Targeted therapies in small cell lung cancer: a review

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***Abstract*:** Small cell lung cancer (SCLC) is an aggressive form of lung cancer that is characterized by a rapid doubling time, early onset of dissemination and high sensitivity to chemotherapy. Despite the potential for cure in patients with limited disease with concurrent chemoradiation and an initial good response to chemotherapy in extensive disease, there is a high chance of disease relapse with an overall poor median survival for both stages. With increasing translational research and a better understanding of the molecular basis of cancer, a number of molecular targets have been identified in various preclinical studies. This review summarizes potentially viable targets and new agents that have been developed and employed in recent, ongoing and future clinical trials to attempt to improve clinical outcomes in this disease.

***Keywords*:** small cell lung cancer (SCLC), targeted therapies, cell signalling inhibitors, angiogenesis inhibitors, apoptosis promoters, multidrug resistance inhibitors, vaccines, BH3 mimetics, MET inhibitors

Introduction

Small cell lung cancer (SCLC) accounts for about 15% of all cases of lung cancer worldwide, is characterized by rapid doubling time, early onset dissemination and high sensitivity to chemotherapy. Patients are staged as limited disease (LD) or extensive disease (ED) based on the anatomical extent as proposed originally by the Veterans Administration Lung Study Group (VALG) [Zelen, 1973]. In the VALG staging system, LD is defined as disease confined to one hemithorax, which can be safely encompassed within a radiation field. All other patients are considered to have ED. Patients with LD have a median survival time of 16–24 months when treated with chemotherapy and concurrent thoracic radiation [Jackman and Johnson, 2005; Turrisi *et al.* 1999]. Chemotherapy remains the standard therapeutic modality for ED, with a median survival of 7–12 months [Jackman and Johnson, 2005]. Although radiotherapy is given with palliative intent in these patients, prophylactic cranial irradiation (PCI) has recently been shown to both decrease the risk of developing brain metastases and to improve disease-free survival (DFS) and overall survival (OS) [Sher *et al.* 2008; Slotman *et al.* 2007]. However, prognosis for patients with SCLC has changed little over the last few decades and there remains an unmet need for more effective treatments.

In recent years, there has been an increase in effort to understand the molecular biology of SCLC and to exploit this knowledge for therapeutic control through the development of so-called targeted therapies. In common with other types of cancer, aberrantly expressed proteins and disordered signaling pathways have been identified that regulate various cellular processes including proliferation, the cell cycle, apoptosis and angiogenesis. There is also scope to activate the immune cascades towards SCLC cells. The goals of targeted therapies in SCLC are to either enhance the efficacy of standard chemotherapy and chemoradiotherapy by concurrent administration or as salvage therapy after failure of standard therapy. With respect to the latter, patients with SCLC are frequently categorized as resistant relapse (within 90 days since completion of chemotherapy) or sensitive relapse (after 90 days since completion of chemotherapy). These categories were defined in the context of second-line chemotherapy and it is not clear how relevant they are in the context of novel targeted therapies. The other setting for targeted therapy development is maintenance therapy. This is most attractive because response rates to chemotherapy in SCLC are high, and so less toxic, orally administered treatments to maintain a complete or partial response and prevent or

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Table 1. Novel targeted agents investigated for use in treatment of small cell lung cancer.

