European Journal of Cancer 60 (2016) 26–39

Available online at www.sciencedirect.com

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journal homepage: www.ejcancer.com

Review

Development of molecularly targeted agents and immunotherapies in small cell lung cancer

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Received 3 November 2015; received in revised form 29 February 2016; accepted 2 March 2016

KEY WORDS
Small cell lung cancer;
Targeted therapies;
Precision medicine;
Molecular analysis;
Angiogenesis;
Cell signalling;
Apoptosis;
Immunotherapies;
DNA repair;
Antibody-drug conjugate

Abstract Small cell lung cancer (SCLC) is a smoking-induced malignancy with multiple toxin-associated mutations, which accounts for 15% of all lung cancers. It remains a clinical challenge with a rapid doubling time, early dissemination and poor prognosis. Despite multiple clinical trials in SCLC, platinum-based chemotherapy remains the mainstay of treatment in the first line advanced disease setting; good initial responses are nevertheless inevitably followed by disease relapse and survival ultimately remains poor. There are currently no molecularly targeted agents licenced for use in SCLC. Advances in sequencing the cancer genome and other high-throughput profiling technologies have identified aberrant pathways and mechanisms implicated in SCLC development and progression. Novel anti-tumour therapeutics that impact these putative targets are now being developed and investigated in SCLC. In this review, we discuss novel anti-tumour agents assessed in SCLC with reference to the complex molecular mechanisms implicated in SCLC development and progression. We focus on novel DNA damage response inhibitors, immune checkpoint modulators and antibody-drug conjugates that have shown promise in SCLC, and which may potentially transform treatment strategies in this disease. Finally, we envision the future management of SCLC and propose a biomarker-driven translational treatment paradigm for SCLC that incorporates next generation sequencing studies with patient tumours, circulating plasma DNA and functional imaging. Such modern strategies have the potential to transform the management and improve patient outcomes in SCLC.

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http://dx.doi.org/10.1016/j.ejca.2016.03.004
0959-8049/

1. Introduction

Lung cancer is the leading cause of cancer-related deaths in Europe with 353,000 deaths in 2012 [1]. Small cell lung cancer (SCLC) is an aggressive neuroendocrine subtype of lung cancer with a propensity to present with metastatic disease (extensive stage disease; ED) at an early stage [2]. Our understanding of the complex molecular mechanisms and pathways underpinning the development and progression of SCLC has improved with recent advancements in cancer genome sequencing and other high throughput profiling technologies [3–10]. However, despite these advances, there have been no significant improvements in the development of anti-tumour strategies for this disease. A plethora of molecular targeted agents have been investigated in SCLC and most have failed to demonstrate clinical benefit [11–43]. This is likely to be due to a combination of factors, including the molecular targets selected, their functional relevance in the pathogenesis of this aggressive disease and the lack of predictive biomarkers of clinical efficacy in SCLC, making appropriate patient selection challenging.

Given the richness of the leads that have been produced with high throughput profiling technologies in other solid malignancies, as well as liquid tumours, there is now a fresh impetus to exploit these technologies in SCLC. Here we detail novel therapies that have been investigated in patients with SCLC in the context of our expanding knowledge of the molecular biology underpinning the disease. We also propose treatment strategies that we believe will provide SCLC patients with the greatest chance of clinical benefit.

2. Development of novel agents in SCLC: the challenges

A number of molecularly targeted therapies have been evaluated in SCLC either as monotherapy or in combination with other anti-tumour agents. These include clinical trials in the first-line setting, as maintenance therapy and in relapsed SCLC (Tables 1 and 2) [11–43]. The majority of these trials have not found a benefit

Table 1
Targeted therapies in first line treatment of small cell lung cancer.

Putative target	Agent	Author	Phase	Therapy	Setting	Outcome
Targeting angiogenesis						
VEGF-A	Bevacizumab	Pujol[2015]	II/III	Combination	F (M) R	Negative
		Patton[2006]	II	Monotherapy	M	15 m OS
		Spigel[2008]	II	Combination	F (M)	Stopped
		Ready[2011]	II	Combination	F	7 m PFS, 11.6 m OS
		Spigel[2009]	II	Combination	F (M)	9.1 m TTP, 12.1m OS
		Spigel[2011]	II	Combination	F (M) R	Negative
RAF-1, VEGFR-2, VEGFR-3 and PDGFRβ	Sorafenib	Sharma[2014]	II	Combination	F (M)	7.4 m OS
VEGFR-1, VEGFR-2, VEGFR-3, PDGFR, c-KIT, FLT-3 and RET	Sunitinib	Spigel[2012]	II	Monotherapy	M	7.6 m PFS
		Ready[2015]	II	Monotherapy	M R	Improved PFS not OS
VEGFR-2, EGFR and RET	Vandetanib	Arnold[2007]	II	Monotherapy	M R	Negative
Targeting cell signalling						
BCR-Abl, c-KIT and PDGFR	Imatinib	Johnson[2003]	II	Monotherapy	F	0.8 m TTP
		Spigel[2007]	II	Monotherapy	M	5.4 m PFS, 8.4 m OS
		Schneider[2010]	II	Monotherapy	F (M)	4.3 m PFS, 7.8 m OS
mTOR	Temsirolimus	Pandya[2007]	II	Monotherapy	M	2.5 m PFS
IGF1R	Cixutumumab	Belani[2013]	II	Combination	F R	Negative
Smoothened	Vismodegib	Belani[2013]	II	Combination	F R	Negative
Targeting apoptosis						
BCL-2	Oblimersen	Rudin[2008]	II	Combination	F	Negative
BCL-2, MCL-1, BCL-W, BCL-XL	Obatoclax	Langer[2014]	II	Combination	F	Negative
Targeting DNA repair defects						
PARP	Veliparib	Owonikoko[2014]	I	Combination	F	Negative
	Olaparib	Ongoing	II	Monotherapy	M R	ISRCTN73164486
Targeting the immune system						
CTLA-4	Ipilimumab	Reck[2013]	II	Combination	F	Improved iRPFS
		Ongoing	II	Combination	F	NCT01331525
		Ongoing	II	Combination	F (M)	NCT02046733
		Ongoing	III	Combination	F	NCT01450761

VEGF – Vascular endothelial growth factor; VEGFR – Vascular endothelial growth factor receptor; PDGFR – Platelet derived growth factor receptor; c-KIT – Stem cell factor receptor; FLT3 – FMS-like tyrosine kinase 3; RET – Rearranged during transfection tyrosine kinase; mTOR - mammalian target of rapamycin; IGFR – Insulin like growth factor receptor; BCL-2 – B-cell lymphoma; MCL-1 – myeloid cell leukaemia 1; HDAC – Histone deacetylase; F – First-line; F (M) – First-line followed by maintenance; R – Randomised; PFS – Progression free survival; TTP – Time to progression; OS – Overall survival; m – Months; PARP – Poly-ADP ribose polymerase; EGFR – epidermal growth factor receptor; CTLA – Cytotoxic T-lymphocyte-associated protein 4; M – maintenance alone; iRPFS – Immune-related progression-free survival.