Small cell lung cancer (SCLC): no treatment advances in recent years

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Abstract: Small cell lung cancer (SCLC) is an aggressive malignancy with a distinct natural history and dismal prognosis. Given its predisposition for early dissemination, patients are commonly diagnosed with metastatic disease and chemotherapy is regarded as the cornerstone of approved treatment strategies. However, over the last 30 years there has been a distinct paucity of significant breakthroughs in SCLC therapy. Thus, SCLC is characterized as a recalcitrant neoplasm with limited therapeutic options. By employing well-established research approaches, proven to be efficacious in non-small cell lung cancer (NSCLC), a growing amount of data has shed light on the molecular biology of SCLC and enhanced our knowledge of the "drivers" of tumor cell survival and proliferation. New therapeutic targets have emerged, but no significant improvement in patients' survival has been demonstrated thus far. In a sense, the more we know, the more we fail. Nowadays this is starting to change and methodical research efforts are underway. It is anticipated that the next decade will see a revolution in the treatment of SCLC patients with the application of effective precision medicine and immunotherapy strategies.

Keywords: Small cell lung cancer (SCLC); treatment; progress; perspective

Introduction: is small cell lung cancer (SCLC) research a modern-day Odyssey?

Lung cancer is among the most common tumor types, representing 13% of newly diagnosed cancers worldwide. Both the absolute and relative frequencies of lung cancer have risen dramatically. Unfortunately, it remains by far the leading cause of cancer-related deaths, accounting for 18% of the total number of deaths (1). Approximately 20% of lung tumors exhibit neuroendocrine differentiation, representing a group of neoplasms that share common morphological and immunohistochemical features, including SCLC. SCLC, accounting for 10% of clinical lung cancer cases, is an aggressive malignancy strongly associated with smoking. It displays a distinct natural history characterized by a high growth fraction, rapid doubling time and early establishment of widespread metastatic lesions (2). While 30% of patients present with disease confined to one hemithorax [limited disease (LD)], the majority of cases have disease not encompassed by one radiotherapy field [extended disease (ED)] (3).

Historically, SCLC, previously known as "oat cell carcinoma", first appeared in the literature in 1936, in an article describing a case of oat cell carcinoma in a patient with asbestosis (4). The lethality of this malignancy was unequivocal, as SCLC rapidly led to fatalities if left untreated (5). Since then, progress has been made in the histopathological diagnosis, staging and treatment of this

neoplasm. Early trials have established the role of radiotherapy over surgery as the initial treatment approach (6). However, survival rates were extremely low and chemotherapy emerged as the optimal modality for patients with distant metastatic disease (7). Combination regimens were proven to be superior to single agent chemotherapy (8) with the introduction of alkylator-based chemotherapy regimens in the 70s and cisplatin-based combinations in the 80s. Ultimately, combined chemo-radiotherapy treatment protocols were tested (9) and incorporated into the treatment of LD-SCLC (10). However, since then our knowledge regarding SCLC has entered a dormant state.

In fact, our efforts towards evolution of SCLC therapy resemble the Odyssey: a journey of a constant confrontation with various obstacles, during which the hero alternates between hope and despair until he reaches Ithaca. Apparently, the initial characterization of this disease as chemo- and radio-sensitive, based on the results of clinical trials conducted in the 80s (11,12), led to excessive optimism concerning our ability to cure SCLC. Continuing the metaphor, perhaps this optimism was taken for contempt of the "Olympian Gods" and every effort to evolve SCLC treatment, henceforth, was doomed to fail. Despite promising preclinical data, the results of clinical studies were disheartening.

Indeed, the current standard of care for LD-SCLC disease is concurrent chemoradiation, with four cycles of cisplatin and etoposide with thoracic radiation therapy during the first or second chemotherapy cycle. Resection is indicated for the limited proportion of patients that present with small peripheral primary tumors and no documented infiltration of the mediastinal lymph nodes. Management of patients with ED typically includes four to six chemotherapy cycles with a platinum agent and etoposide or irinotecan. Following a good response to initial therapy, prophylactic cranial irradiation is indicated in patients with LD-SCLC and suggested for patients with ED-SCLC. Despite the fact that first line treatment provides response rates of up to 80%, the prognosis of SCLC remains dismal. The majority of patients relapse within 6 months after completion of initial treatment, leading to a median survival range of 15 to 20 months and eight to 13 months for patients with LD and ED, respectively (13). During the last few decades, although we should acknowledge that efforts to improve the clinical outcome of SCLC patients have been made, the 5-year survival rate remains 6% (14). Numerous treatment strategies have been evaluated, yet none of them has yielded superior outcomes over standard platinum-based therapy (15). It is interesting to note that the last drug that gained