Target	Agent	Manufacturer	Clinical trial phase
Inhibitors of cell signalling pathways controlling proliferation			
c-kit	Imatinib	Novartis	II
Src	AZD0530	AstraZeneca	II
Src	Dasatinib	Bristol-Myers Squibb	II
EGFR	Gefitinib	AstraZeneca	II
Farnesyltranferase	Tipifarnib	Johnson & Johnson	II
mTOR	Temsirolimus	Wyeth	II
mTOR	Everolimus	Novartis	I, II
IGFR	IMC-A12	ImClone Systems	I
IGFR	CP-751, 871	Pfizer	I
IGFR	AMG 479	Amgen	I, II
c-MET	AMG 102	Amgen	I, II
Hedgehog	GDC-0449	Genentech	I, II
Hedgehog	IPI-926	Infinity Pharmaceuticals	I
Inhibitors of angiogenesis			
VEGF-A	Bevacizumab	Genentech	II
VEGFR-1, 2, 3	Cediranib	AstraZeneca	II
VEGFR, EGFR	Vandetanib	AstraZeneca	II
VEGFR, PDGFR, Raf-1	Sorafenib	Bayer Healthcare	I, II
	Thalidomide	Generic	II, III
VEGFR, PDGFR, FLT-3, RET, KIT	Sunitinib	Pfizer	I, II
VEGF-A, B	Aflibercept	Sanofi-Aventis	II
MMPIs	Marimastat	British Biotech	II, III
	Tanomastat	Bayer Healthcare	II, III
Apoptosis promoters			
Bcl-2	Oblimersen	Genta Inc.	II
Bcl-2	AT-101 (R-(-) gossypol)	Ascenta	I, II
Bcl-2, Mcl-1, Bcl-w, Bcl-XL, A-1	Obatoclax mesylate	Gemin X Pharmaceuticals	I, II
Bcl-2, Bcl-w, Bcl-XL	ABT-263	Abbott Laboratories	I
26S proteasome	Bortezomib	Janssen-Cilag	II
Plk 1 serine / threonine kinase	PIK1 Inhibitor BI 2536	Boehringer Ingelheim	II
HDAC	Vorinostat	Merck & Co Inc	I, II
HDAC	Belinostat	Curagen & Topotarget	I
HDAC	Entinostat	Syndax Pharmaceuticals	I
Immune conjugates and vaccines			
CD56	BB-10901	British Biotech	II
GD3	BEC2/bCG adjuvant vaccine	ImClone Systems	III
p53	Autologous dendritic cell-adenovirus	Introgen Therapeutics	II
Multidrug resistance			
P-glycoprotein, MDR-1	Biricodar	Vertex Pharmaceuticals	II

c-kit, c-kit cytokine receptor, c-MET, c-MET receptor tyrosine kinase, EGFR, epidermal growth factor receptor; FLT-3, FMS-like tyrosine kinase 3; HDAC, histone deacetylase; IGFR, insulin-like growth factor receptor; KIT, c-kit oncogene product; MMMPIs, matrix metalloproteinases; mTOR, mammaliam target of rapamycin; PDGFR, platelet-derived growth factor receptor; Plk 1, polo-like kinase 1; Raf-1, Raf-1 protein kinase; RET, RET proto-oncogene; Src, Src tyrosine kinase; VEGF(R), vascular endothelial growth factor (receptor).

delay relapse would theoretically be of major potential benefit. Table 1 summarizes novel agents of interest for treatment of SCLC. Here, we summarize progress to date with these agents and emerging areas for future studies.

Targeting cell-signaling pathways controlling proliferation

Several targeted agents designed to inhibit critical pathways implicated in cellular proliferation are now licensed for the treatment of various haematological and solid tumours. These include imatinib for chronic myeloid leukaemia and gastrointestinal stromal tumours (GIST) and the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI), gefitinib and erlotinib, for non-small cell lung cancer (NSCLC) [Mok *et al.* 2009; Druker *et al.* 2006; Shepherd *et al.* 2005; Demetri *et al.* 2002]. Despite these successes, results in SCLC have been disappointing.

c-Kit receptor tyrosine kinase

Imatinib (Gleevec®, Novartis) is a phenylaminodipyrimidine derivative that targets the tyrosine kinase domain of the hybrid bcr-abl kinase

protein as well as c-kit and platelet-derived growth factor receptor (PDGFR). It has proved highly effective for the treatment of chronic myeloid leukaemia and gastrointestinal stromal tumours. Interest in testing imatinib in SCLC came from preclinical findings of overexpression of c-kit in 28–73% of SCLC [Krug *et al.* 2005; Potti *et al.* 2003; Blackhall *et al.* 2003]. However, none of four phase II trials of imatinib demonstrated sufficient efficacy in either overall response rate or survival for further development. The first trial administered imatinib at a dose of 600 mg once daily (OD) in untreated ED or relapsed sensitive SCLC. There were no objective responses, however in a retrospective assessment of c-kit expression only four out of 19 patients had tumours positive for c-kit [Johnson *et al.* 2003]. Two other phase II trials evaluated high-dose imatinib [up to 400 mg twice daily] in relapsed or treatment-refractory SCLC with proven c-kit overexpression as identified by immunohistochemistry (IHC), but there were no objective responses [Krug *et al.* 2005]. A single-arm phase II trial evaluated maintenance imatinib after treatment with irinotecan and cisplatin chemotherapy for c-kit overexpressing ED SCLC again with no evidence for benefit [Schneider *et al.* 2006]. In combination with irinotecan and cisplatin chemotherapy, imatinib also failed to demonstrate improvement in overall response rate and survival. Moreover, the combination was toxic with an increase in grade 3–4 neutropenia and diarrhoea, possibly due to impaired clearance of irinotecan in the presence of imatinib [Johnson *et al.* 2006].

