Targeted therapies in lung cancer

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introduction

The quality-of-life and overall survival are improved by platinum-based chemotherapy in patients with localized or disseminated small-cell lung cancer (SCLC) [1, 2]. In non-small-cell lung cancer (NSCLC), platinum-based combinations with new agents (vinorelbine, gemcitabine, taxanes) improve survival in both resected and advanced NSCLC patients [3–6]. Nevertheless, a therapeutic plateau has been reached with classical cytotoxic agents. Recent advances in cancer biology have led to the identification of new targets in neoplastic cells. Hence, targeting agents have been developed, opening new perspectives in lung cancer treatment.

In this article, we review the main targeted therapies in lung cancer by the proposed classification of different cancer cell pathways [7]. In particular, we will focus on cell growth pathways, programmed cell death (apoptosis), neo-angiogenic factors, local invasion and distant metastatic processes.

cancer cell growth pathways

Schematically, cell growth signalling can be divided into three distinct, though closely connected parts. First there are the upstream growth factors and their receptors at the cell membrane. From there, molecular mechanisms of signal transduction and intracellular messengers form a relay informing the nucleus of the given stimulus. Finally, an effector pathway leads the cell eventually to cell division and proliferation.

receptors: ErbB family

In NSCLC, the epidermal growth factor receptor (EGFR or ErbB1) is the most closely studied transmembrane tyrosine kinase receptor of the ErbB family, which also includes ErbB2 (or HER-2/neu), ErbB3 (or HER-3) and ErbB4 (or HER-4). Immunohistochemically, EGFR and HER-2 expression has been reported in 45–90 and 20–30% of patients, respectively, leading to the clinical development of tyrosine kinase inhibitors (TKIs) and targeted antibodies [8].

Phase II studies of erlotinib and gefitinib, two extensively studied EGFR TKIs, have shown response rates ranging from 10 to 25% in pretreated advanced NSCLC patients [9–11]. Additional analysis suggested that female patients, patients with a histology of adenocarcinoma, Japanese patients and non-smokers had higher response rates. Both single agents were compared with a placebo arm in advanced, pretreated NSCLC in two randomized phase III trials. In the BR-21 trial, erlotinib (150 mg/d) was reported to significantly increase median (6.7 versus 4.7 months) and 1-year survival (31 versus 21%) compared with the placebo arm [12]. Surprisingly, the ISEL study comparing gefitinib with placebo in 1692 patients failed to demonstrate an improvement in median survival (5.6 versus 5.1 months, P = 0.11), even in patients with adenocarcinoma (6.3 versus 5.4 months, P = 0.07) [13]. The lack of significant therapeutic efficacy in the ISEL study raises some concerns about the choice of the gefitinib dose (250 mg/d) as erlotinib was used at 150 mg/d, which corresponds to ~600–700 mg/d of gefitinib. Finally, combined with chemotherapy, neither of these two EGFR TKIs demonstrated superiority to chemotherapy alone in terms of survival in four large randomized studies [14–17].

Efforts have been made to link quantitative or qualitative assessments of the target, EGFR, to the efficacy of its inhibitors. In particular, the research community has shown great interest in EGFR mutations since it has been shown that these should be able to predict response to gefitinib [18].

Two comments should be made. First, EGFR mutations can mimic the clinical predictive factors, since mutations are more frequent in never-smokers, adenocarcinomas with or without bronchio-alveolar carcinoma (BAC) features, in patients of East-Asian ethnicity, and in females, all known to better respond to EGFR TKIs [19, 20]. Secondly, survival benefit with erlotinib in the BR-21 trial was not confined to objective responders, and a large proportion of patients had either minor response or stable disease [12]. One of the major effects of EGFR inhibitors is, in fact, to reduce proliferation, and survival should be considered as a better endpoint to evaluate predictive factors rather than the objective response rate. In the BR-21 trial, one of the largest published trials with EGFR status subset analysis, the survival after erlotinib treatment was not influenced by the status of EGFR expression, mutation, or the number of EGFR copies in a multivariate analysis [21]. Other studies reported a high response rate when EGFR TKIs were given in patients with EGFR-mutated tumours or with a high EGFR gene copy number [22, 23]. Indeed, erlotinib was given as a front-line treatment in 38 patients with EGFR-mutated NSCLC in an overall survival at 1 year of 82% [24]. Several critical points should be kept in mind when interpreting these results: (i) EGFR mutations seem to be a marker of good prognosis since in the placebo arm of BR-21, patients with mutations demonstrated a longer median survival time than patients with wild-type EGFR (9.1 versus 3.5 months,
respectively); (ii) EGFR mutations may select a subset of patients with NSCLC responding better to treatment, whether EGFR TKIs or chemotherapy; (iii) some EGFR mutations confer strong sensitivity to EGFR TKIs (exon 19 mutations) whereas other mutations confer modest/mild sensitivity (exon 21) or a resistant phenotype (T790M); (iv) finally, technical issues may limit the value of biomarker studies [21, 25].