approval for treatment of these patients was topotecan in 1998 (16). Based on these sobering data, the absence of real progress is unambiguous, necessitating the vital need for the development of novel strategies in the care of SCLC patients.

The non-small cell lung cancer (NSCLC) research paradigm: a proposed route to "Ithaca"

During the last decade, we have witnessed a revolution in treatment of NSCLC. Significant advances in early detection and therapeutic modalities have led to clinically significant improvements in survival. By employing analogical reasoning, one should expect that SCLC research would have advanced at the same pace. Sadly, however, this is not the case. In order to achieve a deeper understanding of the realities of SCLC we must think critically, taking into account what Odysseus has taught us regarding methods to identify and overcome obstacles and barriers inherent to the nature of SCLC.

Foremost, Odysseus defeated the powerful cyclops Polyphemus when he identified his weakness: having only one eye. Being single-minded regarding SCLC research could be considered to be such an "Achilles heel", as knowledge gained from other neoplasms could be a useful tool. The paradigm of NSCLC may serve as an archetype in organizing our approach to SCLC, while keeping in mind the unique characteristics of this neoplasm.

As chemotherapy has achieved its potential, progress in NSCLC treatment has been based upon the elucidation of the aberrant molecular pathways involved in the pathogenesis and progression of NSCLC. Thus, the identification of certain mutations in the *epidermal growth factor receptor* (*EGFR*) gene or rearrangements of the *anaplastic lymphoma kinase* (*ALK*) gene that act as molecular "drivers" of NSCLC have provided new targets for lung cancer treatment. Nowadays, there is no doubt as to the heterogeneity of this neoplasm and pie charts showing the mutational landscape of NSCLC have become standard. The subsequent development of certain targeted therapies has resulted in significantly improved therapeutic efficacy and survival benefit in patients harboring the corresponding driver mutation. Hence, NSCLC has entered the era of personalized cancer management and molecular testing has emerged as an essential component of the decision making process. However, this is not the case for SCLC. Our knowledge regarding the molecular biology of our enemy, although crucial, is minimal. Thus, treatment is only based on the immunohistological identification of SCLC

features and is the same for all patients. Certain intrinsic SCLC features serve as limitations in our efforts toward demonstrating its biological heterogeneity.

Finding information in unexpected places

Once again, 'tissue seems to be the issue'. Typically, the diagnosis of SCLC is based on biopsy (~75%) or cytology samples and not surgical specimens (<2%) (17). As the majority of patients are unresectable at diagnosis, surgery only rarely forms part of the management of these patients. As previously mentioned, resection is indicated in the rare case of a patient presenting with a small peripheral primary lesion (18). It is interesting to note that comprehensive genomic characterization of SCLC is generally based on the analysis of such specimens (17,19,20). However, the biological features of this disease are expected to be different from the typical widespread disease we commonly encounter in clinical practice. As a rule, SCLC patients have multiple comorbid conditions that hamper their ability to undergo surgical biopsy and less invasive procedures are therefore preferred, reducing the amount of tissue that can be obtained for testing. As a result, SCLC is not included in the neoplasms studied by the Cancer Genome Atlas, as it does not meet the inclusion criteria regarding tissue availability.