Different theories have been postulated about why imatinib failed to make an impact in the treatment of SCLC despite promising preclinical data. In contrast to GISTs where c-kit is activated by mutation, c-kit overexpressed in SCLC is wild type and so a much higher concentration of imatinib may be needed to achieve inhibition [Krystal *et al.* 2000]. Alternatively since c-kit overexpression is not the sole abnormality in SCLC, targeting a single pathway may be insufficient to appreciably impact on growth inhibition [Rossi *et al.* 2009; Griffiths *et al.* 2008].

Epidermal growth factor receptor tyrosine kinase (EGFR-TK)

Gefitinib (Iressa®, Astra Zeneca), the small-molecule EGFR-TKI, was tested in previously treated chemosensitive SCLC in a small phase II trial. There was no improvement in response rate or survival but of note is that EGFR is not expressed as commonly as in NSCLC and mutations are not seen [Moore *et al.* 2006].

Insulin-like growth factor receptor tyrosine kinase

Insulin-like growth factor-1 (IGF-1) receptor is also a transmembrane tyrosine kinase receptor that is overexpressed in various preclinical cancer models including SCLC cell lines. Insulin-like growth factor (IGF) is also an autocrine growth factor acting on IGF-1 receptors in SCLC [Macaulay *et al.* 1990] and this pathway has been demonstrated to lower the threshold for chemotherapy-induced apoptosis via activation of the phosphatidylinositol 3-kinase (PI3K)-Akt pathway, as well as promote invasion and metastasis [Warshamana-Greene *et al.* 2004]. Agents in this class of novel agents under evaluation include AMG 479 (Amgen Inc), IMC-A12 (cixutumumab, ImClone Systems Inc) and CP 571,871 (Pfizer Inc), and AMG 479 is currently in clinical trial in combination with platinum and etoposide chemotherapy in SCLC [NCT00791154].

c-MET receptor tyrosine kinase

There is also interest in targeting the c-MET receptor that is implicated in proliferation, migration and apoptosis. Mutations in c-MET have been identified in a small proportion of SCLC and c-MET expression is increased at the invasive front in SCLC biopsies. Increased expression of the ligand for c-MET (HGF) is also associated with worse survival. A number of agents have been developed and AMG 102 (Amgen Inc) is currently in trial in SCLC as first-line therapy combined with platinum and etoposide [Ma *et al.* 2003; Maulik *et al.* 2002; Takigawa *et al.* 1997].

In addition to inhibiting proliferative signaling pathways at the level of the cell surface receptor, there are a number of downstream targets.

Farnesyltransferase

Farnesyltransferase is an enzyme that is involved in the covalent addition of a farnesyl group to several G-proteins including ras proteins essential for intracellular signal transduction. Tipifarnib (Zarnestra®, Johnson & Johnson) is a farnesyltransferase inhibitor (FTI) that was investigated in a phase II trial as a monotherapy in patients with sensitive relapsed SCLC. No objective responses were seen, nor was there improvement

in progression free survival (PFS) or median OS and so the trial was terminated early [Heymach *et al.* 2004].

Src kinase

Src kinase is an intracellular signal transducer that is implicated in multiple growth factor receptor signaling cascades. Dasatinib (Sprycel®, Bristol-Myers Squibb) and AZD 0530 (Astra Zeneca) are agents that inhibit src signaling *in vitro* and are currently in phase II evaluation for SCLC. Dasatinib is an oral multikinase inhibitor that inhibits src-family kinases, c-kit, PDGFR-β and bcr-abl proteins. Interest in this agent for SCLC was also sparked by its activity in imatinib-resistant CML. AZD 0530 is an inhibitor of the src and the abl kinase enzymes. A pre-planned interim analysis of the phase II trial evaluating the use of AZD 0530 as a maintenance monotherapy after standard chemotherapy in relapsed chemosensitive ED SCLC has been reported recently. The 12-week PFS rate which was the primary endpoint of the study did not satisfy the predetermined criteria (6/20 compared to the expected 13/20) and therefore enrollment was stopped. Up to 50% of the patients also experienced at least one CTC grade 3/4 toxicity [Molina *et al.* 2009; NCTt00528645].

