REVIEW ARTICLE

Incremental Innovation and Progress in Advanced Squamous Cell Lung Cancer: Current Status and Future Impact of Treatment

Corey J. Langer, MD,[a,*] Coleman Obasaju, MD, PhD,[b] Paul Bunn, MD,[c] Philip Bonomi, MD,[d] David Gandara, MD,[e] Fred R. Hirsch, MD,[c] Edward S. Kim, MD,[f] Ronald B. Natale, MD,[g] Silvia Novello, MD, PhD,[h] Luis Paz-Ares, MD,[i] Maurice Pérol, MD,[j] Martin Reck, MD,[k] Suresh S. Ramalingam, MD,[l] Craig H. Reynolds, MD,[m] Mark A. Socinski, MD,[n] David R. Spigel, MD,[o] Heather Wakelee, MD,[p] Carlos Mayo, MD,[b] Nick Thatcher, MD, PhD[q]

[a]*Department of Thoracic Oncology, Abramson Cancer Center, University of Pennsylvania, Philadelphia, Pennsylvania*
[b]*Eli Lilly and Company, Indianapolis, Indiana*
[c]*University of Colorado Cancer Center, Aurora, Colorado*
[d]*Rush University Medical Center, Chicago, Illinois*
[e]*Department of Hematology and Oncology, University of California Davis Comprehensive Cancer Center, Sacramento, California*
[f]*Levine Cancer Institute, Carolinas HealthCare System, Charlotte, North Carolina*
[g]*Cedars-Sinai Comprehensive Cancer Center, West Hollywood, California*
[h]*University of Turin, Turin, Italy*
[i]*Hospital Universitario Doce de Octubre and Centro Nacional de Investigaciones Oncológicas, Madrid, Spain*
[j]*Department of Medical Oncology, Léon Bérard Cancer Center, Lyon, France*
[k]*Lung Clinic Grosshansdorf, Airway Research Center North, Member of the German Center for Lung Research, Grosshansdorf, Germany*
[l]*Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University, Atlanta, Georgia*
[m]*U.S. Oncology Research, Ocala, Florida*
[n]*Florida Hospital Cancer Institute, Orlando, Florida*
[o]*Sarah Cannon Research Institute, Nashville, Tennessee*
[p]*Stanford University School of Medicine, Palo Alto, California*
[q]*The Christie Hospital, Manchester, United Kingdom*

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***Corresponding author.**

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Address for correspondence: Corey J. Langer, MD, Department of Thoracic Oncology, Abramson Cancer Center, University of Pennsylvania, 16 Penn Tower, 3400 Civic Center Blvd., Philadelphia, PA 19104. E-mail: Corey.langer@uphs.upenn.edu

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ABSTRACT

Squamous cell lung cancer (sqCLC) is an aggressive form of cancer that poses many therapeutic challenges. Patients tend to be older, present at a later stage, and have a high incidence of comorbidities, which can compromise treatment delivery and exacerbate toxicity. In addition, certain agents routinely available for nonsquamous cell histologic subtypes, such as bevacizumab and pemetrexed, are contraindicated or lack efficacy in sqCLC. Therapeutic progress has been much slower for advanced sqCLC, with median survival times of approximately 9 to 11 months in most studies. Herein, we discuss the current therapeutic landscape for patients with sqCLC versus with nonsquamous NSCLC. Current evidence indicates that new targeted treatments, notably monoclonal antibodies such as ramucirumab and necitumumab, and immunotherapies such as nivolumab and pembrolizumab can provide survival prolongation, although the benefits are still relatively modest. These incremental improvements, all realized since 2012, in aggregate, will very likely have a clinically meaningful impact for patients with sqCLC. We also discuss recent genomic studies of sqCLC that have identified potentially actionable molecular targets, as well as the relevant targeted agents in clinical development. Finally, we discuss the magnitude of survival benefit and the risk-to-benefit ratio that would prove clinically meaningful in this underserved patient population with unmet needs.

Keywords: NSCLC; Squamous cell lung cancer; Advanced; Therapeutic landscape; Clinically meaningful outcomes

Introduction

NSCLC is a heterogeneous disease, with squamous cell lung cancer (sqCLC) accounting for approximately 25% to 30% of cases.[1,2] sqCLC is aggressive and often challenging to treat, with treatment advances lagging behind those of adenocarcinoma for several reasons: (1) patients with sqCLC tend to be older[3] and typically present with advanced disease;[4] (2) the central location of most squamous tumors close to large blood vessels[5] can present treatment challenges, including bleeding and hemoptysis, that in turn can contraindicate certain therapeutic agents; and (3) as the predominant risk factor is smoking,[1,6] patients have a higher incidence of comorbidities than do their counterparts with nonsquamous NSCLC,[7,8] and these in turn are associated with poorer survival[9–11] and a higher incidence of adverse events after chemotherapy,[12] which can compromise treatment planning, delivery, and success. As a result, active cancer interventions are often not prescribed,[9,13] with many patients receiving only supportive care. Although the proportion of patients with sqCLC has declined in developed countries,[14–16] sqCLC remains a major global concern,[17–19] especially in Eastern Europe, where smoking rates remain high.[16]

The U.S. Surveillance, Epidemiology and End Results survey (1990–2005) revealed that between 1990 and 2005, significant improvements in survival were observed for patients with metastatic NSCLC, irrespective of histologic subtype; however, between 2002 and 2005, survival significantly increased for patients with metastatic adenocarcinoma versus for patients with sqCLC.[20] This observation coincided with the approval and increased use of EGFR tyrosine kinase inhibitors (TKIs) such as gefitinib and erlotinib during the latter time period. The benefits of EGFR TKIs and other agents targeting oncogenic drivers, such as anaplastic lymphoma kinase (ALK) inhibitors, have largely been confined to advanced adenocarcinoma, in which these molecular abnormalities are almost exclusively observed.[21–25] Until late 2015, no targeted therapies were approved for first-line treatment of sqCLC,[26–33] and median survival in advanced sqCLC remained static at approximately 9 to 11 months[34,35] versus approximately 12 to 14 months for nonsquamous NSCLC.[34–38] New treatment strategies that would provide clinically meaningful outcomes without adversely affecting quality of life (QoL) are therefore needed for sqCLC. Fortunately, intense research into the molecular pathogenesis of sqCLC is ongoing and novel targeted agents and immunotherapies have recently been approved.