During his journey, Odysseus had to visit Hades, the world of the dead, to seek the advice of the prophet Tiresias. Helpful travel directions for a safe return to Ithaca came from an unexpected source, a spirit. Likewise, in order to circumvent the need for ample tissue samples, novel approaches in research are being employed. Cell lines, patient-derived xenografts (PDX) and genetically engineered mouse models (GEMM) have been successfully utilized in drug-development preclinical studies (21). Moreover, PDX and GEMM provide a powerful tool in evaluating the intrinsic mechanisms underlying SCLC genesis and proliferation and metastasis *in vivo*, in a system that closely resembles humans (22-24). Furthermore, circulating tumor cells (CTCs) may serve as a liquid biopsy. Although molecular analysis of CTCs in SCLC is still in its infancy, proof-of-concept studies have shown that it is feasible (25). In fact, the above described tools can be combined as demonstrated in a provocative and innovative effort from Hodgkinson *et al.* in which CTCs derived from peripheral blood of SCLC patients were used to create mice xenografts [CTC-derived xenografts (CDX)]. Serial blood sampling could enable us to obtain a representative picture of the primary tumor at different treatment phases. Hence, these manipulable models may prove valuable in translational drug discovery and development research.

Similarly, seeking "prophecies" to enhance our understanding of SCLC biology, we should analyze tumor specimens not only from patients that respond to treatment but also from non-responders, or even those who progress after an initial response to treatment. However, due to rapid physical and functional deterioration during disease progression, some SCLC patients are not able to tolerate invasive methods for obtaining tissue samples. Erratic approaches to overcome this limitation suggest biopsying residual disease after completion of first line treatment, when patients are in a better clinical condition, potentially enabling detection of the resistant clone that could lead to disease progression. Furthermore, the development and validation of methods to longitudinally monitor the genomic evolution of the primary tumor (e.g., cell free-DNA) by obtaining blood samples could also prove useful. Whatever the method used, the ability to take serial biopsies with adequate, both in terms of quantity and quality, tumor material from NSCLC patients has been fundamental in elucidating the mechanisms of drug resistance and in developing novel, more potent therapies (26). Prerequisites to achieve the same for SCLC would include optimization of biopsy techniques, introduction of clinical trials that encourage re-biopsy in the setting of disease relapse and reduction of tissue requirements for a more focused genomic analysis (27).

Choose your fights wisely

Since the 90s, it has been widely appreciated that identification of the prevalent genomic alterations in SCLC would reveal the molecular pathways involved in tumor development and provide new therapeutic targets. Pioneering research in this field unveiled the genetic hallmarks of SCLC: inactivation of the tumor suppressor genes *TP53* (75–90% of cases) (28,29) and retinoblastoma gene (*RB1*) (60–90%) (30). However, initial enthusiasm was hampered by the realization that loss-of-function mutations were not the ideal drug targets as restoration of tumor-suppressor function cannot be achieved through conventional drug development strategies (31). Hence, these mutations can be likened to Charybdis and Scylla, two sea-monsters that lived in the opposite sites of a narrow strait. Odysseus and his sailors were caught between two equally deadly alternatives. When they realized that

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they had no other option but confront the monsters, they continued onward, sailing their ship past Scylla and Charybdis and suffering some fatalities. Similarly, recent efforts have focused on more comprehensive genomic characterization of SCLC in order to move beyond TP53 and RB1 mutations.

It has been shown that tobacco smoke contains over 60 different mutagens (32). Given the indisputable link between tobacco-smoking and SCLC tumorigenesis, a wide variety of diverse genetic defects are expected to form the mutational landscape of this disease. Genomic research has demonstrated the high mutational burden of SCLC in surgical resection specimens, core biopsies and fine-needle aspirations. Thus, frequent genetic alterations apart from TP53 and RB1 mutations include 3p deletions (33), loss of PTEN (34), activating PI3K mutations (35), upregulation of wild-type c-kit (36), MYC amplification (37) and telomerase activation (38). In contrast to NSCLC, EGFR and KRAS mutations are uncommon (28,39) and linked to combined SCLC/adenocarcinoma cases. Currently, studies utilizing genomic and proteomic profiling technology are providing further insights into SCLC biology. Apart from confirming the data from previous studies (40,41), these techniques have brought to light both genetic changes and aberrantly activated signaling pathways that could be considered novel targets for treatment. These include CREBBP, EP300, MLL, SLIT2 and EPHA7 mutations, FGFR1 amplifications (20), RLF-MYCL1 gene-fusion and SOX2 amplification (19), TMEM132D, SPTA1, VPS13B (42) and activating RET mutations (17), BCL2 (40), RICTOR (43) and KIAA1432 gene amplifications (44), intrinsic and autonomous activation of the Hedgehog pathway (45) and finally repair-protein PARP1 and enhancer of zeste homolog 2 (EZH2) overexpression (46).