The mammalian target of rapamycin (mTOR)

mTOR inhibitors act on intracellular serine/threonine protein kinases that regulate cell growth, cell proliferation, cell motility, cell survival, protein synthesis, and transcription. Two mTOR inhibitors that have been evaluated in SCLC are temsirolimus (CCI-779, Torisel®, Wyeth) and everolimus (RAD001, Afinitor®, Novartis). In one phase II trial that investigated temsirolimus as a maintenance therapy, the PFS was 1.9 months for those patients receiving 25 mg temsirolimus whilst those patients on 250 mg had a PFS of 2.5 months ($p = 0.24$) [Pandya *et al.* 2007]. Two phase II trials evaluating everolimus as a monotherapy in treatment of relapsed SCLC have been conducted. The results of one of the trials were recently reported at the 13th World Conference in Lung Cancer 2009. In the phase II study evaluating everolimus as a maintenance monotherapy following completion of standard chemotherapy in relapsed SCLC, everolimus was well tolerated with only a few CTC grade 3 toxicities and no grade 4 or more toxicities. However, there was no significant improvement in disease control rate (DCR 26%, duration of disease control 2.7–6.3 months), which was the primary endpoint of the study. The median PFS and OS were 1.4 months and 5.5 months, respectively [Kotsakis *et al.* 2009]. A preliminary report from the other phase II trial showed that everolimus, although reasonably well tolerated, had limited activity in SCLC [Owonikoko *et al.* 2008].

A phase I dose escalation study of everolimus in combination with cisplatin/etoposide chemotherapy in previously untreated patients with LD SCLC has also been undertaken. The preliminary findings are that dose escalation in both the daily and weekly schedules was limited by a high rate of grade 3/4 haematological adverse events (60%) compared to chemotherapy alone (38%). The trial is still open for enrollment, however, the study design has now been amended to include mandatory primary prophylaxis of granulocyte-colony stimulating factors [Besse *et al.* 2009].

Targeting angiogenesis

Angiogenesis is essential for sustained growth and metastatic spread of cancer, and has been implicated as a poor prognostic factor in SCLC [Blackhall and Shepherd, 2004]. High levels of the potent angiogenic promoter, vascular endothelial cell growth factor (VEGF) are also associated with poorer outcome in SCLC patients [Salven *et al.* 1998].

Matrix metalloproteinases

The matrix metalloproteinase inhibitors (MMPIs) were among the first agents proposed to act in part *via* inhibition of angiogenesis to be evaluated in SCLC. Two agents were investigated in randomized trials in SCLC: marimastat (BB 2516, British Biotech) and tanomastat (BAY 12-9566, Bayer Healthcare Pharmaceuticals), but neither improved survival and side effects adversely impacted on quality of life [Rigas *et al.* 2003; Shepherd *et al.* 2002].

Thalidomide

The mechanism of action of thalidomide is not well understood but includes antiangiogenesis. The French Intergroup conducted a randomized phase III trial that suggested a survival advantage (11.7 months *versus* 8.7 months; $p = 0.03$) with the addition of thalidomide as a maintenance therapy *versus* placebo following response to a four-drug chemotherapy regimen in ED SCLC. However, there was a higher incidence of toxicities including thrombosis and neuropathy in the

thalidomide arm, which led to about half the patients needing withdrawal or dose reduction [Pujol *et al.* 2007]. The London Lung Cancer Group then conducted a 724-patient randomized phase III trial that evaluated thalidomide *versus* placebo in combination with carboplatin and etoposide chemotherapy then as maintenance in ED-SCLC. Despite the rapid accrual and size of the study, there was no overall survival advantage in favour of thalidomide [Lee *et al.* 2007]. This may be explained in part by the use of a lower dose, to decrease toxicity, compared to the French Intergroup Study.

Vascular endothelial growth factor and VEGF receptor (VEGFR)

The promise of antiangiogenic therapy for treatment of solid tumours was first realized with bevacizumab (Avastin®, Genentech Inc), a humanized monoclonal antibody targeting the VEGF-A receptor that is licensed for breast cancer, colorectal cancer and NSCLC. This agent has attracted most interest for evaluation in SCLC but its role remains undetermined.

In LD SCLC, bevacizumab has been evaluated as a maintenance therapy and in combination with concurrent chemoradiation. A maintenance phase II study of bevacizumab at a dose of 15 mg/kg after initial concurrent cisplatin, irinotecan and radiotherapy demonstrated good tolerability with objective responses of 80%, 2-year PFS of 54% and a median PFS of 15 months [Patton *et al.* 2006]. Another single-arm phase II study evaluated maintenance bevacizumab (10 mg/kg) following concurrent irinotecan, carboplatin and radiotherapy in LD SCLC. This study was suspended after enrolling 29 patients due to safety concerns when three fatalities were reported from tracheo-oesophageal and aerodigestive fistulae formation during maintenance therapy. All three patients had encountered grade 3 oesophagitis during chemoradiation. There was also one death from treatment-related bowel perforation. The response rate on analysis of data was 88%, with four complete responses, 11 partial responses, one stable disease and one progressive disease from evaluable patients; 12 patients were nonevaluable due to various factors. The primary endpoint was not reached for this study and the regimen is unlikely to be developed further due to the toxicities encountered [Spigel *et al.* 2008]. Bevacizumab is currently being investigated for use concurrently in a single-arm phase II study with carboplatin and irinotecan chemoradiotherapy, followed by maintenance bevacizumab in LD SCLC, results of which are awaited [NCT00308529].