This review describes the importance of incremental innovation and progress in achieving clinically meaningful improvements in survival for patients with sqCLC. Current treatment options, the recent impact of immunotherapy approaches, and the potential impact of emerging biomarkers and targeted therapies on survival for sqCLC are discussed.

Incremental Progress in the Treatment of NSCLC

The improvement in survival for patients with advanced NSCLC, including sqCLC, has been the result of relatively small incremental gains rather than substantial increases due to individual treatment developments.[20] Over the past three decades, stepwise increases in survival for advanced NSCLC have paralleled the change from first-line single-drug platinum treatment to platinum-doublet chemotherapy to platinum-doublet chemotherapy with or without targeted therapies (for nonsquamous NSCLC only) (Fig. 1 and Table 1)[34,35,37–49] as well as the advent of second-line and third-line regimens, with a positive impact on survival.[50–54]

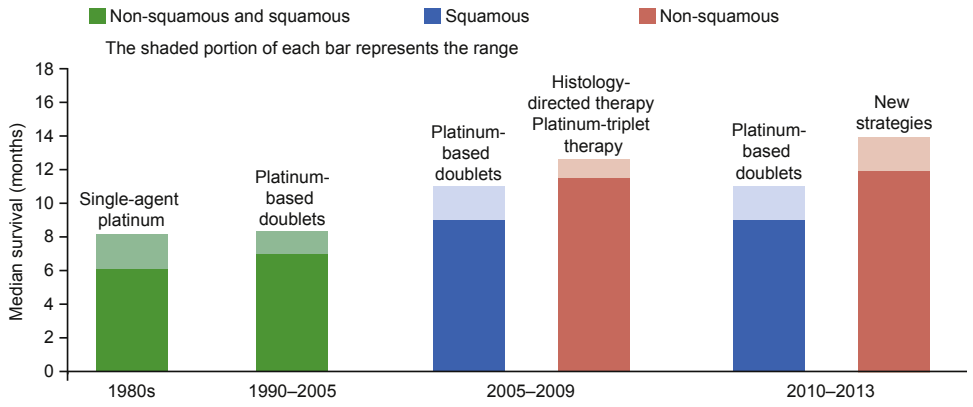

Figure 1. Examples of incremental advances in survival for first-line advanced/metastatic NSCLC.[34,35,37-48]

Before routine use of chemotherapy (mostly in the 1980s), median survival for advanced NSCLC was 3 to 5 months.[55] The advent of cytotoxic platinum doublets in the 1990s increased median overall survival (OS) compared with that provided by single agents, with the increase being similar for adenocarcinoma and sqCLC and reaching approximately 8 to 11 months after the introduction of platinum doublets containing paclitaxel, vinorelbine, or gemcitabine.[40–48] Triplet therapy yielded greater toxicity but no additional survival benefit versus that from two-drug combinations.[56,57] Subsequent studies showed discordance between safety or efficacy outcomes for bevacizumab and pemetrexed by histologic subtype, with benefits confined to patients with nonsquamous NSCLC versus sqCLC.[27,34]

First-Line Therapy for Nonsquamous NSCLC

In the mid-2000s, the vascular endothelial growth factor inhibitor bevacizumab in combination with platinum-based chemotherapy demonstrated a survival benefit compared with chemotherapy alone in patients with a nonsquamous histologic subtype and no antecedent history of hemoptysis (see Table 1).[37,38] More recently, in patients with adenocarcinoma, pemetrexed-cisplatin significantly improved median OS versus with gemcitabine-cisplatin (see Table 1).[34] The survival benefits of pemetrexed extended into the first-line maintenance setting irrespective of whether patients received pemetrexed as a component of their initial platinum-based chemotherapy combination.[36,58]

In patients with activating *EGFR* mutations and *ALK* rearrangements, EGFR TKIs and crizotinib, respectively, have significantly improved objective response rates and progression-free survival (PFS), with major reductions in toxicity compared with standard platinum-doublet chemotherapy.[59–65] For these reasons, current guidelines indicate the need for molecular testing and treatment with EGFR TKIs or ALK inhibitors for patients with positive test results.[66–69] In the case of afatinib, a second-generation EGFR TKI and ErbB family blocker, a major survival advantage has been observed compared with that provided by chemotherapy in patients with exon 19 deletion.[70]

Demonstrating OS benefits for EGFR TKIs and crizotinib has proved challenging in randomized studies on account of crossover treatments after first-line therapy. However, evidence of improved OS is available from historical comparisons, retrospective analyses, and comparisons between patients who did and did not receive targeted treatments.[22,71,72]

First-Line Therapy for sqCLC

More modest improvements in survival have been observed for sqCLC. Activating *EGFR* mutations or anaplastic lymphoma receptor tyrosine kinase gene (*ALK*) rearrangements are exceedingly rare in sqCLC,[21,23–25] and most patients with sqCLC do not undergo molecular testing for these alterations unless they have minimal or no prior tobacco exposure. Consequently, few treatment-naive patients with sqCLC are candidates to receive EGFR TKIs or ALK inhibitors. Additionally, bevacizumab is contraindicated in sqCLC[73,74] because of pulmonary hemorrhage, which was first observed in a randomized phase II trial,[27] prompting the exclusion of patients with sqCLC from subsequent phase III trials.[37]