The heterogeneity of SCLC is now being established. The genetic signature of these tumors may serve as a useful tool to classify lung tumors and identify subgroups of SCLC with distinct biological features. In such a manner, the map of mutations in never-smoker SCLC patients (47) differs from in smokers (48) and these patients would probably benefit from different treatment strategies. Similarly, patients presenting with small peripheral primary tumors might exhibit a different mutational-dependency than patients with widespread metastatic disease.

Nevertheless, the major challenge remains to organize all these chaotic genetic data into something clinically meaningful. It is believed that only a small subset of the numerous somatic mutations observed in SCLC are crucial

for tumor cell proliferation and progression. A prerequisite for a genetically-informed approach to SCLC would be identification of these "driver" mutations among the numerous, random or secondary, "passenger" mutations which do not confer a clonal growth advantage to the tumor cells. Furthermore, the paradigm of NSCLC has taught us that driver mutations may be rare genetic defects, found only in a small fraction of tumors. However, pie charts illustrating driver mutations in NSCLC contain data from the analysis of thousands of tissue samples. By contrast, thus far less than 200 SCLC samples have been analyzed using next-generation sequencing in the relative studies. The implementation of bioinformatic approaches to the analysis of a large series of SCLC tissue samples would definitely improve functional characterization of SCLC genomic alterations and pave the way for precision medicine (49-51). Sharing this information on certain websites, such as www. mycancergenome.com would facilitate physicians' access to genetic data and available clinical trials.

On the other hand, recent data imply that SCLC might be an immunologically manipulable neoplasm. Long-term SCLC survivors are characterized by predominant activity of immune-effector over immune-suppressive mechanisms (52). Indeed, it could be postulated that the high rate of somatic mutations reported in SCLC may contribute to increased immunogenicity. This hypothesis reinforced by reports of improved survival in patients with neurological paraneoplastic syndromes exhibiting anti-Hu immune responses (53) provide the theoretical rationale for evaluation of immunotherapy strategies in the management of SCLC patients.

Focusing interest back on SCLC

SCLC is classed as an "orphan disease". Over the past years, the attitude of both researchers and the pharmaceutical industry regarding SCLC has been nihilistic. A minor decline in SCLC incidence during the last 30 years (54) together with the recent breakthroughs in translational research in NSCLC may have caused SCLC to be disregarded. This lack of enthusiasm is reflected by the small number of randomized clinical trials in SCLC. A quick search for phase III randomized trials in the published literature reveals more than six times as many NSCLC trials compared to SCLC. Only 125 of 2,499 presentations during the 16th World Conference on Lung Cancer were dedicated to SCLC (55). Since January 2010, approximately 100 interventional phase II and phase III clinical trials have

Table 1 Selected novel chemotherapy agents evaluated in randomized phase III clinical trials in SCLC treatment

Agent	Clinical trial	Line	Result
Amrubicin	Satouchi et al. (62)	1st	No benefit
	von Pawel et al. (63)	2nd	No benefit
Belotecan	Oh et al. (64)	1st	No benefit[1]
Palifosfamide	Jalal et al. (65)	1st	No benefit[1]
Picoplatin	Ciuleanu et al. (66)	2nd	No benefit[1]

[1], Data presented in conference abstract. SCLC, small cell lung cancer.

been enrolled in the registry of ClinicalTrials.gov (56), with a shift towards evaluating new agents in ED-SCLC and relapsed disease (57). Considering the low possibility of a positive phase II trial going forward to a successful phase III trial (58), these remarkably low numbers are clearly insufficient.

