDGFR)-alpha, another protein with tyrosine kinase activity, are implicated in the pathogenesis of tumours lacking KIT mutations [62].

Imatinib is an orally administered competitive inhibitor of several tyrosine kinases, including KIT and PDGFR [63, 64]. In a phase II extension trial, patients with unresectable or metastatic KIT-positive GIST ($n = 147$) were randomly assigned to receive long-term imatinib therapy (400 or 600 mg/day) [65]. The median OS was 57 months, with no significant difference between the imatinib dosages. A large EORTC phase III trial subsequently evaluated imatinib (400 mg once or twice daily) in 946 patients, also with unresectable or advanced KIT-positive GIST [66]. This study showed a median PFS of 20 months with imatinib 400 mg/day compared with 26 months with 800 mg/day. The SO033 trial compared similar treatment arms and included 746 patients with advanced GIST

### Table 2. Efficacy rates in randomised phase III studies of rituximab used first line in patients with follicular lymphoma

<table>
<thead>
<tr>
<th>Trial reference</th>
<th>Regimen</th>
<th>No. of patients</th>
<th>ORR (%)</th>
<th>EFS/TTP/TF (median or rate)</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marcus et al. [47]</td>
<td>CVP: cyclophosphamide + vincristine + prednisone</td>
<td>159</td>
<td>57</td>
<td>TTP: 15 months</td>
<td>4-year OS: 77%</td>
</tr>
<tr>
<td>Hiddemann et al. [48]</td>
<td>CHOP: cyclophosphamide + doxorubicin + vincristine + prednisone</td>
<td>205</td>
<td>81 ($P &lt; 0.0001$)</td>
<td>TTP: 34 months ($P &lt; 0.0001$)</td>
<td>4-year OS: 83% ($P = 0.029$)</td>
</tr>
<tr>
<td>Herold et al. [49]</td>
<td>R-CHOP: CHOP + rituximab</td>
<td>222</td>
<td>96 ($P = 0.01$)</td>
<td>TF rate: 12.5% ($P &lt; 0.001$)</td>
<td>2-year OS: 95%</td>
</tr>
<tr>
<td>Salles et al. [50]</td>
<td>CHVP + I: cyclophosphamide + adriamycin + etoposide + prednisolone + interferon-2a + rituximab</td>
<td>183</td>
<td>71.6 b</td>
<td>5-year EFS: 37%</td>
<td>5-year OS: 79%</td>
</tr>
<tr>
<td></td>
<td>R-CHVP + I: CHVP I + rituximab</td>
<td>175</td>
<td>81.1 ($P &lt; 0.05$) b</td>
<td>5-year EFS: 53% ($P &lt; 0.001$)</td>
<td>5-year OS: 84%</td>
</tr>
</tbody>
</table>

*After 3-year follow-up, mortality was 3.0% in R-CHOP arm versus 7.6% in CHOP arm ($P = 0.016$).

*18-month data; $P$ value for all strata of response.

ORR, objective response rate; EFS, event-free survival; TTP, time to progression; TF, treatment failure; OS, overall survival; PFS, progression-free survival.

![Figure 2. Mortality rates of NHL and new drugs approved in the United States for the treatment of NHL. Adapted and used with permission from Molina et al. [52], based on data from the USA SEER programme [53]. NHL, non-Hodgkin’s lymphoma; SEER, Surveillance Epidemiology and End Results.](https://example.com/figure2.png)

- NHL mortality (SEER Programe, USA)
- Capcitabine (1998)
- Etosporboc (1988)
- Fludarabine (1991)
- Rituximab (1997)

+1.6% / year

-2.8% / year

*Age adjusted to 2000 US standard population.
[67]. After a median follow-up of 4.5 years, the median OS was 55 and 51 months in patients treated with 400 and 800 mg/day, respectively, while median PFS was 18 and 20 months in the two groups, respectively. In the recently reported meta-analysis of these two trials [68], a significant improvement in PFS was observed in the 800 mg/day arm, without improvement in OS. Of note, the improvement in PFS was significant only in the subgroup of patients with mutations on KIT exon 9, leading to recommendations for the use of this dose in KIT mutation positive patients with advanced disease [69]. Importantly, in all these studies, almost half of imatinib-treated patients are alive at 5 years [65, 67].