Retrospective analyses of earlier studies in NSCLC with platinum-doublet chemotherapy did not show a significant difference in survival outcomes between patients with nonsquamous and squamous histologic subtypes (see Table 1).[45,46] In a later large randomized trial, a survival benefit was observed in sqCLC for gemcitabine-cisplatin versus for pemetrexed-cisplatin (see Table 1).[34] For sqCLC, a platinum agent plus either gemcitabine or a taxane remains the most frequently used first-line combination,[75–77] with the selection of agents generally based on toxicity and preexisting medical issues. Yet, over the past decade, modest progress has been

observed with the introduction of nab-paclitaxel. In a phase III study (N = 1052), first-line nab-paclitaxel–carboplatin demonstrated a significant improvement in response rate versus that provided by paclitaxel-carboplatin for patients with sqCLC (41% versus 24%, response rate ratio = 1.68; 95% confidence interval (CI): 1.27–2.22, $p < 0.001$).[35] Although the improvement in response rate did not translate into a significant OS benefit in either sqCLC (10.7 versus 9.5 months, hazard ratio [HR] = 0.89) or nonsquamous NSCLC (13.1 versus 13.0 months, HR = 0.95 [see Table 1]),[35] nab-paclitaxel plus a platinum agent is a first-line treatment option for patients with sqCLC. Recently, the cisplatin derivative nedaplatin plus docetaxel showed a survival benefit versus with cisplatin-docetaxel in Japanese patients with sqCLC (see Table 1).[49]

When the improvements in OS afforded by individual first-line therapies in advanced NSCLC are viewed critically, it is evident that they have generally been modest irrespective of histologic subtype. In aggregate, however, these incremental improvements have yielded much larger clinically important benefits.

Second- and Subsequent-Line Therapy for Nonsquamous NSCLC and sqCLC

Single-agent second- or subsequent-line therapy has also provided a modest survival benefit in advanced NSCLC.[53,54,78,79] Docetaxel was the first agent approved in the United States for second-line NSCLC therapy. Although the efficacy and safety of docetaxel in combination with other agents (e.g., erlotinib, vinorelbine, or gemcitabine) has been investigated in the second-line setting, several studies showed no improvement in efficacy and/or increased toxicity with combination therapy over docetaxel alone.[80–84] Furthermore, phase III trials seeking to improve survival by adding targeted agents such as cetuximab[85] or ziv-aflibercept[86] were negative.

The differential effects of pemetrexed by histologic subtype have also been demonstrated in the second-line setting. Although similar survival outcomes were observed overall in a phase III trial comparing pemetrexed with docetaxel,[79] a secondary analysis showed a survival benefit for pemetrexed for nonsquamous NSCLC, whereas patients with sqCLC fared better with docetaxel.[50] This observation contributed to a change in indication of pemetrexed to exclude sqCLC in the second-line setting.[87]

For targeted agents such as erlotinib in unselected patients, including those with sqCLC, survival benefits have been observed only in comparison with placebo controls or best supportive care.[54,78] Comparisons of erlotinib or gefitinib with docetaxel have generally shown similar survival outcomes in unselected patients or patients with EGFR wild-type tumors,[51,88,89] although OS was significantly longer with docetaxel than with erlotinib (8.2 versus 5.4 months, HR = 0.73, 95% CI: 0.53–1.00, $p = 0.05$) in the TAILOR study.[51]

Targeted Agents and Immunotherapy Approaches in sqCLC

Considerable research is being focused on novel targeted agents and immunotherapy approaches for advanced sqCLC. Necitumumab is the first targeted agent to be approved in the first-line setting, and three agents have been approved in the second-line setting.

Antiangiogenesis

Although targeting angiogenesis has proven challenging in sqCLC owing to the increased risk for pulmonary hemorrhage with agents such as bevacizumab,[27,29] the antiangiogenic vascular endothelial growth factor receptor 2 inhibitor ramucirumab plus docetaxel has been approved in the United States and Europe for the second-line treatment of metastatic or advanced NSCLC, respectively, in all histologic subtypes,[90,91] thereby expanding the limited therapeutic armamentarium for sqCLC. In the second-line phase III REVEL study (N = 1253), ramucirumab plus docetaxel demonstrated improved median OS versus with docetaxel alone in the overall population (10.5 versus 9.1 months, HR = 0.86, 95% CI: 0.75–0.98, $p = 0.023$).[92] Comparable, but nonsignificant, OS benefits were observed in the sqCLC subgroup (n = 328 [26%], 9.5 versus 8.2 months, HR = 0.88, 95% CI: 0.69–1.13) (Fig. 2). Similar benefits were observed in response rate and PFS. Of note, ramucirumab did not increase toxicity (in particular, the rates of hemoptysis or pulmonary hemorrhage) in the sqCLC subgroup versus in the nonsquamous subgroup.

Anti-EGFR

EGFR amplification occurs in 7% to 10% of sqCLC tumors,[21] and overexpression of the EGFR protein is more common in sqCLC than in nonsquamous NSCLC.[93] EGFR overexpression correlates with increased gene copy number, and an association between increased gene copy number and poor prognosis has been observed.[93] The phase III FLEX trial of first-line therapy (N = 1125) investigated the addition of the EGFR inhibitor cetuximab to chemotherapy.[94] A statistically significant but clinically modest improvement in OS was observed with cetuximab plus chemotherapy versus with chemotherapy alone in patients with sqCLC (10.2 versus 8.9 months, HR = 0.80, 95% CI: 0.64–1.00) compared with in those with adenocarcinoma (12.0 versus 10.3 months, HR = 0.94, 95% CI: 0.77–1.15). A meta-analysis of four randomized trials examining the

Table 1. Incremental Improvements in Survival with First-Line Treatment of Advanced/Metastatic NSCLC