Scientific interest and research funding has been directed towards NSCLC drug development and SCLC seems to have be forgotten. Lung cancer researchers and the pharmaceutical companies appear to be living in the land of the Lotus-Eaters. Here it was that some of the Odysseus' sailors ate the lotus. This fruit was so delicious that those who tasted it lost their desire to return home. Odysseus, showing great leadership skills, realized the threat and forced his crew back to the ships and tied them up, readdressing their focus on reaching Ithaca. Similarly, pioneers in SCLC should live up to the challenge posed and lead efforts to facilitate progress in this particular field of oncology. An important step toward this goal is the Scientific Framework for Small Cell Lung Cancer (59), an international initiative created by the National Cancer Institute (NCI) based on the Recalcitrant Cancer Research Act of 2012 (60). Basic, translational and clinical research scientists produced a consensus statement that provides recommendations to guide our efforts in meeting the underlying challenges of SCLC. The five proposed pillars that we should build to provide foundation for fruitful research projects are: (I) optimization of research tools used in preclinical studies of SCLC; (II) growing knowledge about the molecular biology of SCLC; (III) development of novel screening and early detection approaches for high risk populations; (IV) evaluation of therapeutic strategies targeting specific dependencies acquired by SCLC; and (V) elucidation of the biological mechanisms that govern response or resistance to therapy. Alongside highlighting funding opportunities, this scientific framework has drawn attention to SCLC by focusing on research priorities.

Precision medicine and immunotherapy: have we reached the land of the Phaeacians?

Currently, there are no diagnostic approaches that facilitate early detection of SCLC and have a significant impact on patient survival (61). Therefore, the discovery of effective treatments is of paramount importance. Efforts have been made to improve the efficacy of cytotoxic chemotherapy but so far have not improved clinical outcomes (62-66) (*Table 1*). In fact, it is widely accepted that empiric chemotherapy for SCLC has probably plateaued and further evaluation of chemotherapy variations is probably not warranted.

Based on recent advances in defining the molecular landscape of SCLC, a shift towards a translational approach to treatment is emerging. Various molecular targeted therapies have already been evaluated in different settings in SCLC. However, to date no agent has been approved as the clinical trials results have, for the most part, been disappointing (67-86) (*Table 2*).

Digging deeper into the rationale, design and patients enrolled in these trials, it is possible to speculate on the reasons for this failure. Firstly, although in the majority of trials there was a valid theoretical background, with the identification of a single target, the patient population was not selected on the basis of a predictive biomarker. Thus, the targeted therapy was empirically evaluated. Low frequency of the targeted molecular aberration in the study population would therefore negatively influence results. Moreover, driver mutations in this neoplasm have not yet been identified so any trial blocking a secondary molecular pathway with no effect on SCLC oncogenesis would, by definition, be negative. Additionally, considering the high rate of co-existing mutations in SCLC specimens, it is likely that strategies utilizing single agent therapy are unlikely to achieve a clear impact on survival. The substantial clonal heterogeneity observed in SCLC probably necessitates the employment of multi-kinase tyrosine kinase inhibitors or

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Table 2 Selected molecular targeted agents evaluated in clinical trials in SCLC treatment

Agent	Target	Clinical trial	Phase/line	Result
Bevacizumab	VEGF	Pujol et al. (67)	II–III/1st	No benefit
Aflibercept	VEGF	Allen et al. (68)	II/2nd	No benefit in OS
Thalidomide	Immunomodulatory/angiogenesis	Lee et al. (69)	III/1st, maintenance	No benefit
Sunitinib	Multiple kinases, VEGFR	Ready et al. (70)	II/maintenance	Benefit in PFS
Sorafenib	Multiple kinases, VEGFR	Gitlitz et al. (71)	II[1]/2nd	Insufficient efficacy
Imatinib	C-kit	Schneider et al. (72)	II[1]/maintenance	Insufficient efficacy[2]
Gefitinib	EGFR	Moore et al. (74)	II[1]/2nd	Insufficient efficacy
Dasatinib	C-kit, c-Src	Miller et al. (75)	II[1]/2nd	Insufficient efficacy
Temsirolimus	mTORC1	Pandya et al. (73)	II/maintenance	Insufficient efficacy[3]
Everolimus	mTORC1	Tarhini et al. (76)	II[1]/2nd	Insufficient efficacy
Cixutumumab	IGF-1R	Belani et al. (77)	II/1st	No benefit[4]
Vismodegib	SMO	Belani et al. (77)	II/1st	No benefit[4]
Tipifarnib	Farnesyl transferase	Heymach et al. (78)	II[1]/2nd	Insufficient efficacy
Marimastat	Matrix metalloproteinase	Shepherd et al. (79)	III/maintenance	No benefit
Oblimersen	Bcl-2	Rudin et al. (80)	II/1st	No benefit
Navitoclax	Bcl-2 and Bcl-x(L)	Rudin et al. (81)	II[1]/2nd	Limited activity, potential biomarker
Bortezomib	Proteasome	Lara et al. (82)	II/≥2nd	Insufficient efficacy
Vandetanib	RET, VEGFR, EGFR	Arnold et al. (83)	II/maintenance	Insufficient efficacy
Romidepsin	HDAC	Otterson et al. (84)	II[1]/2nd	Insufficient efficacy
AT-101 (Gossypol)	Small molecules in apoptosis[5]	Baggstrom et al. (85)	II[1]/2nd	Insufficient efficacy
Pazopanib	VEGFR	Kotsakis et al. (86)	II[1]/2nd	Moderate efficacy[4]

