Impact of Broadening Trial Eligibility Criteria for Patients with Advanced Non–Small Cell Lung Cancer: Real-World Analysis of Select ASCO-*Friends* Recommendations

R. Donald Harvey[1], Suanna S. Bruinooge[2], Li Chen[3], Elizabeth Garrett-Mayer[2], Whitney Rhodes[3], Edward Stepanski[3], Thomas S. Uldrick[4], Gwynn Ison[5], Sean Khozin[6], Wendy S. Rubinstein[5], Caroline Schenkel[2], Robert S. Miller[7], George A. Komatsoulis[7], Richard L. Schilsky[2], and Edward S. Kim[8]

ABSTRACT

Purpose: Cancer clinical trials often accrue slowly or miss enrollment targets. Strict eligibility criteria are a major reason. Restrictive criteria also limit opportunities for patient participation while compromising external validity of trial results. We examined the impact of broadening select eligibility criteria on characteristics and number of patients eligible for trials, using recommendations of the American Society of Clinical Oncology (ASCO) and Friends of Cancer Research.

Experimental Design: A retrospective, observational analysis used electronic health record data from ASCO's CancerLinQ Discovery database. Study cohort included patients with advanced non–small cell lung cancer treated from 2011 to 2018. Patients were grouped by traditional criteria [no brain metastases, no other malignancies, and creatinine clearance (CrCl) ≥ 60 mL/minute] and broadened criteria (including brain metastases, other malignancies, and CrCl ≥ 30 mL/minute).

Results: The analysis cohort included 10,500 patients. Median age was 68 years, and 73% of patients were White. Most patients had stage IV disease (65%). A total of 5,005 patients (48%) would be excluded from trial participation using the traditional criteria. The broadened criteria, however, would allow 98% of patients (10,346) to be potential participants. Examination of patients included by traditional criteria (5,495) versus those added (4,851) by broadened criteria showed that the number of women, patients aged 75+ years, and those with stage IV cancer was significantly greater using broadened criteria.

Conclusions: This analysis of real-world data demonstrated that broadening three common eligibility criteria has the potential to double the eligible patient population and include trial participants who are more representative of those encountered in practice.

See related commentary by Giantonio, p. 2369

Introduction

Numerous cancer trials accrue slowly or miss enrollment targets (range, 9%–49% of trials; refs. 1–7) due to strict eligibility criteria. A 2016 analysis of corrective actions for poor-accruing trials found that eligibility criteria were among primary causes of enrollment delays, with broadening eligibility criteria as the primary remedy for phase II trials (8). Among 231 phase I trials (1991–2016), common reasons for exclusion were performance status (PS) ≥ 1, brain metastases, and strict renal/hepatic function requirements (9). These restrictions were associated with fewer eligible patients, longer enrollment periods (26 vs. 17 months), and increased study terminations.

Broadening eligibility criteria also addresses study design factors that limit study participation, thereby causing inequities in trial access particularly among certain populations and creating concerns about external validity of results. A 2019 review of trial participation indicated 21.5% of patients were excluded primarily because of strict eligibility criteria (10). An examination of real-world data (RWD) from Denmark showed that clinical characteristics excluded 61% of patients with melanoma from pivotal trials during 2010–2015; brain metastases and/or PS ≥ 2 affected 75% of those excluded (11). These patients (when treated following approval with study agents) showed improvement in outcomes versus historical controls.

In October 2017, the American Society of Clinical Oncology (ASCO) and Friends of Cancer Research (*Friends*) published recommendations to broaden eligibility criteria (12) for: brain metastases (13), organ function, primary/concurrent malignancies (14), human immunodeficiency virus status (15), and minimum enrollment age (16). This investigation quantified and characterized among patients with advanced non–small cell lung cancer (aNSCLC) trial eligibility using the ASCO-*Friends*' broadened versus traditional eligibility criteria.