Study	Population	Regimen	Median OS, mo		
			All Histologic Subtypes	Nonsquamous	Squamous
Single-agent platinum chemotherapy					
EST 1583 (n = 699)[a,39]		Carboplatin	7.3		
Platinum-doublet chemotherapy					
Wozniak et al. (n = 432)[44]	Advanced NSCLC	Cisplatin	6		
	PS 0-1	Vinorelbine-cisplatin	8		
			($p = 0.018$)		
Sandler et al. (n = 522)[43]	Advanced NSCLC	Cisplatin	7.6		
		Gemcitabine-cisplatin	9.1		
			($p = 0.004$)		
ECOG 1594 (n = 1207)[42,45]	Stage IIIb/IV	Platinum doublet	7.9	Adenocarcinoma:	
	PS 0-2	Paclitaxel-cisplatin	7.8	9.1	6.9
		Gemcitabine-cisplatin	8.1	8.1	9.4
		Docetaxel-cisplatin	7.4	7.7	8.1
		Paclitaxel-carboplatin	8.1	7.6	9.3
Rosell et al. (n = 618)[41]	Stage IIIb/IV	Paclitaxel-carboplatin	8.2		
	PS 0-2	Paclitaxel-cisplatin	9.8		
			(HR = 1.22, 95% CI: 1.06-1.40, $p = 0.019$)		
TAX 326 (n = 1218)[40]	Stage IIIb/IV	Vinorelbine-cisplatin	10.1		
		Docetaxel-cisplatin	11.3		
			($p = 0.044$)		
Lilenbaum et al. (n = 561)[47]	Stage IIIb/IV	Paclitaxel	6.7		
	PS 0-2	Paclitaxel-carboplatin	8.8		
			(HR = 0.91, 95% CI: 0.77-1.17, $p = 0.25$)		
GLOB3 (n = 381)[48]	Stage IIIb/IV			Adenocarcinoma:	
	KPS ≥80%	Vinorelbine-cisplatin	9.9	11.7	8.9
		Docetaxel-cisplatin	9.8	11.6	9.8
			($p = 0.58$)		
SWOG (S9308, S9509, and S0003; n = 792)[46]	Stage IIIb (pleural effusion only)/IV			Adenocarcinoma:	
	PS 0-1	Paclitaxel-carboplatin		9.1	8.8
		Vinorelbine-cisplatin		8.1	6.9

(continued)

Table 1. Continued

Study	Population	Regimen	Median OS, mo		
			All Histologic Subtypes	Nonsquamous	Squamous
Newer cytotoxics					
Scagliotti et al. (n = 1725)[34]	Stage IIIb/IV	Pemetrexed-cisplatin	10.3	11.8	9.4
	PS 0-1	Gemcitabine-cisplatin	10.3	10.4	10.8
			(HR = 0.94, 95% CI: 0.84-1.05)	(HR = 0.81, 95% CI: 0.70-0.94, $p = 0.005$)	(HR = 1.23, 95% CI: 1.00-1.51, $p = 0.05$)
Socinski et al. (n = 1052)[35]	Stage IIIb/IV	Nab-paclitaxel-carboplatin	12.1	13.1	10.7
	PS 0-1	Paclitaxel-carboplatin	11.2	13.0	9.5
			(HR = 0.92, 95% CI: 0.80-1.07, $p = 0.27$)	(HR = 0.95)	(HR = 0.89)
WJOG5208L (n = 355)[49]	Stage IIIb/IV or recurrent	Nedaplatin-docetaxel			13.6
	PS 0-1	Cisplatin-docetaxel			11.4
					(HR = 0.81, 95% CI: 0.65-1.02, $p = 0.037$)
Targeted therapies					
Sandler et al. (n = 878)[37,38]	Stage IIIb/IV			Adenocarcinoma[b]:	
	PS 0-1	Paclitaxel-carboplatin		10.3	
		Bevacizumab + paclitaxel-carboplatin		14.2	
				(HR = 0.69, 95% CI: 0.58-0.83)	

[a]Only data for carboplatin arm are shown.
[b]OS for nonsquamous NSCLC: 10.3 months with paclitaxel-carboplatin versus 12.3 months with bevacizumab + paclitaxel-carboplatin (HR = 0.80, 95% CI: 0.69-0.93).
OS, overall survival; PS, performance status; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; CI, confidence interval; KPS, Karnofsky performance status.