[1], Non-randomized trial; [2], biomarker-driven study; [3], both study arms were experimental; [4], data presented in conference abstract; [5], inhibitor of the antiapoptotic Bcl-2, Bcl-XL, Bcl-W, and Mcl-1 proteins and inducer of the pro-apoptotic noxa and puma proteins. SCLC, small cell lung cancer; VEGF, vascular endothelial growth factor; OS, overall survival; VEGFR, vascular endothelial growth factor receptor; PFS, progression-free survival; EGFR, epidermal growth factor receptor; IGF-1R, insulin-like growth factor type-1 receptor; SMO, smoothened receptor; HDAC, histone deacetylase.

combined targeted therapy strategies to achieve durable and clinically meaningful responses (87). Lastly, most phase II trials conducted were non-randomized, single-arm studies and results were compared to historical data. This process is biased and often gives false signals regarding drug efficacy. Nevertheless, the drug-development process in NSCLC can be useful in guiding us through these challenges. On the one hand, key objectives of phase I trials could also include identification of possible predictive biomarkers in expanded patient cohorts at the maximum tolerated dose. On the other, launching small, randomized phase II trials that employ biomarker enrichment strategies (88) may prove cost-effective, while increasing confidence in the chances of a successful phase III trial.

Therapeutic progress in SCLC is long overdue. Towards accelerating the pace of drug development, pharmacogenomic approaches to define sensitivity to certain drugs have been adopted. The NCI's Developmental Therapeutics Program is currently using the NCI-60 tumor cell line collection to determine sensitivity to more than 400 targeted agents and 100 FDA-approved oncology treatments *in vitro* (89,90). This approach has already identified some interesting drugs, such as polo-like kinase (PLK) inhibitors, HSP-90, Aurora kinase, HDAC and PARP inhibitors (21,91,92). Research into predictive biomarkers for these strategies is currently ongoing. Screening existing drugs as part of a drug repositioning, bioinformatic approach might also prove useful since tricyclic antidepressants have

recently been shown to exert potent antineoplastic activity *ex vivo* (93). Thus, integrated pharmacogenomics could prove helpful in prioritizing drug candidates for clinical trial evaluation. However, data derived from these analyses should still be interpreted with caution (94) and understood as a basis for hypothesis.

This is an exciting time in SCLC treatment. As active research in SCLC is in progress, novel therapeutic targets have emerged and multiple molecular targeted agents and immunotherapy strategies are currently being evaluated, with promising results in early studies. For example, the Aurora A kinase inhibitor, alisertib, is currently being evaluated in a randomized phase II trial as second line therapy in combination with paclitaxel (NCT02038647). Preclinical data suggesting MYC amplification as a possible predictive biomarker (91) remain to be confirmed. In a multi-histology, phase II basket trial, alisertib demonstrated an overall response rate of 21% in patients with relapsed SCLC (95).

Similarly, PARP inhibition is supported by a solid preclinical rationale (46,96) and a possible predictor of response (92). Following encouraging initial results from phase I trials (97), several PARP inhibitors (talazoparib, veliparib) are being tested in multiple clinical trials as monotherapy (NCT01286987), in combination with chemotherapy (NCT01638546, NCT01642251) in various settings, and even as maintenance treatment (NCT02289690).

Moreover, SCLC models have been shown to be quite sensitive to cyclin-dependent-kinase 7 (CDK7) inhibition (98). As a result, a phase Ib/II study of roniciclib, a CDK7 inhibitor, in combination with chemotherapy as first-line treatment in patients with ED-SCLC is currently ongoing (NCT01573338).