In ED, SCLC two phase II trials investigating bevacizumab have been reported. One trial that evaluated cisplatin, irinotecan and bevacizumab in ED SCLC showed an overall response rate (ORR) of 75% and a median survival (MS) of 11.7 months [Ready *et al.* 2007]. Another phase II trial that combined bevacizumab with cisplatin and etoposide in ED SCLC reported an ORR of 69% and MS of 11.1 months [Sandler *et al.* 2007]. While these results are promising, patients eligible for bevacizumab are a highly selected population since exclusion criteria for bevacizumab are haemoptysis, presence of brain metastases and hypertension. Results from the randomized hase II SALUTE study, evaluating platinum-etoposide plus bevacizumab *versus* platinum-etoposide plus placebo in patients with previously untreated ED SCLC, have recently been presented in abstract form. While there was a statistically significant improvement in PFS (5.5 *versus* 4.4 months for bevacizumab arm compared to the placebo arm, $p = 0.01$), the ORR was numerically greater but not statistically significant (30% *versus* 24%, $p = 0.33$) and there was no improvement in the median OS (9.4 *versus* 10.9 months, p value not reported). Furthermore there was an increased incidence of CTC grade 3/5 toxicities in the bevacizumab arm compared to the placebo arm (75% *versus* 60%) and higher rates of serious adverse events (39% *versus* 23% for bevacizumab and placebo arm, respectively) [Spigel *et al.* 2009]. The Hoosier Oncology group has also recently completed a second-line study of bevacizumab and paclitaxel in patients with sensitive relapsed SCLC, results of which are awaited. [NCT00317200].

A number of small molecules that inhibit the tyrosine kinase domain of the VEGF receptor are also of interest. Cediranib (AZD2171, Recentin®, Astra Zeneca), a TKI with potent activity against the VEGF receptors −1, −2 and −3, was investigated in a phase II trial as second line treatment for SCLC. Of 25 patients recruited, one patient was reported to have a partial response (PR) and nine had stable disease (SD) but there was no improvement in the primary endpoint of OS [Ramalingam *et al.* 2008]. Vandetanib (Zactima®, Astra Zeneca) is a multitargeted TKI with dominant activity *in vitro*

against the VEGF receptor and weaker inhibition of the EGFR receptor. A randomized phase II trial was conducted to investigate vandetanib as a maintenance therapy after complete or partial response following chemotherapy, with or without radiotherapy, in LD and ES SCLC. The study overall was reported to be negative for any survival benefit but in planned subgroup analyses there was a trend to longer MST in patients with LD SCLC who received vandetanib [Arnold *et al.* 2007]. The hypothesis that vandetanib given concurrently with chemotherapy, rather than as a maintenance therapy in the study of Arnold *et al.* 2007 is currently being explored [NCT00613626].

Two other small multitargeted TKIs, sorafenib and sunitinib, are also currently under evaluation in SCLC. Sorafenib (Nexavar®, Bayer Healthcare Pharmaceuticals) is a potent Raf1 inhibitor that is also active against VEGFR-2, VEGFR-3, and PDGFR-β. In a phase II trial, sorafenib was administered at a daily oral total dose of 800 mg to 82 patients with SCLC who had progressed after one platinum-based regimen and patients were stratified by platinum sensitivity. There were four partial responses (three in patients sensitive to platinum) and 25 achieved stable diesase (12 in patients sensitive to platinum). The median PFS was 2 months, and MST was 7 months and 5 months in the platinum-sensitive and -refractory groups, respectively. Main toxicities included grade 3 skin toxicity in 25% and grade 3/4 flu-like syndrome in 14% of patients [Gitlitz *et al.* 2008]. Other phase I and II trials evaluating sorafenib in SCLC are ongoing [NCT00466232, NCT00182689].