In vitro, EGFR monoclonal antibodies such as cetuximab can inhibit cell lines resistant to EGFR TKIs, providing an interesting alternative approach to specific blocking of EGFR function [26]. As a single agent, cetuximab showed modest activity in pre-treated patients [27]. Two single-arm phase II trials testing cetuximab in combination with a platinum-based doublet in previously untreated patients showed responses in the range of 26–29%, with median survival times of 10–11 months [28, 29]. Randomized phase II and phase III studies are ongoing.

EGFR dimerizes and becomes functionally active after binding to the ligand. The preferred EGFR partner for dimerization is HER-2, which has been reported to have a negative prognostic value in NSCLC [30, 31]. Trastuzumab, a monoclonal antibody directed against HER-2, has been evaluated in NSCLC. It has no significant clinical activity when given either as a single agent or in combination with platinum-based chemotherapy, even in NSCLC with overexpression of HER-2 [32–35]. Mutation of the HER-2 receptor has been described in NSCLC and may be relevant to identify tumours sensitive to trastuzumab [36]. Dual HER-1/2 or pan-HER targeting of advanced NSCLC is under investigation (HKI-272, CI1033).

signal transduction messengers
Many molecules are involved in cell transduction pathways, each of them being a potential target. We discuss here the most studied or most promising drugs.

farnesyl transferase inhibitors (FTIs)
The enzyme farnesyl transferase is involved in the posttranslational modification of ras proteins by linking covalently a farnesyl group onto ras. After farnesylation, ras can be translocated to the cell membrane and then activate signal transduction pathways involved in proliferation and inhibition of apoptosis. FTIs aim to block farnesylation and ras signalling. However, given that more than 100 molecules can be processed by farnesyl transferase, FTIs could have other unknown targets. Nevertheless, FTIs have been evaluated in NSCLC where ras is mutated in ~20% of patients. Tipifarnib (R115777) showed no significant anti-tumour activity as a single agent either in untreated advanced NSCLC or in sensitive-relapse SCLC [37, 38], whereas lonafarnib, in combination with chemotherapy, seemed to restore sensitivity to taxanes [39]. The latter results need to be confirmed in further studies.

targeting mTOR
The serine/threonine kinase AKT and its downstream receptor mediator called mammalian target of rapamycin (mTOR) are activated in >50% of lung carcinomas [40]. Furthermore, AKT activity is frequent in pre-neoplastic lesions suggesting that the activation of this pathway is a very early event in lung oncogenesis. In vitro studies have shown that in situ pre-neoplasia can be reversed after inhibition of the AKT pathway [41]. These and other data suggest a possible synergy with either classical chemotherapy [42] or other targeted agents [43–45], which raises great expectations for possible applications in preventive chemotherapy or even in advanced stages.

mTOR inhibitors are a class of signal transduction inhibitors with anti-cancer activity that were initially developed as immunosuppressive agents. The mTOR inhibitor rapamycin, a macrolyclic lactone produced by Streptomyces hygroscopicus, was the first inhibitor to be used in the clinical setting. Rapamycin (sirolimus, Wyeth) and its derivatives temsirolimus (CCI-779, Wyeth), everolimus (RAD-001, Novartis Pharma AG) and AP-23573 (Ariad Pharmaceuticals) are currently being evaluated in cancer clinical trials. These agents bind to immunophilin FKMP-12 to form a complex that interacts with the mTOR kinase thereby blocking its activity. This in turn results in the inhibition of key transduction pathways including those regulated by p70s6 kinase and the eukaryotic initiation factor 4E-binding protein (4E-BP1), leading eventually to cell cycle arrest in G1. The phosphorylation of p70s6 kinase is thought to be closely associated with response to treatment rather than PTEN or pAKT status [46]. No major toxicity was seen during phase I studies [47] and lung trials are ongoing. EGFR TKIs and mTOR inhibitors combinations are currently being evaluated [48].