RET inhibition has also been evaluated, in an empiric manner. Vandetanib failed to prolong survival when used as a maintenance treatment (83) in unselected patients. However, recently a rare activating RET mutation (M918T) has been identified in a metastatic SCLC lesion and cell lines overexpressing the mutant protein were shown to be susceptible to RET inhibition (17). It remains to be seen whether this preclinical observation could be translated into improved clinical outcomes in the small percentage of SCLC patients harboring the specific RET mutation.

In the same manner, mTORC1 inhibitors have failed to improve outcomes in unselected SCLC patients (73,76), though the PI3K-AKT-mTOR pathway remains in the spotlight of drug development. A proof-of-concept phase II trial has been designed in order to evaluate PF-

05212384 (PKI-587), a dual PI3K/mTOR inhibitor in pretreated SCLC patients that exhibit features suggestive of PI3K-pathway activation. Recently, an integrated pharmacogenomics study has recognized RICTOR amplification as a predictive biomarker for mTORC1/2 inhibition (99). Biomarker-driven, randomized clinical trials are needed to test this hypothesis.

In addition, a novel class of biopharmaceutical agent is under evaluation in clinical studies. Rovalpituzumab tesirine is an antibody-drug conjugate (ADC) showing promising efficacy in a selected SCLC population. It consists of a Delta-like protein 3 (DLL3) targeted antibody linked to a potent pyrrolobenzodiazepine dimer toxin (100). In a phase Ia/Ib clinical trial the ADC resulted in a 44% overall response rate and 95% clinical benefit rate, demonstrating substantial clinical activity in pretreated patients with DLL3 positive SCLC (101).

Similar to other tumor types, immunotherapy looks set to revolutionize SCLC treatment (102). Although early trials with IFN-a in combination with chemotherapy (103) or vaccines in the adjuvant setting (104) have failed to improve outcomes, successes with immune checkpoint inhibitors in NSCLC have renewed interest in the development of immunologic strategies for SCLC treatment. Early signs indicative of an additive effect of immunotherapy on chemotherapy came from a phase II trial of ipilimumab, an anti-CTLA4 monoclonal antibody, in combination with carboplatin and paclitaxel as first-line treatment in ED-SCLC patients (105). In relapsed disease, anti-PD1 monoclonal antibodies (pembrolizumab, nivolumab) are having an impact with impressive response rates, comparing favorably to historical outcomes (106,107). Nevertheless, questions are being raised whether PDL-1 expression is the ideal biomarker to predict response to anti-PD1 inhibition.

All the above mentioned studies represent a ray of light in the 30-year darkness of failure and struggle against this dismal disease. Perhaps this is the last stop in our journey to Ithaca, as was the friendly, safe land of the Phaeacians for Odysseus. However, the past has taught us that overwhelming optimism may only lead us to failure once again. Only time will tell whether targeted therapy and immunotherapy can improve clinical outcomes to such a degree that they constitute a meaningful change in SCLC treatment.

Conclusions

In spite of recent advances in elucidating the aberrant

molecular pathways that dictate SCLC oncogenesis, this malignancy remains an important public health problem, leading to the death of approximately 16,000 patients per year in the United States (14). For decades, cytotoxic chemotherapy has remained the backbone of treatment but, while SCLC is a chemo-sensitive disease, experience shows that high response rates are not universally translated into a cure. Nevertheless, it is high time progress was made in SCLC research and we have all the necessary tools at our disposal. Every failure is a lesson learnt, every success a battle fought. Our aim must be to improve the prognosis of patients with SCLC.

We are still on the long journey to Ithaca and should not let the Sirens of excessive optimism distract us from our goal. With determination and cunning we can reach Ithaca. By any means, whatever the final result may be, the entire research process will make us wiser.

"As you set out for Ithaca, hope the voyage is a long one, full of adventure, full of discovery……And if you find her poor, Ithaca won't have fooled you. Wise as you will have become, so full of experience, you will have understood by then what these Ithakas mean" (*The Canon* by CP Cavafy, translated by Edmund Keeley and Philip Sherrard).

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Footnote

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