Sunitinib (SU11248, Sutent®, Pfizer) is an oral, small-molecule, multitargeted receptor tyrosine kinase inhibitor active against PDGFR-α and PDGFR-β, VEGFR-1, VEGFR-2 and VEGFR-3, stem cell factor receptor (kit), FMS-like tyrosine kinase 3 (FLT3), colony stimulating factor receptor (CSF-1R) and the glial cell-line derived neurotrophic factor receptor (RET). Several studies of sunitinib are active [NCT00620347, NCT00616109, NCT00453154].

Aflibercept (Sanofi-Aventis and Regeneron Pharmaceuticals) is an angiogenesis inhibitor with a unique mechanism of action. It is a fusion protein comprised of segments of the extracellular domains of VEGFR-1 and VEGFR-2 fused to the constant region (Fc) of human IgG1 that functions as a soluble decoy receptor, binding to VEGFA and B, thereby preventing binding to their cell receptors. Aflibercept is currently being investigated in a phase II trial *versus* placebo in combination with topotecan in ED SCLC that has progressed after first-line therapy [NCT00828139]. Clearly there is intense activity in the evaluation of antiangiogenics for SCLC but it is too early to determine the viability of this strategy for routine clinical use.

Promotion of apoptosis

The ability of cancer cells to evade apoptosis or programmed cell death is of seminal importance as a therapeutic target since this process underpins cancer cell survival and treatment resistance. Agents of interest to promote induction of apoptosis include those that act 'directly' on apoptotic machinery and those that have an 'indirect' action on other cellular processes which ultimately lead to induction of apoptosis. The 'direct' apoptosis promoters that are of greatest interest in SCLC are those that inhibit the action of bcl-2.

Bcl-2

Bcl-2 is an antiapoptotic protein that is found in high concentrations in SCLC cell lines and tumours and is implicated in acquired resistance to conventional chemotherapy in preclinical SCLC models [Yan *et al.* 1996; Jiang *et al.* 1996]. Oblimersen (G 3139, Genasense®, Genta Inc) is a stable, antisense oligonucleotide to a section of the bcl-2 mRNA, and the first anti bcl-2 agent to be tested in SCLC. Preclinical and early clinical studies were highly promising [Zangemeister-Wittke *et al.* 1998] but the results of a randomized phase II trial undertaken to evaluate oblimersen *versus* placebo in combination with carboplatin and etoposide as first-line treatment for ED SCLC were disappointing. The 1-year survival rate for patients on oblimersen was 24% compared to 47% for placebo and grade 3/4 haematological toxicities were also higher for oblimersen [Rudin *et al.* 2008]. Hope for a breakthrough is now pinned on the so-called BH3 mimetics or small molecule bcl-2 inhibtiors. BH3 mimetics act by occupying the hydrophobic pocket of the bcl-2 protein, thus preventing binding to proapoptotic components. Obatoclax mesylate (GX 15-070, Germin X Pharmaceuticals) and ABT-263 (Abbott Laboratories) are two BH3 mimetics that have shown promise in preclinical models and are currently undergoing investigation for use in the treatment of SCLC

[NCT00682981, NCT00521144]. Indeed, in animal models ABT-737 induced marked regression and cure of SCLC xenografts [Hann *et al.* 2008]. AT-101 (gossypol acetic acid, Ascenta Pharmaceuticals) is an orally administered bcl-2 inhibitor from the BH3 mimetic family which has been evaluated in the phase I/II setting in combination with topotecan in platinum-pretreated patients with relapsed or refractory SCLC. Patients were stratified into two cohorts depending on their time to relapse from prior chemotherapy (>60 days *versus* <60 days). AT-101 appeared safe for administration in conjunction with topotecan, with no appreciable difference in the toxicity profile compared to topotecan alone. However, there was no evident improvement in efficacy with a lack of objective responses; therefore, further enrollment to this trial was halted [Heist *et al.* 2009].

In contrast to the 'direct' apoptosis promoters described above, there are also agents that induce apoptosis through an 'indirect' mode of action.

26S ubiquitin-proteosome complex

Bortezomib (Velcade®, Janssen-Cilag) is an inhibitor of the 26S ubiquitin-proteosome complex that inhibits bcl-2 mediated apoptosis resistance in cancer cells and has shown promising activity in preclinical models [Mortenson *et al.* 2005]. A phase II trial of bortezomib as a monotherapy in platinum-pretreated relapsed ED SCLC failed to demonstrate efficacy. Bortezomib is now being evaluated in phase I trials in combination with topotecan in various solid tumours including SCLC [NCT00770731, NCT00541359, NCT00388089, NCT00068484].