retinoids
Retinoids, including vitamin A (retinol) and its analogues, are critical for a variety of biologic functions, in particular epithelial differentiation [16]. RAR and RXR are the two known families of retinoid nuclear receptors. In each family, there are several isoforms that control both distinctive and common target genes. Retinoids have been extensively studied in lung cancer chemoprevention, with controversial results, since they may actually enhance lung cancer incidence in smokers [49, 50]. Bexaroten, a selective RXR inhibitor, has shown promising efficacy with a tolerable toxicity profile [51]. In two large phase III studies, however, it was not shown to improve overall survival in chemo-naïve patients with advanced NSCLC, in combination with chemotherapy [52, 53]. The synthetic retinoid fenretinide [N-(4-hydroxyphenyl)retinamide, 4-HPR] has been evaluated in patients with pre-treated SCLC with no objective responses [54]. Despite the strong rationale for their use, retinoid treatment in lung cancer still needs further clinical evaluation. As smoking could strongly influence the global effect of retinoids or carotenoids, future studies on the effect of these products should include stratification by smoking status [55].

protein kinase C (PKC)–α
PKC–α, a member of the family of phospholipid-dependent, cytoplasmic serine–threonine kinases, has increased expression in tumour compared with normal tissue and has been implicated in malignant transformation and proliferation [56]. Preclinical evidence of anti-tumor activity by inhibition of PKC–α was demonstrated in a lung cancer model in a variety of
in vitro and in vivo experiments [57]. LY900003 (aprincosarn, ISIS 3521) is the sodium salt of a 20mer phosphorothioate oligonucleotide that hybridizes to the 3’-untranslated region of human PKC-mRNA and inhibits its expression through RNase-mediated cleavage of hybridized PKC-mRNA. In untreated NSCLC patients, LY900003 has been tested in addition to a cisplatin-based chemotherapy [58]. The toxicity of the combination was very similar to that generally expected for the standard cisplatin regimen. In a randomized phase III study, LY900003 did not prolong survival in advanced NSCLC when combined with carboplatin/paclitaxel [59] or cisplatin–gemcitabine [60]. There are several possible explanations for the failure of this agent to improve survival: inadequate dose, inadequate dosing or inadequate target. The immature technology of antisense oligonucleotides may be partially responsible for the negative results.

cell cycle
After DNA damage, the cell cycle process is a critical regulator of proliferation and growth. The progression of a cell through the cell cycle is promoted by a number of cyclin-dependent kinases (CDKs) which, when complexed with specific regulatory proteins called cyclins, drive the cell forward through the cell cycle. Cyclin-dependent kinase inhibitors (CDKIs) are CDK counterparts that serve as negative regulators of the cell cycle. The CDKIs include a promising set of anticancer targets. Flavopiridol was the first pan-CDK inhibitor to enter clinical trials. No objective response was reported in the first phase II trial in 20 previously untreated advanced NSCLC patients [61]. Preclinical data suggest that flavopiridol could enhance the activity of cytotoxic drugs such as cisplatin and etoposide [62]. In a phase I trial, it was safely combined with cisplatin, but it displayed high toxicity with carboplatin and further clinical assessments are awaited [63]. Roscovitine, another CDK inhibitor, is currently being evaluated in combination with gemcitabine and cisplatin [64].
aapoptosis
The ability to resist and bypass programmed cell death, a process that is normally induced as a response to some external physiological signal or internal stress, is one of the main features of cancer cells. Apoptotic effectors are interesting candidates as anticancer targets.

targeting Bcl2
The Bcl-2 family consists of a homologous network of genes that regulate apoptosis or programmed cell death. Bcl-2 protects mitochondrial membrane activity, thereby preventing the release of cytochrome c and the formation of the apoptosome and caspase-9 activation. Thus, it is an anti-apoptotic protein. The mutation and overexpression of Bcl-2 by a specific translocation [(t(14,18)) is a major oncogenic event in follicular lymphoma and is possibly an important prognostic factor in large B cell lymphoma [65]. Surprisingly, according to a recent review, Bcl-2 expression could confer a favourable prognosis to patients with NSCLC [66].