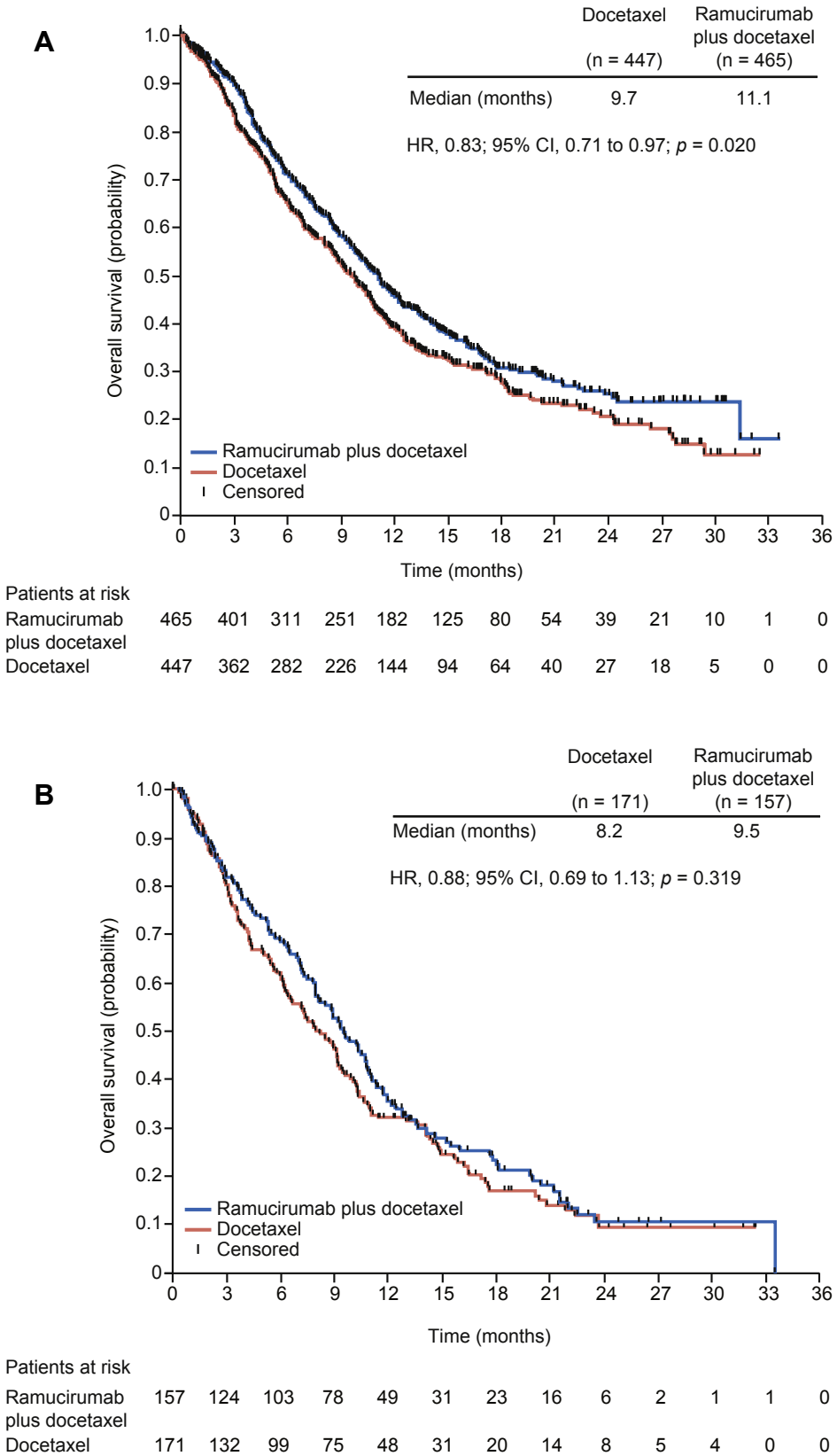

Figure 2. Overall survival in the phase III REVEL study. (*A*) Patients with nonsquamous NSCLC; (*B*) Patients with squamous cell lung cancer. CI, confidence interval; HR, hazard ratio; sqCLC, squamous cell lung cancer. Reprinted with permission from Garon et al.[92]

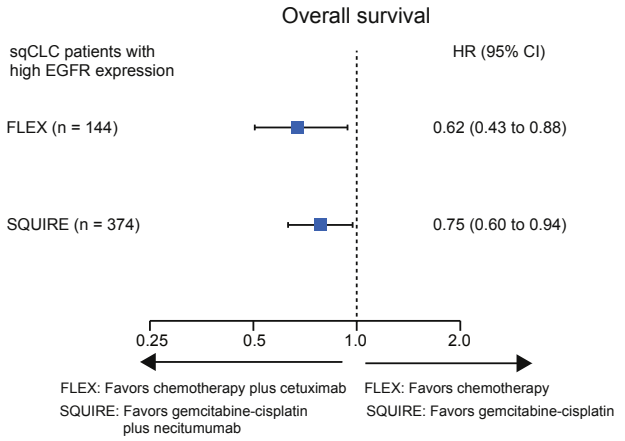

Figure 3. Overall survival in patients with squamous cell lung cancer (sqCLC) with high EGFR expression in the phase III FLEX[99] and SQUIRE[100] studies. CI, confidence interval; HR, hazard ratio.

risk-to-benefit profile of cetuximab as first-line therapy for advanced NSCLC demonstrated that the addition of cetuximab to platinum-based chemotherapy significantly improved OS, PFS, and response rate, with a manageable safety profile versus with chemotherapy alone.[95]

It was hoped that identification of predictive biomarkers such as EGFR protein expression or gene copy number would allow an informed selection of patients most likely to benefit from therapies targeting EGFR. Increased EGFR gene copy number by fluorescent in situ hybridization (FISH) was first shown to be predictive for cetuximab efficacy in a phase II study with 229 chemotherapy-naive patients with advanced NSCLC.[96] However, in a retrospective analysis of the first-line BMS099 study of cetuximab plus carboplatin-taxane versus carboplatin-taxane (which did not show a significant OS benefit with cetuximab), no significant associations were observed for EGFR protein expression by immunohistochemistry or EGFR FISH positivity.[97,98] In an analysis of patients from the phase III FLEX study with available tumor EGFR immunohistochemistry data (1121 of 1125 patients), the median OS of patients in the high–EGFR expression group (H-score $\geq$200) was longer for cetuximab plus chemotherapy than for chemotherapy alone (12.0 versus 9.6 months, HR = 0.73, 95% CI: 0.58–0.93, p = 0.011), with no meaningful increase in side effects.[99] No corresponding survival benefit was observed in the low–EGFR expression group (H-score <200). Similarly, prolonged OS was observed in the sqCLC subgroup with high EGFR expression with the cetuximab combination versus with chemotherapy alone (HR = 0.62, 95% CI: 0.43–0.88) (Fig. 3).[99] Of note, determination of the H-score cutoff of 200 or higher was based on association with response rate, and the effect on OS was assessed on the same patient population. A formal randomized, phase III study (SWOG 0819; NCT00946712) examined cetuximab efficacy (with variable inclusion of bevacizumab) in the first-line advanced NSCLC (including sqCLC) setting, with a subgroup analysis investigating the predictive role of increased EGFR gene copy number measured by FISH.[101,102] Although cetuximab in combination with chemotherapy did not significantly increase OS versus chemotherapy alone in the overall population, OS was significantly improved in the sqCLC FISH–positive subgroup (11.8 versus 6.4 months, HR = 0.56, 95% CI: 0.37–0.84, p = 0.006).[103]