Polo-like kinase 1

Another strategy is to inhibit polo-like kinase 1, which in turn leads to cell cycle arrest followed by apoptosis in a variety of tumor cells while causing reversible cell cycle arrest without apoptosis in normal cells. Plk1, named after the polo gene of *Drosophila melanogaster*, is a serine/threonine protein kinase involved in regulating mitotic spindle function in a non-ATP competitive manner. The Plk1 inhibitor BI 2536 (Boehringer Ingelheim Pharma) was investigated as a monotherapy in relapsed sensitive SCLC in an open-label two-stage phase II trial but after stage I the trial was terminated due to lack of antitumour activity [Gandhi *et al.* 2009]. Histone deacetylase (HDAC) inhibition also induces apoptosis [Schrump *et al.* 2008].

Histone deacetylase

A number of trials are ongoing to investigate various HDAC inhibitors such as vorinostat (Zolinza®, Merck & Co Inc), belinostat (PXD 101, Curagen & TopoTarget) and entinostat (SNDX-275, Syndax Pharmaceuticals) [NCT00926640, NCT00702962, NCT00697476]. Of all the apoptosis promoting agents currently in development, the spotlight is on the BH3 mimetics as the agents with greatest potential for therapeutic efficacy.

Multidrug resistance inhibitors

Small cell lung cancer is initially exquisitely sensitive to chemotherapy but it invariably relapses and acquires a chemoresistant phenotype. Biricodar (VX-710, Incel™, Vertex Pharmaceutical) is a multidrug resistance inhibitor that acts on P-glycoprotein and multi-drug resistance-associated protein-1 (MDR-1), both of which are proteins involved in chemotherapy resistance in cancer. It was studied in a phase II trial in patients with relapsed SCLC in combination with doxorubicin and vincristine. The response rate observed was low (at 19%), and furthermore there was a high incidence of grade 3/4 neutropenia (53%) including two mortalities from sepsis. Due to the low response rate and high incidence of significant toxicities, the study was terminated early [Peck *et al.* 2001].

Immune conjugates and vaccines

The majority of SCLCs express cell surface CD56 (NHK-1 or neural cell adhesion molecule). N901 is a murine monoclonal anti-CD56 antibody linked to ricin that, in phase I evaluation, induced a tumour response in one patient with SCLC [Lynch *et al.* 1997]. Excess toxicity due to immune reactions, however, was also seen. The anti-CD56 antibody has now been humanized and linked to a microtubule-depolymerizing compound (BB-10901) to reduce toxicity. BB-10901 (IMGN901, huN901-DM1, British Biotech) is a fusion of a monoclonal antibody against CD56 and cytotoxic maytansinoid chemotherapy DM-1. It acts by delivering the cytotoxic component DM-1 internally *via* a transmembrane receptor, leading to tubulin polymerization and subsequent cell death. A preliminary report of the phase I/II trial of BB-10901 (British Biotech Pharmaceuticals trial BBIO-C10/IVB/001) was

presented recently. Patients with SCLC, those with a diagnosis of other pulmonary tumours of neuroendocrine origin including neuroendocrine carcinomas, NSCLC with neuroendocrine features, extrapulmonary small cell carcinoma, metastatic carcinoid tumours and other CD56+ solid tumours were also included. The study was divided into two substudies – Study 001 and 002. Primary endpoints were safety, tolerability, maximum tolerated dose (MTD) and efficacy at the dose of 60 mg/m^2. Study 001 is now completed whilst Study 002 is still ongoing. BB-10901 has shown encouraging early activity in patients with pretreated, relapsed or refractory SCLC, with activity demonstrated in second- or greater-line settings and a favourable safety profile [Fossella *et al.* 2009].

BEC2 (mitumomab, ImClone Systems) is an anti-idiotypic murine IgG2b monoclonal antibody that is known to mimic GD3, a ganglioside found on the cell surface of most SCLC cells. BEC2 monoclonal antibody is used in conjunction with bacille Calmette-Guerin (bCG) vaccine to mount an endogenous immune response to GD3. A large EORTC phase III trial was undertaken to evaluate the use of BEC-2/bCG adjuvant vaccination as a maintenance therapy *versus* none in patients with LD SCLC who have responded to chemotherapy. The vaccine was well tolerated, but there was no improvement in the PFS or OS in the study arm compared to the control arm. (16.4 months *versus* 14.3 months, $p = 0.28$) [Giaccone *et al.* 2005].