These data compare with a reported median survival time of 15–19 months, and 5-year survival rates of ≤20%, among patients with high-risk or recurrent GIST before the introduction of imatinib [56–59]. Thus, in the absence of controlled studies, historical comparison suggests that first-line treatment with imatinib may improve survival by almost threefold compared with previous care. Imatinib is also well tolerated and hence may allow patients to return to work or normal activities. Imatinib is now the standard first-line treatment for patients with unresectable or metastatic GIST [69, 70].

Surgery remains the standard treatment of localised resectable GIST [69] and imatinib has an important adjuvant role in this setting. A randomised, phase III, double-blind placebo-controlled trial evaluated oral imatinib as adjuvant therapy for 1 year following resection of a primary KIT-positive GIST (n = 713). Imatinib significantly improved 1-year recurrence-free survival compared with placebo (98% versus 83%; HR 0.35; P < 0.0001) [71]. Imatinib is now approved for the adjuvant treatment of adults who are at significant risk of relapse following resection of KIT-positive GIST, as well as those with unresectable and/or metastatic disease [72].

Importantly, not all patients benefit equally from imatinib therapy. Prognostic classification systems for GIST, and hence for selecting high-risk patients suitable for imatinib adjuvant therapy, continue to evolve [73–76]. As mentioned above, when imatinib is used in the treatment of advanced GIST, PFS and OS are significantly more prolonged in patients with tumours expressing the KIT exon 11-mutant genotype, as compared with the KIT exon 9-mutant and the wild-type genotype [61, 77, 78]. When used in the adjuvant setting, however, the role of imatinib 800 mg/day is unclear. The optimal duration of adjuvant therapy is also unclear. One year of treatment is currently recommended based on trial data [70], but more prolonged therapy might offer greater benefit. Further trials are underway to investigate treatment for up to 3 years [79].

The neoadjuvant use of imatinib before surgical resection may shrink GIST and thereby reduce surgical morbidity and help maintain organ function. Preliminary data suggested that this approach was feasible [80]. A recent retrospective pooled subgroup analysis of clinical trial patients treated preoperatively with imatinib suggests that patients who responded were more likely to have shown locally unresectable GIST, and these patients were more likely to have complete resections [odds ratio (OR) 0.06; P = 0.00001], a more prolonged 12- and 24-month disease-free survival after imatinib treatment and complete resection (OR 0.1, P = 0.06 and OR 0.13, P = 0.003) and a better 24-month OS (OR 0.04, P = 0.004) [81]. Current guidelines for the management of GIST recommend that imatinib pretreatment should be used where R0 surgery is not feasible, where it could be through less mutilating surgery following cytoreduction or where pretreatment may reduce surgical morbidity [70].

The long-term benefit of imatinib is limited by the development of resistance, which can occur through the emergence of secondary mutations of the KIT protein [82]. Options for the management of imatinib-resistant GIST include surgery, radiotherapy or pharmacotherapy with the multitarget tyrosine kinase inhibitor, sunitinib [83].

sunitinib malate

Sunitinib (Sutent® Pfizer Italia Srl, Mario del Tronto, Italy) is an orally administered tyrosine kinase inhibitor that acts upon multiple proteins, including KIT, PDGFR and vascular endothelial growth factor receptor (VEGFR) proteins [84]. Sunitinib was approved in 2006 for use in patients with unresectable and/or metastatic malignant GIST after failure of imatinib owing to resistance or intolerance [85]. In a randomised, double-blind, phase III trial in this population (n = 312), sunitinib increased the time to tumour progression by over fourfold as compared with placebo: median 27.3 versus 6.4 weeks (HR 0.33; P < 0.0001) and improved survival [83].

Sunitinib is also approved for use in advanced/metastatic renal cell carcinoma (MRCC) [85]. Renal cell carcinoma is the most common cancer of the kidney and is associated with recurrence following surgery, resistance to chemotherapy and radiotherapy and a poor prognosis upon metastasis [86]. Within the last two decades, the treatment of MRCC has been marked by the introduction of immunotherapies (interferon-α and interleukin-2), which induced at best a marginal impact on OS, and more importantly in the last 5 years by the introduction of molecular targeted agents directed against the VEGFR and PDGFR kinases, including sunitinib [86]. After showing efficacy as second-line therapy in an uncontrolled trial of patients with MRCC [87], sunitinib was compared against standard first-line therapy with interferon-α in previously untreated patients. Sunitinib doubled the median PFS versus interferon-α (primary end point: 11 versus 5 months, respectively; P < 0.001) and improved OS (26.4 versus 21.8 months, respectively; HR 0.821; P = 0.051) [88]. Sunitinib therapy was also associated with significantly improved health-related quality of life compared with interferon-α [89].