The phase III SQUIRE trial of first-line necitumumab, a second-generation EGFR inhibitor, combined with gemcitabine-cisplatin in patients with metastatic sqCLC (N = 1093) demonstrated significant improvements in OS versus with gemcitabine-cisplatin alone (11.5 versus 9.9 months, HR = 0.84, 95% CI: 0.74–0.96, p = 0.01), in PFS (5.7 versus 5.5 months, HR = 0.85, 95% CI: 0.74–0.98, p = 0.02), and in disease control rate (82% versus 77%, p = 0.043).[100] An exploratory analysis demonstrated that patients with sqCLC with high EGFR expression (H-score $\geq$200), but not low EGFR expression (H-score <200), had significantly improved OS with the addition of necitumumab versus with gemcitabine-cisplatin alone (see Fig. 3). However, the difference in HR between the two EGFR expression groups was not significant (interaction p value = 0.24). Further analysis showed a trend toward greater OS benefit with necitumumab versus with chemotherapy alone in patients with EGFR FISH–positive tumors (12.6 versus 9.2 months, HR = 0.70, 95% CI: 0.52–0.96).[104] Although the same positive predictive trend for EGFR gene copy number assessed by FISH was seen in both the SQUIRE and SWOG 0819 studies (see earlier),[102,104] further validation of FISH as a predictive assay for anti-EGFR antibodies must be performed before valid clinical conclusions can be drawn. The safety profile of necitumumab was consistent with that expected for an EGFR antibody in combination with chemotherapy, with venous thromboembolic events more common and increased incidence of skin reactions with a grade of 3 or higher and hypomagnesemia.[100] Necitumumab plus gemcitabine-cisplatin is approved in the United States for the treatment of metastatic sqCLC[33] and in Europe for the treatment of advanced EGFR-expressing sqCLC,[105] and it constitutes a true incremental advance for patients with sqCLC in the first-line setting. However, the lack of a validated predictive biomarker for anti-EGFR monoclonal antibodies remains an issue.

Finally, afatinib recently demonstrated superiority over erlotinib for disease control rate (51% versus 40%, p = 0.002), PFS (2.6 versus 1.9 months, HR = 0.81, 95% CI: 0.69–0.96, p = 0.010), and OS (7.9 versus 6.8 months, HR = 0.81, 95% CI: 0.69–0.95, p = 0.008) in second-line

advanced sqCLC.[106] In early 2016, it was approved in both the United States and Europe for use in this setting.[107,108]

Immunotherapy Approaches in sqCLC

Multiple agents targeting immunologic pathways are in clinical development for NSCLC, including sqCLC. The cytotoxic T-lymphocyte–associated antigen-4 (CTLA-4) and anti–programmed cell death protein 1 (anti–PD-1) pathways are two checkpoint pathways critical for controlling T-cell immune responses, which coordinate the immune response to tumors.[109] By targeting these pathways, immunotherapies aim to restore the immune system and allow T cells to function appropriately against tumors.

Ipilimumab, an anti–CTLA-4 monoclonal antibody, prevents T-cell downregulation.[110] In subset analyses of a phase II study in all NSCLC histologic subtypes, a phased regimen of ipilimumab plus carboplatin-paclitaxel, in which ipilimumab was grafted onto the third cycle of carboplatin-paclitaxel, exhibited a trend toward greater PFS benefits versus with carboplatin-paclitaxel alone for patients with sqCLC (HR = 0.55, 95% CI: 0.27–1.12) than for patients with nonsquamous NSCLC (HR = 0.82, 95% CI: 0.52–1.28) without overtly exacerbating the toxicities associated with carboplatin-paclitaxel.[110] Similar results were observed for OS, with a nonsignificant improvement in 3-month survival for phased ipilimumab plus carboplatin-paclitaxel compared with for carboplatin-paclitaxel alone in patients with sqCLC (10.9 versus 7.9 months, HR = 0.48, 95% CI: 0.22–1.03), but no benefit for nonsquamous NSCLC (HR = 1.17, 95% CI: 0.74–1.86).[110,111] This observation laid the foundation for ongoing phase III trials investigating ipilimumab in combination with carboplatin-paclitaxel for first-line treatment of metastatic/recurrent sqCLC (NCT01285609 and NCT02279732 [enrollment complete]), which started in 2011 and 2014, respectively.

The U.S. and European approvals of the anti–PD-1 agent nivolumab for second-line treatment of advanced sqCLC were based on the results of the phase III Checkmate 017 study of nivolumab versus docetaxel (N = 272).[112] Patients who received nivolumab had significantly longer median OS than patients who received docetaxel (9.2 versus 6.0 months, HR = 0.59, 95% CI: 0.44–0.79, $p < 0.001$), increased median PFS (3.5 versus 2.8 months, HR for death or disease progression = 0.62, 95% CI: 0.47–0.81, $p < 0.001$), and increased response rate (20% versus 9%, $p = 0.008$). The 1-year survival rates were 42% and 24%, respectively. Median duration of response was not reached in the nivolumab group, whereas it was 8.4 months in the docetaxel group. Grade 3 or 4 treatment-related adverse events were reported less frequently with nivolumab than with docetaxel (7% versus 55%). In an exploratory analysis in a limited number of patients that used low cutoffs for programmed death ligand 1 (PD-L1) expression, the OS and PFS benefits with nivolumab were observed regardless of levels of tumor expression of PD-L1.