The only clinical trials involving this pathway in lung cancer concern SCLC. G3139, or Genasense, is an 18-base antisense phosphorothioate oligonucleotide complementary to the bcl-2 mRNA in the region encoding the first six amino acids of Bcl-2. Twelve patients with resistant SCLC were treated with an association of G3139 and paclitaxel [67]. There was no objective response, but two patients had stable disease and no major toxicity was observed. Therefore, a seemingly efficient tool exists, but the target may not give a sufficient survival advantage to procure any significant clinical improvement.

Proteasome inhibitors. The 26S proteasome degrades ubiquitinated proteins, and it plays a central role in the regulation of a wide variety of proteins involved in cell cycle regulation and apoptosis, such as cyclins, CDKs and CDKIs, c-myc or nuclear factor kappa B.

Bortezomib is a proteasome inhibitor approved by the Food and Drug Administration (FDA) for use in the treatment of relapsed and refractory multiple myeloma patients. Proteasome inhibition with bortezomib has also shown activity and manageable toxicity in mantle cell and other lymphomas, and in solid malignancies, including NSCLC [68, 69]. It has been tested in 155 pre-treated patients with advanced NSCLC in a randomized phase II study [70]. Bortezomib alone induced a partial response in 8% of patients, while in combination with docetaxel, partial response was reported in 9%. A similar study with pemetrexed has been conducted, and a single agent first-line study is ongoing.

Death receptors. Death Receptors belong to the Tumor Necrosis Factor Receptor (TNFR) gene superfamily. They contain a homologous cytoplasmic sequence termed the ‘death domain’. Adapter-molecules like FADD, TRADD or DAXX themselves contain death domains so that they can interact with the death receptors and transmit the apoptotic signal to the death-machinery when death receptors are activated. AMG 951 consists of amino acids 114–281 of the native Apo2L/TRAIL. AMG 951 triggers apoptosis through activation of two specific receptors that belong to the TNFR superfamily; death receptor 4 (DR4) and death receptor 5 (DR5) [71]. In NSCLC, AMG 951 is currently evaluated in association with bevacizumab, paclitaxel and carboplatin.

angiogenesis and invasive potential
Targeting angiogenesis. When the size of a tumour reaches 2–3 mm in diameter, further tumour growth needs a vascular supply [72]. Angiogenesis is therefore a critical step toward local and systemic spread. Although angiogenesis is not a primary oncogenic event, controlling it should be an effective approach against cancer. Like every targeting approach, the problem is how to identify an optimal stage of angiogenesis in which a specific molecule inhibits the turning point of the cancer’s natural history.

A wide range of agents is currently under development. The most studied approach is the vascular endothelial growth factor (VEGF) blockade by monoclonal antibodies. Bevacizumab is a recombinant, humanized, monoclonal, anti-VEGF antibody composed of human IgG1 framework regions and antigen-binding complementarity-regions from a murine antibody (A 4 6 1) that blocks the binding of human VEGF to its receptors. A randomized, multi-centre, phase II trial was conducted
involving a total of 99 patients with newly diagnosed stage IIIB (with pleural effusion), stage IV or recurrent NSCLC. Patients were randomized to receive carboplatin (AUC 6 mg/ml/min) plus paclitaxel (200 mg/m²) chemotherapy every 3 weeks, or carboplatin + paclitaxel chemotherapy with bevacizumab 7.5 or 15 mg/kg every 3 weeks [73]. Principal endpoints were time-to-disease progression and best tumour response rates. Bevacizumab (15 mg/kg) plus carboplatin–paclitaxel increased the response rate (31.4 versus 18.8%) and median time to progression (7.4 versus 4.2 months) compared with chemotherapy alone. A modest increase in median survival (17.7 versus 14.9 months) was noted for the highest dose of bevacizumab. Perhaps most importantly for clinical practice, adverse events such as hypertension, thrombosis, proteinuria and epistaxis did not exceed grade II. The main tolerability concern was the occurrence of bleeding episodes. Indeed, haemoptysis/haematemesis occurred in 5 patients (of whom five in the 7.5 mg/kg group) who died, representing an overall incidence of 9%. Nevertheless, the incidence was 34% in squamous cell histology and only 4% in other histologies. Further, all of the six cases were tumour related. Finally, cavitation, necrosis and squamous cell histology were found to be possible risk factors.