Other molecular targeted agents developed for use in MRCC include bevacizumab (Avastin®; Roche Pharma AG, Grenzach-Wyhlen, Germany), a humanised mAb against VEGF that improves PFS in MRCC when added to interferon-α therapy [90, 91]. Data from a phase II trial suggest that sunitinib may also have useful activity in patients with MRCC refractory to treatment with bevacizumab [92].

Several promising biomarkers for the effects of sunitinib have been evaluated, although none have yet proved clinically useful. Phase II data suggested that a low haemoglobin level independently predicted a shorter PFS in MRCC patients [87], although in a phase III trial sunitinib was more effective than interferon-α in extending PFS across all clinical risk categories.
Several studies have correlated changes in VEGF-A, VEGFR-2 and VEGFR-3 with sunitinib exposure and efficacy, as assessed by objective tumour response and PFS in patients with MRCC [92, 94]. However, expression of factors can vary widely between patients and further research is required. Preliminary studies also suggest that VEGF and VEGFR-2/-3 may be a potential biomarker of sunitinib activity in metastatic breast cancer [95] and that VEGFR-3 and interleukin-8 might be useful predictors of activity and response in metastatic neuroendocrine tumours [96]. A different set of candidate biomarkers of sunitinib in GIST has emerged. While VEGF and VEGFR-2 levels showed some relationship with drug exposure in a phase I/II trial in patients with imatinib-refractory metastatic GIST, they did not correlate with outcome [97]. Patients with a PFS of >6 months did show significantly greater increases in circulating endothelial cells (CEC) and smaller decreases in monocyte levels those who did not, suggesting that these might represent surrogate measures of clinical benefit. However, a causative relationship between these markers and drug effect cannot be assumed (conceivably, the observed CEC and monocyte changes might occur in slow-growing tumours) and the study did not control for other factors that could have affected prognosis [98]. Phase III data suggest that decreases in circulating plasma KIT levels may also be useful as a surrogate marker for TTP in patients with GIST following imatinib failure [99]. Patients with decreases in KIT levels from baseline during sunitinib therapy had a mean TTP of approximately double that of those with no decrease (P < 0.0001). Finally, in GIST, the most interesting biomarker correlated to the response to sunitinib may actually be the nature of primary and secondary mutations of the KIT gene that drive the tumour, strongly suggesting that the biological effects of this agent on tumour environment may not be its prominent mode of action in this tumour [78].

Angiogenesis inhibitors

By preventing the development of new blood vessels necessary for tumour growth and spread, angiogenesis inhibitors offer a promising approach for novel cancer therapies. The best characterised antiangiogenesis agents are those that target the interaction between VEGF, a key mediator of angiogenesis, and its tyrosine kinase receptors. For example, the anti-VEGF antibody bevacizumab is approved for use in the treatment of advanced or metastatic carcinoma of the colon or rectum, breast cancer, non-small-cell lung cancer (NSCLC) and MRCC [100]. Vandetanib is an oral tyrosine kinase inhibitor that targets VEGFR and EGFR and that is in development for NSCLC [101].