Another anti–PD-1 agent, pembrolizumab, received accelerated approval in the United States for second-line treatment of patients with advanced NSCLC, including sqCLC, whose tumors express PD-L1. Approval was based on the results of a subgroup analysis of patients in the KEYNOTE-001 study[113] with a PD-L1 expression tumor proportion score (TPS) of 50% or higher (n = 61) for whom a response rate of 41%[114] and long duration of response was observed.[115]Additionally, in the second-line phase II/III KEYNOTE-010 study (N = 1034), pembrolizumab demonstrated longer OS versus with docetaxel in patients with both a PD-L1 TPS of at least 50% and a TPS of at least 1%.[116] Other anti–PD-1 and anti–PD-L1 agents, such as atezolizumab and durvalumab, are in phase III development for advanced NSCLC, including sqCLC.

PD-L1 expression as a predictive biomarker for treatments targeting the PD-1 pathway is still being investigated.[117,118] The preliminary evidence suggests that smoking may correlate with heightened response to anti–PD-L1 agents[119] and that the benefits of these agents may be more pronounced in those with greater mutation burden,[120] as is typical in advanced sqCLC.[21]

Immunotherapy approaches for sqCLC are highly promising, but additional data from large randomized clinical trials are needed to fully evaluate their efficacy and safety profiles. However, the approval of nivolumab in sqCLC has proved transformative already, with docetaxel relegated to the third-line setting.

Potential Biomarkers and Targeted Therapies

The genome of lung adenocarcinoma has been increasingly classified since the early 2000s; as of 2015, multiple actionable molecular targets have been identified.[22] Until recently, however, little was known of potential oncogenes in sqCLC.[21,23,25,121,122] It is apparent that the oncogenic profiles of adenocarcinoma and sqCLC are different. SqCLC tumors are genetically complex and have a high frequency of mutations in proteins, many of which are not mutually exclusive.[21,25] Rather than single oncogenic driver mutations that may be targeted in adenocarcinoma, the molecular targets for therapy in sqCLC involve overexpression or amplification of multiple receptors.

Targets include EGFR expression (as already described), ErbB family inhibition, fibroblast growth factor receptor-1 (FGFR1) amplification, discoidin domain receptor tyrosine kinase 2 (DDR2) mutations, and phosphoinositide-3-kinase pathway changes (phosphatidylinositol 3-kinase catalytic subunit alpha

Table 2. Targeted Agents Directed against FGFR1 Amplification in sqCLC in Phase II/III Clinical Development for Advanced/Metastatic sqCLC

Targeted Agent	Development Phase	Treatment Setting	Treatment Regimen	Study No.
AZD4547	II	Maintenance	Single agent	NCT02117167
	II/III	≥Second-line	Single agent	NCT02154490
Ponatinib	II	All lines	Single agent	NCT01935336
Lucitanib	II	≥Second-line	Single agent	NCT02109016
Nintedanib	II	First-line	Combination with gemcitabine-cisplatin	NCT01346540
		Second- / third-line	Single agent	NCT01948141
Dovitinib	II	Second- / third-line	Single agent	NCT01861197

sqCLC, squamous cell lung cancer; FGFR1, fibroblast growth factor receptor-1.

mutation and phosphatase and tensin homolog mutation or deletion) (Table 2 and Fig. 4).[21,23,25,93,123–125]

FGFR1 amplification has been identified in up to 25% of sqCLC tumor specimens[21,23,123,126] and has been associated with tumor growth and survival.[123] When a 3.5-fold amplification cutoff is used, the FGFR1 amplification rate is approximately 5% in sqCLC.[127] Alterations in the phosphoinositide-3-kinase pathway affect cell survival and proliferation[128] and are common in sqCLC, with phosphatidylinositol 3-kinase catalytic subunit alpha mutations and phosphatase and tensin homolog mutations or deletion occurring in approximately 30% to 50% of tumors.[21,23] Actionable targets that occur with low frequency include mutations in the discoidin domain receptor tyrosine kinase 2 gene (*DDR2*) (~3%–4%)[25,124,129] and ErbB2 amplification (4%).[130] Preclinical studies suggest that DDR2 mutations may promote squamous cell proliferation, migration, and invasion[129] and may be successfully targeted by dasatinib[124]; however, a phase II study of dasatinib in advanced sqCLC in unselected patients was terminated on account of excess dasatinib toxicity.[131]

The deployment of targeted therapies is challenging in sqCLC because of the genetic diversity, mutation burden, and lack of clear oncogenic drivers in this disease. Thus far, novel targeted therapies for sqCLC have demonstrated only marginal to modest clinical benefits as monotherapies.[132–134] Ultimately, we may need to wait until novel combinations of targeted agents or targeted agents with conventional chemotherapy are identified before substantial improvements in survival are observed.

New Clinical Trial Designs in sqCLC

The diverse genetic characteristics of sqCLC also make it challenging to recruit enough patients from an