Taken together, these results allowed the pursuit of the schedule in a phase II/III trial [74]. The main differences from the first trial were the exclusion of squamous cell histology and the exclusion of a thrombotic or haemorrhagic history including haemoptysis disorders. Patients with brain metastases were also excluded. Eight hundred and forty-two patients were randomly assigned to standard treatment or standard treatment plus bevacizumab 15 mg/kg every 3 weeks. The primary end point was overall survival. Median survival was significantly longer in the bevacizumab group than in the standard group (12.3 months versus 10.3 months). Response rate (35 versus 15%, $P < 0.001$) and progression-free survival (6.2 versus 4.5 months, $P < 0.001$) were also better in the triple-therapy group. Concerning adverse events, there were significantly more haemorrhages (4.4 versus 0.7% with more than grade II, $P < 0.001$) and hypertension (7 versus 0.7% with more than grade II, $P < 0.001$) in the bevacizumab group. This study led to bevacizumab approval in the USA at the end of 2006. Roche recently announced the positive results of the European counterpart bevacizumab trial (gemcitabine/cisplatin with or without bevacizumab) (press release 21 February 21 2007). Both tested doses of bevacizumab (15 or 7.5 mg/kg every 3 weeks) improved progression-free survival compared with chemotherapy alone. Thus, this association should become the next standard of first-line therapy in non-squamous NSCLC.

Various VEGF receptor (VEGFR) TKIs have been evaluated in phase II clinical trials. For example, PTK/ZK is a potent and orally active inhibitor of VEGFR tyrosine kinase, with higher specificity for the KDR/flk-1 receptor tyrosine kinase than the fll-1, fll-4, platelet-derived growth factor (PDGF) receptor tyrosine kinase and c-kit tyrosine kinase. Thus, all known receptors of VEGF are inhibited by PTK/ZK. The treatment primarily reduces the number of tumour microvessels, accompanied by haemodynamic dilatation of the remaining vessels [75]. In two phase III studies in patients with metastatic colorectal cancer receiving chemotherapy with FOLFOX4 and concurrent PTK/ZK or a placebo, progression-free survival was not improved in the PTK/ZK arm either in the first-line or second-line setting [76, 77]. There is still a lack of surrogate markers predicting response even if elevated lactate dehydrogenase (LDH) and plasma VEGF-A could be relevant [78, 79]. In 110 relapsed or progressive NSCLC (including SCC) after first-line treatment with cisplatinum-based chemotherapy, PTK/ZK given once a day (55 pts) or twice daily (55 pts) was associated with pulmonary haemorrhages in 3 patients, grade 3/4 hypertension in 13 and grade 3/4 thrombosis in 4 patients [80]. In the first cohort (once a day), PTK/ZK induced a 2% response rate and a 33% stabilization rate at 12 weeks.

ZD6474 is an inhibitor of VEGFR-2, VEGFR-3 and HER1 (EGFR), albeit to a lesser extent. In a phase II trial, 127 patients with pre-treated NSCLC were randomized to three arms: docetaxel plus ZD6474 100 mg/d, ZD6474 300 mg/d or a placebo. Common adverse events included diarrhoea, rash and asymptomatic QTc prolongation. Results suggested efficacy with a progression-free survival of 19 versus 17 versus 12 weeks respectively. A confirmatory phase III trial is ongoing. In a Japanese NSCLC population, ZD6474 was given as a single agent at three different doses (100, 200 or 300 mg/d) after one or two platinum-based chemotherapy regimens [45]. A response rate of 13% was seen irrespective of the dose level, but the median duration of treatment was longer in the 300 mg/d arm. Grade 3/4 toxicities were more frequent in the 300 mg/d arm (67 versus 39 and 29% in the 200 mg/d and 100 mg/d arms). QTc-related events were reported in 72% of the patients at the level of 300 mg/d, 61% of the patients at 200 mg/d and 29% of the patients at 100 mg/d. ZD6474 (300 mg/d) was compared with gefitinib (250 mg/d) in 168 Caucasian NSCLC patients after failure of one–two line platinum-based chemotherapy. In this randomized phase II trial, median progression-free survival was significantly longer in the ZD6474 arm (11 versus 8.1 weeks, $P = 0.025$). In 37 progressive patients in the gefitinib arm, ZD6474 achieved a disease control >8 weeks in 16 patients, whereas only 7 out of 29 ZD6474 patients that switched to gefitinib achieved a disease control >8 weeks (46).