Materials and Methods

This retrospective, observational study examined common eligibility criteria in cancer trials: (i) brain metastases, (ii) renal function, and (iii) prior/concurrent malignancies. Data for the analysis were obtained from CancerLinQ Discovery a safe-harbor deidentified dataset compiled from electronic health records (EHR) of 50 U.S. oncology

[1]Winship Cancer Institute of Emory University, Druid Hills, Georgia. [2]ASCO, Alexandria, Virginia. [3]ConcertAI, Boston, Massachusetts. [4]Fred Hutchinson Cancer Research Center and University of Washington, Seattle, Washington. [5]FDA, Silver Spring, Maryland. [6]Janssen Research and Development, New York, New York. [7]ASCO CancerLinQ, Alexandria, Virginia. [8]Levine Cancer Institute, Atrium Health, Charlotte, North Carolina.

Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

R.D. Harvey and S.S. Bruinooge contributed equally as co-first authors of this article.

R.L. Schilsky and E.S. Kim contributed equally as co-senior authors of this article.

Corresponding Author: Suanna S. Bruinooge, American Society of Clinical Oncology, 2318 Mill Road, Suite 800, Alexandria, VA 22314. Phone: 571-483-1313; E-mail: suanna.bruinooge@asco.org

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Translational Relevance

Overly restrictive clinical trial eligibility criteria make it challenging to translate research findings to all populations likely to receive a new treatment following approval. Less restrictive eligibility criteria over the course of drug development may generate data on a broader population and improve speed of accrual. This may be accomplished by progressive broadening of eligibility criteria across trial phases. We show that expansion of three common eligibility criteria, renal function measures, presence of brain metastases, and history of prior malignancy, increases patients potentially eligible in the dataset analyzed by almost 2-fold. While this analysis was conducted in a population with advanced non–small cell lung cancer, the findings are likely applicable to other advanced malignancies. These expanded eligibility criteria should be widely adopted while pursuing additional expanded inclusion criteria to generate findings more relevant to patients treated in routine clinical practice, maximize patient access to trials, and expedite trial enrollment.

practices (17). We included standardized data and data curated by trained clinical data abstractors from 2011 to 2018 records (18–20).

Study criteria included patients with aNSCLC diagnosis (stage IIIb, IIIc, or IV; see Supplementary Materials and Methods), receipt of systemic therapy, and ≥2 documented clinical visits. Patients with missing serum creatinine laboratory values were excluded.

Criteria for traditional and broadened eligibility criteria are outlined in **Table 1**. Traditional criteria excluded patients with creatinine clearance (CrCl) ≤ 60 mL/minute (21). Broadened criteria included patients with CrCl ≥ 30 mL/minute. A minority of cases (33%) included CrCl in EHR data. CrCl was calculated for 7,031 cases using the Cockcroft–Gault equation (22, 23).

Patients with additional cancer diagnosis codes unrelated to NSCLC were classified as having a prior/concurrent cancer. These patients would be excluded by traditional criteria and included by broadened criteria. All diagnosis codes related to lung cancer metastases sites (e.g., adrenal gland, bone, brain, and other) were considered metastases, rather than another cancer. From a clinical perspective, metastases may be more likely than second primary cancers at these anatomic sites. Miscoding of metastases as primary cancers is not infrequent.

Data curation identified patients with brain metastases, including coding primary brain neoplasms as brain metastases. All patients with brain metastases were excluded under traditional criteria and included under broadened criteria.

PS values were presented using the Eastern Cooperative Oncology Group (ECOG) scale as documented in EHR or converted from Karnofsky (24). If multiple PS values existed, we used the value closest to date of therapy initiation.

Descriptive statistics summarize the two populations, including proportions, means, and interquartile ranges (IQR). Comparisons were made between patients included on the basis of traditional criteria versus patients excluded on the basis of traditional criteria, but included using broadened criteria (i.e., independent, nonoverlapping patient groups) using χ^2 tests. Alpha was set at 0.01 due to the large sample size. Data management and analyses were conducted in Python 3.7.0 and R 3.5.1.

Results

A total of 10,500 cases were included in the analysis (**Fig. 1**; **Table 2**). Median age was 68 years (IQR, 60–74), and 56% were males. A total of 75% of patients were White. Most patients had stage IV disease (65%).

Of the total cohort, 1,509 (14%) patients had prior/concurrent cancers (**Table 3**), most commonly prostate (154 patients, 2%), colorectal (120, 1%), and breast (31, 0.3%) cancers. These 1,509 patients would be excluded under traditional criteria, but included using broadened criteria. All cases were coded for presence/absence of brain metastases. A total of 21% of patients (2,226) had brain metastases and would be excluded by traditional eligibility criteria.