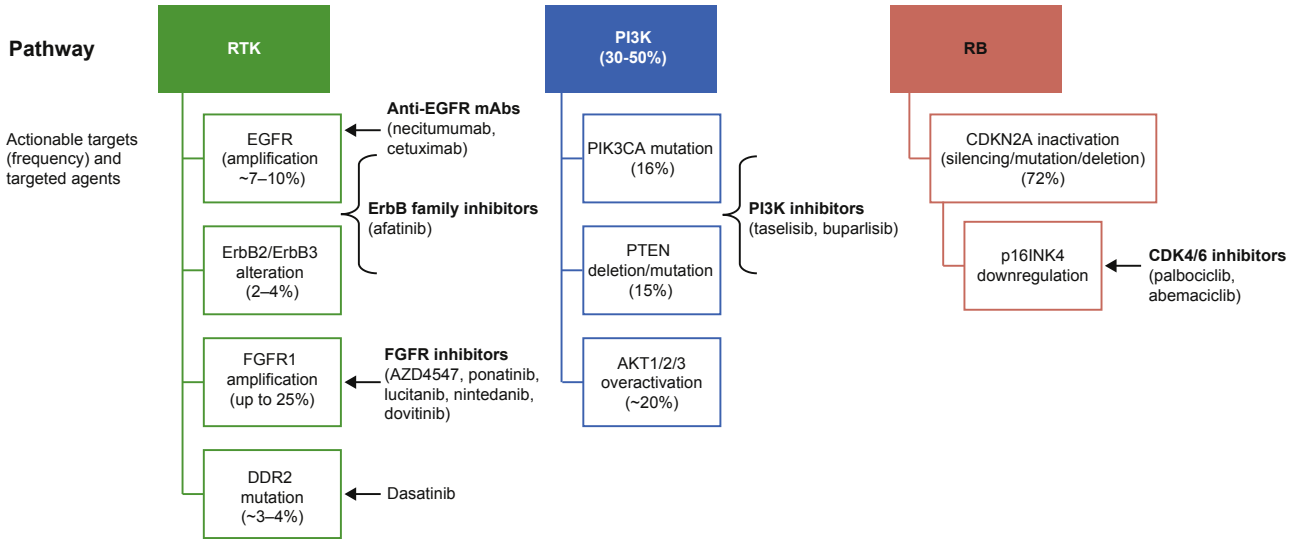

Figure 4. Selected signaling pathways with actionable molecular targets (and their frequencies) in squamous cell lung cancer with targeted agents approved or in development.[21,25,125] RTK, receptor tyrosine kinase; PI3K, phosphoinositide-3-kinase; RB, retinoblastoma; ErbB2/3, erb-b2 receptor tyrosine kinase 2/3; FGFR, fibroblast growth factor receptor; DDR2, discoidin domain receptor tyrosine kinase 2; PIK3CA, phosphatidylinositol 3-kinase catalytic subunit alpha; PTEN, phosphatase and tensin homolog; AKT, alpha serine/threonine-protein kinase; CDKN2A, cyclin-dependent kinase inhibitor 2A; CDK4/6, cyclin-dependent kinase 4/6.

enriched population to clinical trials for targeted therapies. The biomarker-driven Lung Cancer Master Protocol (Lung-MAP; S1400) study of second or greater lines of treatment of recurrent advanced/metastatic sqCLC (NCT02154490) aims to address this issue.[135] Lung-MAP uses a targeted screening approach; patients are tested only once according to a "master protocol" and assigned to different substudies on the basis of biomarker identification, with each evaluating a different targeted drug. Patients who are ineligible for the biomarker-driven substudies receive nivolumab or nivolumab plus ipilimumab. The Lung-MAP study design has already changed to accommodate the approvals of nivolumab and pembrolizumab by moving to second line and beyond, and it will continue to evolve as more biomarkers with targeted therapies are identified.

Defining Clinically Meaningful Improvements in Survival in sqCLC

Given the modest clinical benefits observed with new targeted agents and the additional survival gains with immunotherapies, the question arises as to what will constitute a clinically meaningful advance for patients with sqCLC in ongoing and future clinical trials. In 2012, in the context of future clinical trial design, the American Society of Clinical Oncology (ASCO) Cancer Research Committee convened four disease-specific working groups composed of experts in pancreatic, breast, colon, and lung cancers.[136] The aim was to help guide the development of randomized phase III trials that would produce clinically meaningful benefits for patients—either significantly improved survival, QoL, or both. All four working groups chose OS as the primary measure of clinically meaningful outcome, although it was noted that PFS and other surrogate end points in clinical trials remain of value, as prolongation of PFS would potentially provide longer palliation of symptoms and better QoL. Additionally, it was recommended that incremental gains in survival should not be accompanied by unacceptable increases in toxicity compared with that of current treatments, and new treatments that exhibited increased toxicity would also need to yield relatively greater increases in survival.

The working group recommendation for sqCLC stipulated a minimum improvement in median OS of 2.5 to 3 months, with a target HR of 0.77 to 0.80 as a clinically meaningful outcome for trials of first-line therapy, but these recommendations were not made for second- or third-line therapy.[136] It is apparent from the small incremental improvements in survival that are evident from the clinical trial data for NSCLC in recent decades that many agents in the current therapeutic armamentarium would not have been approved if regulatory authorities had based their decisions strictly on the ASCO working group criteria.[136] Therefore, when a clinically meaningful outcome is being determined, new treatments should be compared with the current standard of care in the context of the balance between efficacy (response, PFS, OS, and patient-reported outcomes) and toxicity. This is particularly important in advanced sqCLC, in which many patients are elderly, have challenging comorbidities, or have poor performance status, each of which already affects whether they can receive chemotherapy.[9,13,137,138]

Conclusions

The characteristics of patients with sqCLC make it challenging to develop new treatment options, leading to a lack of targeted first-line treatments for this disease. Therefore, every incremental innovation and improvement in survival, QoL, and risk-to-benefit profile may yield a clinically meaningful impact for patients, even if it does not necessarily measure up to the new ASCO standards. The benefits provided by anti–PD-1 agents (nivolumab and pembrolizumab) constitute an important exception. Importantly, given the genetic complexity of sqCLC tumors, the potential clinical impact of targeting individual molecular drivers should not be overestimated. Current evidence suggests that treatment advances for sqCLC will continue to be incremental over the next 5 years. Although new targeted therapies may individually result in small therapeutic gains for sqCLC, when considered in aggregate, these effects may provide important, clinically meaningful benefits for patients. Indeed, only when we examine the complete set of data, often accumulated over a long period of time, can we appreciate the full clinical value that incremental innovations in cancer treatments bring to patients.

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