The development of surrogate markers specific to the unique actions of angiogenesis inhibitors has proved to be particularly difficult [86, 102, 103]. Obtaining a biopsy of tumour tissue for analysis can provide important information (e.g. on microvessel density) but is limited by its invasiveness and the potential for sampling error [103]. The effects of angiogenesis inhibitors on tumour size, perfusion, permeability and metabolism have been usefully measured using radiological imaging techniques (e.g. magnetic resonance imaging) [104, 105]. However, these techniques are investigational tools for use in early-phase trials and have no place in directing routine therapy. In principle, the measurement of circulating angiogenic factors such as VEGF could offer a convenient and minimally invasive surrogate test, but so far these have been of limited use. A retrospective analysis of data from phase II trials suggested that low baseline VEGF levels predicted a better PFS in patients treated with vandetanib therapy for advanced NSCLC [106]. Recently, a comprehensive analysis of 35 cytokines and angiogenic factors (CAFs) was carried out during a phase II trial in which NSCLC patients were treated with vandetanib monotherapy, carboplatin plus paclitaxel and or combination of all three agents. Vandetanib and chemotherapy treatment led to distinct patterns of changes in multiple CAFs and changes in certain CAFs correlated with clinical outcome. Increases in interleukin-8 with the triple regimen, matrix metalloproteinase-9 with chemotherapy and VEGF with vandetanib monotherapy were associated with increased progression risk, while increases in intercellular adhesion molecule-1 was associated with decreased risk during vandetanib therapy. However, these markers differed between the treatment arms, making their interpretation difficult. The measurement of CEC and bone marrow-derived endothelial precursor cells has also been evaluated as a biomarker. Mobilised by pro-angiogenic factors, these cells contribute to the production of new tumour vasculature. In tumour-bearing mice, vandetanib increased the levels of mature CEC (perhaps due to sloughing of endothelium) and this was associated with reductions in tumour microvessel density and volume [107]. However, none of these circulating biomarkers have been developed to the point at which they are useful in directing therapy in clinical practice.

Mammalian Target of Rapamycin Inhibitors

Mammalian target of rapamycin (mTOR) is a protein kinase that regulates the synthesis of various proteins necessary for cell cycle progression, proliferation, angiogenesis and survival. mTOR inhibitors that have been evaluated in cancer therapy include temsirolimus (Torisel®; Wyeth Lederle SpA, Catania, Italy), everolimus (Afinitor®; Novartis Pharma AG, Nuremburg, Germany) and ridaforolimus . Temsirolimus is approved for first-line use in MRCC based on phase III data showing survival benefits in patients with clinical risk factors for short survival [108]. Everolimus is also approved for use in MRCC, either after failure with sunitinib or sorafenib (United States) or after VEGF-targeted therapy (Europe) and additionally has been investigated in the treatment of breast and lung cancer [109–112]. Ridaforolimus has been tested in preliminary trials in patients with various solid and haematological malignancies [113, 114].

Establishing surrogate markers of the effect of mTOR inhibitors is complicated by the diverse complex effects of mTOR on cell signalling. mTOR inhibition per se has been demonstrated by measuring decreases in levels of phosphorylated 4E-binding protein-1 (4E-BP1), one of the two translation initiation factors that mTOR phosphorylates and which mediate its effects [113, 114]. However, there was no correlation between 4E-BP1 and tumour size in patients with advanced malignancies treated with ridaforolimus [114]. An
increase in serum cholesterol level was significantly associated with the change in tumour size in this trial, suggesting a possible role of cholesterol as a biomarker [114]. In a preliminary study, positron emission tomography was used to document a decrease in glucose metabolism during everolimus treatment in NSCLC patients [112], although its relationship with tumour effects or therapeutic outcome is unclear. Finally, again the most efficient biomarker correlated with the antitumour activity of this class of compound was found to be the loss of the tuberous sclerosis complex (TSC) 1/2 proteins in PEComas associated with sclerotic tuberosis. In this model, where tumour proliferation is driven by TSC loss and subsequent mTOR inhibition, sirolimus was found to exert dramatic antitumour activity [115].

**combination of molecular targeted agents**

In principle, the use of combinations of targeted therapies is attractive for various reasons. In combination, these agents could achieve a greater blockade of one transduction pathway by inhibiting sequential transduction sites, by increased inhibition through simultaneously impacting the extracellular targets with an mAb and the intracellular tyrosine kinase by its inhibitor, by simultaneously impacting a transduction pathway and its bypassing mechanism or by targeting different transduction pathways in a potentially additive strategy. In clinical practice, however, there are numerous difficulties that arise when considering the combination of different agents. For example, the understanding of preclinical and clinical pharmacodynamics is poor and it is currently impossible to predict new toxic effects or possible additive toxicity, although pharmacokinetic interactions between agents may be expected. The search to identify the most promising combinations is ongoing and several clinical models exploring the interaction between targeted treatments have provided encouraging preliminary results. For example, in patients with breast cancer, the associations between trastuzumab and bevacizumab, trastuzumab and the tyrosine kinase inhibitor, lapatinib, and trastuzumab and pertuzumab (an anti-HER2 mAb) are being assessed in large randomised phase III clinical trials in adjuvant and metastatic settings. One could speculate that combining these therapies represents the next step in revolutionising the treatment of cancers. Furthermore, the clinical benefit expected from these combinations could enhance the potential cost impact of such therapy.