Sorafenib (BAY 43-9006) is a potent inhibitor of RAF-1, a key enzyme in the RAS/RAF/MEK/ERK signalling pathway, and an inhibitor of VEGFR-2 and PDGFR-β involved in angiogenesis. Sorafenib is registered for the treatment of patients with renal cell carcinoma who failed prior treatment [81]. As a single agent in 52 pre-treated stage III or IV NSCLC patients, sorafenib did not induce partial response but tumour shrinkage or cavitations were observed in 29% of patients [82]. One patient died of haemoptysis. Median progression-free survival was 2.7 and 5.3 months in patients with stable disease. The most frequent grade 3/4 events were hand–foot skin reaction (10%) and hypertension (4%). These encouraging results led to an ongoing phase III trial evaluating sorafenib as a maintenance treatment after a paclitaxel–carboplatin combination in first-line setting.

Sunitinib (SU11248) inhibits VEGFR1, PDGFR and c-kit, and is currently approved by the FDA for the treatment of renal cell carcinoma and gastrointestinal stromal tumour (GIST). Sunitinib was evaluated in 110 previously-treated NSCLC patients [83]. A first cohort of 63 patients was treated at 50 mg/d for 4 weeks followed by 2 weeks’ rest. Given the notable grade
Table 1. Current status of selected targeted agents in NSCLC

<table>
<thead>
<tr>
<th>Agent</th>
<th>Type</th>
<th>Targets</th>
<th>Phase</th>
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<tbody>
<tr>
<td>Bevacizumab</td>
<td>Ab</td>
<td>VEGF</td>
<td>FDA approved</td>
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<tr>
<td>VEGF trap</td>
<td>Fusion protein</td>
<td>VEGF</td>
<td>Phase II</td>
</tr>
<tr>
<td>PTK787/ZK222584</td>
<td>TKI</td>
<td>VEGFR-1, VEGFR-2, PDGFR</td>
<td>Phase II</td>
</tr>
<tr>
<td>(Vatalanib)</td>
<td>TKI</td>
<td>VEGFR, PDGFR, Flt-3, c-kit</td>
<td>Phase II</td>
</tr>
<tr>
<td>SU 11248 (Sunitinib)</td>
<td>TKI</td>
<td>VEGFR-2, PDGFR (and RAP*)</td>
<td>Phase III</td>
</tr>
<tr>
<td>BAY 43-9006 (Sorafenib)</td>
<td>TKI</td>
<td>VEGFR-2, VEGFR-3, EGFR</td>
<td>Phase III</td>
</tr>
<tr>
<td>ZD6474</td>
<td>TKI</td>
<td>EGFR</td>
<td>Phase II</td>
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<td>Erlotinib</td>
<td>TKI</td>
<td>HER2</td>
<td>Phase II</td>
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<td>Gefitinib</td>
<td>TKI</td>
<td>EGFR, HER2</td>
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<td>EGFR</td>
<td>Phase III</td>
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<td>Ab</td>
<td>HER2</td>
<td>Phase II</td>
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<tr>
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<td>TKI</td>
<td>EGFR, HER2</td>
<td>Phase II</td>
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<tr>
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<td>Macrolide derivative</td>
<td>mTOR</td>
<td>Phase II</td>
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<tr>
<td>RAD001</td>
<td>Macrolide derivative</td>
<td>mTOR</td>
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<tr>
<td>Bortezomib</td>
<td>boronic acid analogue</td>
<td>Proteasome</td>
<td>Phase II</td>
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<tr>
<td>AMG951</td>
<td>Portion of the native Apo2L/TRAIL</td>
<td>Death receptors DR4 and DR5</td>
<td>Phase Ib/II</td>
</tr>
</tbody>
</table>

Ab, antibody; FP, fusion protein; TKI, tyrosine kinase inhibitors.