The high incidence of p53 mutation in SCLC has provided a target for the development of vaccines that activate cytotoxic T cells. A vaccine to the p53 protein has been trialled in 29 patients with ES SCLC. Autologous dendritic cells were genetically modified to express the wild-type p53 protein to induce a cytotoxic T-cell response. Of the 29 patients, 57% mounted a T-cell response. Interestingly, patients who mounted a T-cell response were found to have a higher response rate to second-line chemotherapy compared to those who did not (75% *versus* 30%, $p = 0.08$) [Antonia *et al.* 2006]. This finding is provocative for further evaluation of this autologous dendritic vaccine in combination with chemotherapy. In the meantime, a phase II trial is now underway evaluating the use of all-trans retinoic acid (ATRA) *versus* none in conjunction with autologous dendritic cell vaccine in patients with ED SCLC [NCT00618891], following evidence that the use of ATRA may improve the response rate of tumour vaccines by eliminating immature myeloid cells that play a role in tumour-induced immunosuppresion [Kusmartsev *et al.* 2003].

New directions

It is widely recognized that several targeted agents have altered the paradigm of treatment in some cancer groups. However, we have yet to see a revolution of the same magnitude in the treatment of SCLC, both in the adjuvant and metastatic setting. The preclinical findings of the various aberrant processes in this type of cancer have not yet been successfully translated into better outcomes with the addition of the novel targeted agents. While there appears to be no shortage of novel agents to test in SCLC the results from studies to date, some of which have involved hundreds of patients, have largely proved disappointing, and imply that different approaches to target selection and evaluation, in addition to drug development and trial design, are urgently required if a breakthrough for this disease is to be made.

An emerging pathway of therapeutic interest in SCLC that is unlike other pathways targeted to date is the hedgehog signaling pathway that is believed to play a role in stem cell renewal and autocrine neoplastic stimulation. Elegant studies that identified the hedgehog protein (Hhg) to be expressed in the airway epithelium during repair and acute injury also found Hhg to be overexpressed in SCLC cell lines and Hhg inhibition caused growth arrest *in vitro* [Watkins *et al.* 2003]. Hedgehog signaling pathway inhibitors GDC-0449 (Genentech Inc) and IPI-926 (Infinity Pharmaceuticals) are currently being evaluated in phase I trials [NCT00887159, NCT00761696]. Interestingly, GDC-0449 demonstrated impressive activity in basal cell carcinoma (BCC) [Von Hoff *et al.* 2009]. Results for this agent in SCLC are not yet available but it is important to note that, in BCC, mutations are present in the patched component of the Hhg pathway and these have not been identified in SCLC.

Translational research to correlate target pathway activation/inhibition with clinical endpoints is essential to maximize knowledge gained from trials and to identify predictive markers with which to direct targeted agents to patients who are most likely to benefit. However, SCLC is rarely resected and so biopsy tissue for molecular

studies is very limited and serial biopsies are a major challenge. As a case in point, peripheral blood mononuclear cells (PBMCs) were used as a surrogate for tumoural expression of bcl-2 during clinical trials of oblimersen [Rudin *et al.* 2008]. Circulating tumour cells (CTCs) may provide a better surrogate and are abundant in patients with SCLC, particularly ED stage. CTCs obtained from peripheral blood samples can now be applied in early clinical trials of new agents to screen patients for expression of a particular target and/or as a pharmacodynamic tool to monitor for response to treatment since CTCs drop precipitously in number following chemotherapy [Hou *et al.* 2009]. Serological biomarkers of cell death (M30 and M65) have also been characterized for expression and clinical significance in SCLC and can be applied as pharmacodynamic biomarkers for trials of apoptosis inducing agents [Greystoke *et al.* 2008]. A further approach is to combine agents in parallel, multiarm phase II trials in order to decrease the time taken to evaluate new agents. For example the Hhg antagonist, GDC-0449, is being evaluated in one arm of a randomized phase II trial that is also evaluating the IGF-1R inhibitor, IMC-A12 [NCT00887159]. AMG 102 and AMG 479, Met and IGF-1R inhibitors, respectively, are also being evaluated in tandem in a parallel phase II design [NCT00791154]. With new translational tools, increasing knowledge of SCLC biology and innovative trial designs it should hopefully not be too long before we see a significant therapeutic breakthrough with targeted therapy for this highly aggressive disease. Currently, hopes are perhaps highest for the BH3 mimetics designed to promote apoptosis and overcome chemoresistance. Enthusiasm for inhibitors of angiogenesis and growth factor receptor pathway inhibitors is waning, although the IGFR and Met inhibitors remain at a very early stage in development.

Conflict of interest statement

None declared.

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