**economic perspectives**

At nearly €57 billion, cancer accounts for an estimated 6.4% of total health care costs in Europe [116]. In France, cancers are the second most important source of costs for the French health care system (€14 billion), after cardiovascular disease (€17 billion [117]). Cancer drugs are estimated to account for ~5% of all drug costs [116]. By comparison, cancer is estimated to have accounted for 16.7% of all disability-adjusted life years lost in the European Union in 2002 and hence represents the third largest disease burden after mental illness and cardiovascular disease [117]. National registry data from France show that cancer causes approximately fourfold more premature deaths (43 962/year) than cardiovascular disease (14 425/year) [119]. Thus, the proportion of total health care costs spent on cancer does not necessarily reflect the contribution of cancer to the global disease burden.

From 2004 to 2007, the mean annual costs of care per cancer patient increased by 23.2% to €10 557 (Figure 3). The observed increase was similar to increases in the areas of cardiovascular disease (27.8%), diabetes (20.4%) and respiratory (28.5%) medicine and less than that of psychiatric disease (42.6%) and Alzheimer’s disease/dementias (56.4%). Overall, annual cancer costs per patient are slightly higher than those of cardiovascular disease, diabetes and respiratory disease but remain lower than those of psychiatric disease, Alzheimer’s disease/dementias, human immunodeficiency virus infection and chronic kidney disease [120, 121].

The increase in the costs of cancer drugs in recent years is due mainly to the use of innovative anticancer drugs, including molecular targeted agents [117]. In France, €0.97 billion was spent in 2008 on innovative anticancer drugs. This represents just over half of the expenditure on all innovative drugs (€1.7 billion) and ~0.6% of the total health care budget of €154 billion [117]. However, hospitalisation costs are estimated to account for ~70% of the direct costs of cancer care. Drugs are estimated to account for ~12% of the total direct costs, although this percentage varies between countries [116, 117]. Therefore, the increase in the costs of drug therapy due to the use of molecular targeted agents has had a limited effect to date on the total costs of cancer care.

**optimising the use of molecular targeted agents**

In light of their contribution to the costs of cancer care relative to conventional chemotherapy, the prescription of molecular targeted agents is tightly regulated. In France, the national plan stipulates the need for speciality and sub-speciality degrees among prescribers. Other measures include evidence-based treatment guidelines, multidisciplinary staff meetings and personalised treatment plans. Importantly, in order to optimise their cost-effectiveness, molecular targeted agents should be used only in patients with tumours expressing the relevant molecular target. Clearly, a standardised and reliable means of measuring the target must be made available to prescribers. Tests should be reproducible and quantitative. In the case of solid tumours, the test should be adaptable for the analysis of paraffin-embedded tumour samples and not influenced by fixation conditions. Furthermore, there must be widespread access to the test at the national level. For example, the French Institut National du Cancer has funded systems for the measurement of mutations in EGFR and in KRAS (Kirsten rat sarcoma 2 viral oncogene homologue), a protein whose activation predicts a relatively poor drug response to anti-EGFR antibodies used in the treatment of colorectal cancer (Table 3).

Ideally, molecular target tests should be developed alongside the development of the associated molecular targeted agent. However, in practice, the priorities and rationales of drug
marketing may differ from those of scientific research. Marketing departments in the pharmaceutical industry tend to favour ‘organ’-based drug registrations, while scientific data increasingly suggest than only certain subsets of patients, or more precisely molecular subsets of tumour types from a single organ, in these organ-based classifications will benefit from the therapy, i.e. those that express the relevant biomarker target. Also, the development of biomarkers is a difficult and costly process. Indeed, it may be very difficult to identify the optimal target and to develop it for clinical use, as exemplified by the aforementioned challenges in HER2 testing in women with breast cancer.