3/4 toxicities (asthenia in 27%, myalgia in 18%, nausea 10%), a subsequent cohort was treated at 37.5 mg/d continuously. This resulted in a reduction of grade 3/4 asthenia, myalgia and nausea (3, 3, 0% respectively), an increase of grade 3/4 neutropenia (11 versus 3% in the first cohort), and a stable incidence of grade 3 hypertension (5%). Lethal haemorrhages were reported in three patients (two pulmonary and one cerebral haemorrhage). In the first cohort, 11% partial response and 44% stable disease were observed (27% of the patients were not evaluated). Sunitinib activity is currently being evaluated in consolidation after first-line chemotherapy in stage IIIB–IV NSCLC.

A phase I/II trial evaluated the concomitant association of bevacizumab 15 mg/kg every 3 weeks with the HER-1 receptor tyrosine kinase inhibitor erlotinib at 150 mg/day [84]. The eligible population was non-squamous NSCLC with more than one prior chemotherapy. Forty patients were enrolled. Twenty percent showed partial response and 65% had stable disease. The median overall survival was 12.6 months with progression-free survival of 6.2 months. These results need to be confirmed, but an additive or synergistic effect seems to exist in selected tumours.

Targeting metalloproteinases. The metalloproteinases (MMPs) are a family of zinc-dependent neutral endopeptidases that are capable of degrading virtually all of the components of the extracellular matrix. These proteases, which are synthesized by connective tissue cells, are important for the remodelling of the extracellular matrix that accompanies physiologic processes as well as tumour growth, invasion and metastasis [85]. Hofman et al. showed, using DNA-microarrays, reverse transcriptase–polymerase chain reaction (RT–PCR) and immunohistology, that MMP-12 expression significantly correlates with local recurrence and metastasis [86]. The 3-year relapse-free rate was 32% in patients with high MMP-12 and 82% in patients with low MMP-12 expression. The relative risk for tumour relapse in all R0-resected patients was 4.8-fold higher than in patients with high expression. Gouyer et al. confirmed the importance of metalloproteinase expression to predict relapse after surgical resection. The tissue inhibitor of metalloproteinase-1 was an independent predictor of prognosis and was not linked to other prognostic factors such as stage [87]. Despite the great interest of the target, all clinical applications have so far proved disappointing.

The first phase III trial was published in 2002 and evaluated the role of marimastat as maintenance therapy in SCLC patients with partial or complete response to chemotherapy [88]. No overall survival difference was detected among the 532 eligible patients. Grade 3/4 musculoskeletal toxicities were observed in 18% of the patients, the dose was reduced in 33% of the patients and marimastat stopped in 32% of the patients. Prinomastat is a potent inhibitor of gelatinase A (MMP-2), stromelysin-1 (MMP-3) and collagenase-3 (MMP-13). Prinomastat was evaluated in 362 chemotherapy-naïve patients with advanced NSCLC who received gemcitabine/cisplatin +/- prinomastat [89]. The results were all negative. In another trial, 774 chemotherapy-naïve patients with advanced NSCLC were randomized to received paclitaxel/carboplatin +/- BMS-275291 [90]. The toxicity was significantly higher in the BMS-275291 arm and no improved survival was observed. It is now recognized that the family of metalloproteinases includes more than 20 enzymes. Like other targeted therapies, beyond the pharmacokinetic data, it seems necessary to clarify the precise molecular target of interest, and also to specify which targets are really inhibited by the candidate compounds.

Research into metalloproteinases remains active and several studies involving new compounds are ongoing (CP-471.358 from Pfizer [91], BAY 12-9566 from Bayer [92], MMI 270 from Novartis [93], Metastat [94]).

Conclusion

In their synthesis of cancer biology, Hanahan and Weinberg listed six hallmarks of cancer. More than 500 molecular targeted therapy products are currently being developed,
covering the entire range of those six hallmarks. In lung cancer, two targeted therapies are have already been approved by the FDA in advanced NSCLC: the EGFR TKI erlotinib and the anti-angiogenic bevacizumab. Orally available anti-angiogenic compounds and pan-HER inhibitors may be the next generation of approved agents given their activity in advanced NSCLC. The field of predictive markers has to be actively clarified given the significant toxicities and costs of those new agents. Adjuvant trials integrating these agents are also awaited in order to potentially cure more resectable patients. Few studies have been conducted in patients with SCLC, which is sometimes considered as an orphan disease whereas it still concerns nearly 15% of our patients.

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