Despite the controversy over the optimal means of HER2 testing, the use of trastuzumab in women with breast cancer is nevertheless strongly directed by the HER2 status [31, 32]. Other molecular targeted agents whose use is also well directed by a specific molecular target test include the use of rituximab according to CD20 expression at the surface of NHL tumour cells and the use of gefitinib (Iressa® AstraZeneca UK Ltd, Macclesfield, UK), an anti-EGFR tyrosine kinase inhibitor, in patients with non-small-cell lung cancer expressing mutations in EGFR [122, 130], or the use of crizotinib in EML4-ALK-translocated NSCLC patients [131]. However, the use of many other molecular targeted agents—such as the angiogenesis inhibitors and mTOR inhibitors—is directed only to an intermediate degree, or not at all, by biomarker testing owing to the reasons discussed above (Table 3). The further development and clinical application of these latter classes is limited by the lack of surrogate markers that can reliably and usefully measure their biological effects and identify patients who will benefit from treatment.

**molecular targeted agents in non-neoplastic diseases**

Many molecular targeted agents have shown therapeutic effects in non-neoplastic diseases. For example, the immunosuppressive effects of rituximab are exploited in the treatment of various autoimmune conditions, including rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, antineutrophil cytoplasmic antibody-mediated vasculitis, cryoglobulinemic vasculitis and pemphigus. Recent data suggest that rituximab might also preserve pancreatic beta-cell function in patients with type 1 diabetes mellitus [132]. Recent research has indicated the potential for additional uses for bevacizumab in the resolution of ascites and marked reduction in hepatic size and vascularity in patients with hereditary haemorrhagic telangiectasia, a condition associated with vascular abnormalities [133]. The use of bevacizumab also led to tumour shrinkage, with associated decreases in vascular permeability, blood flow and reversibility of hearing loss in patients with type 2 neurofibromatosis, a genetic condition characterised by the development of benign tumours of the eighth cranial nerve [134]. Intravitreal bevacizumab has also been shown to delay the degeneration of visual acuity and macular thickness in patients with inflammatory eye diseases, namely choroidal neovascularisation and cystoid macular oedema [135].

**conclusions**

The use of molecular targeted agents represents a paradigm shift in the care of certain cancers and these agents are progressively being integrated into therapeutic strategies. In some cases, these agents have profoundly changed the natural history of the disease, e.g. trastuzumab in HER2-positive breast cancers, rituximab in NHL, imatinib in GIST and sunitinib in MRCC. For regulatory reasons, new molecular targeted agents are first evaluated in advanced and metastatic disease, wherein many have prolonged survival. However, their most profound impact has been observed in the adjuvant setting, where they may contribute to curative therapy (i.e. in preventing recurrence) rather than mere palliation. The neoadjuvant use of certain agents may also help to improve outcomes after resection, although these strategies require further evaluation. Many other agents are in preclinical or clinical development and any limitation on the approval of such agents for advanced
or metastatic disease may have a major impact on cancer care overall. In addition to their non-cancer uses, molecular targeted agents are also likely to find new applications in other areas of medicine, including numerous autoimmune disorders and perhaps even in type 1 diabetes.

The expansion in the use of molecular targeted therapies will have important cost implications for health care systems. However, molecular targeted therapies are not more costly than treatments for other major chronic diseases, especially when one considers the contribution of cancer to the global disease burden, the associated socioeconomic costs of cancer and the long-term remission that allows recipients of adjuvant therapy to lead productive lives. Nevertheless, given the pressure on health care resources, robust measures to optimise the cost-effective use of molecular targeted agents are important. While the cost-effective use of some molecular targeted therapies is aided by molecular biomarkers, for others the development of such tests is required if their use is to be extended into adjuvant therapy and their benefit to be maximised.

**acknowledgements**

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**Table 3.** Selected approved molecular targeted agents categorised according to the degree to which their prescribing is directed by biomarkers associated with treatment response [20, 45, 72, 85, 100, 122–129]

<table>
<thead>
<tr>
<th>Category and agent</th>
<th>Drug mechanism</th>
<th>Approved cancer indication</th>
<th>Biomarker status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Optimal:</strong> use is strongly directed by biomarkers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trastuzumab (Herceptin®)</td>
<td>mAb against HER2</td>
<td>Metastatic breast cancer</td>
<td>HER2 positive</td>
</tr>
<tr>
<td>Rituximab (MabThera®)</td>
<td>Chimeric monoclonal IgG1 antibody against CD20</td>
<td>NHL</td>
<td>CD20 positive</td>
</tr>
<tr>
<td>Gefitinib (Iressa®)</td>
<td>TKI: EGFR</td>
<td>NSCLC</td>
<td>EGFR mutant</td>
</tr>
<tr>
<td><strong>Intermediate:</strong> use is directed to some degree according to a biomarker</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imatinib (Glivec®)</td>
<td>TKI: KIT, PDGFR</td>
<td>GIST</td>
<td>KIT positive</td>
</tr>
<tr>
<td>Erlotinib (Tarceva®)</td>
<td>TKI: EGFR</td>
<td>NSCLC</td>
<td>EGFR-IHC positive</td>
</tr>
<tr>
<td>Cetuximab (Erbitux®)</td>
<td>Chimeric monoclonal IgG1 antibody against EGFR</td>
<td>Metastatic colorectal cancer</td>
<td>EGFR-IHC positive, KRAS wild type</td>
</tr>
<tr>
<td>Panitumumab (Vectibix®)</td>
<td>Human IgG2 mAb against EGFR</td>
<td>Metastatic colorectal cancer</td>
<td>EGFR-IHC positive, KRAS wild type</td>
</tr>
<tr>
<td>Lapatinib (Tyverb®)</td>
<td>TKI: EGFR/HER2</td>
<td>Advanced/metastatic breast cancer</td>
<td>HER2 positive</td>
</tr>
<tr>
<td><strong>Suboptimal:</strong> use not directed by a biomarker</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bevacizumab (Avastin®)</td>
<td>mAb to VEGF</td>
<td>Metastatic carcinoma of the colon or rectum; metastatic breast cancer; unresectable advanced, metastatic or recurrent NSCLC; advanced and/or metastatic renal cell cancer</td>
<td>–</td>
</tr>
<tr>
<td>Sunitinib (Sutent®)</td>
<td>TKI: PDGFR, VEGF receptor, KIT, FLT3, CSF-1R, RET</td>
<td>Unresectable and/or metastatic malignant GIST (after failure of imatinib)</td>
<td>–</td>
</tr>
<tr>
<td>Sorafenib (Nexavar®)</td>
<td>TKI: EGFR</td>
<td>Hepatocellular carcinoma; advanced renal cell carcinoma</td>
<td>–</td>
</tr>
<tr>
<td>Everolimus (Afinitor®)</td>
<td>mTOR inhibitor</td>
<td>Advanced renal cell carcinoma</td>
<td>–</td>
</tr>
<tr>
<td>Temsirolimus (Torisel®)</td>
<td>mTOR inhibitor</td>
<td>Advanced renal cell carcinoma; relapsed and/or refractory mantle cell lymphoma</td>
<td>–</td>
</tr>
</tbody>
</table>

Please see Summary of Product Characteristics for each product for full prescribing information.

HER2, human epidermal growth factor receptor-2; NHL, non-Hodgkin’s lymphoma; TKI, tyrosine kinase inhibitor; EGFR, endothelial growth factor receptor; NSCLC, non-small-cell lung cancer; PDGFR, platelet-derived growth factor receptor; GIST, gastrointestinal stromal tumour; IHC, immunohistochemistry; KRAS, Kirsten rat sarcoma 2 viral oncogene homologue gene; VEGF, vascular endothelial growth factor; FLT3, Fms-like tyrosine kinase 3; CSF-1R, colony-stimulating factor type 1 receptor; RET, glial cell line-derived neurotrophic factor receptor; mTOR, mammalian target of rapamycin.
disclosure

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references

55. Halak M, Fingerle-Rowe W, Fink AF et al. First-line treatment with fludarabine (F), cyclophosphamide (C), and rituximab (R) (FCR) improves overall survival (OS) in previously untreated patients (pts) with advanced chronic lymphocytic leukemia (CLL): results of a randomized phase III trial on behalf of an international group of investigators and the German CLL Study Group. Blood 2009; 114: (Abstr 535).


119. Centre d’épidémiologie sur les causes médicales de décès (CépiDc) / Institut National de la Santé et de la Recherche Médicale (INSERM) Database. 2005.