Overall, 5,005 patients (48%) were excluded by one or more of three traditional criteria, leaving only 5,495 (52%) eligible. More than 20% of patients (2,252) were excluded by traditional eligibility criteria due to CrCl ≤ 60 mL/minute alone. Use of the broadened criteria would only exclude 154 patients (1.5%), leaving nearly all patients (10,346, 98%) potentially eligible.

Table 1. Comparison of definitions for traditional clinical trial eligibility criteria, ASCO-*Friends*' broadened criteria, and criteria used in study.

	Traditional eligibility criteria	ASCO-*Friends*' broadened criteria	Criteria used in study
Prior and concurrent cancer: in addition to NSCLC	Exclude patients with another primary cancer in 2 years prior to trial enrollment	Include patients with another primary cancer that does not interfere with safety or efficacy of study therapy	Included all cases with another primary cancer diagnosis: (i) counted primary diagnostic codes at sites of likely NSCLC metastases as metastases
Brain metastases	Exclude patients with brain metastases	Include patients with treated and/or stable brain metastases, as well as patients with active brain metastases	Included all patients with brain metastases (i) irrespective of treatment status and clinical stability (ii) counted primary brain diagnostic codes as metastases
Renal function	Exclude patients if CrCl ≤ 60 mL/minute	Include patients if CrCl ≥ 30 mL/minute for study therapy without kidney toxicity	Included patients if CrCl ≥ 30 mL/minute: (i) used Cockcroft–Gault formula to calculate CrCl for patients without evidence of CrCl measure

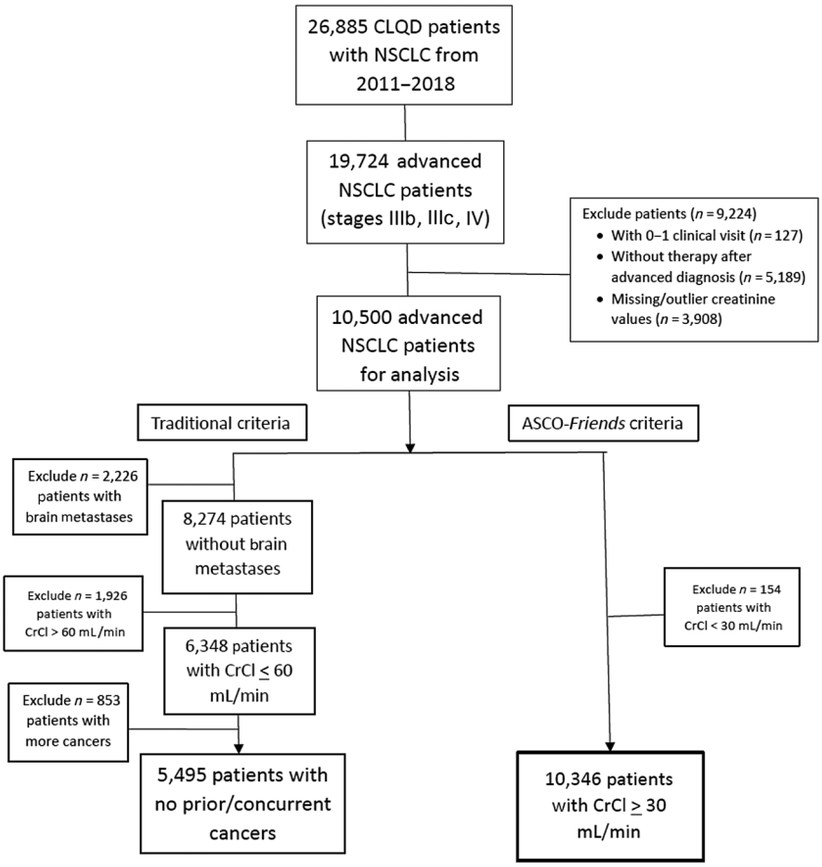

Figure 1.
Cohort comparison with traditional and broadened eligibility criteria.

Patients included by traditional criteria (5,495) versus patients added (4,851) by broadened criteria and excluded by traditional criteria (**Table 2**; columns E and G) differ in important ways (**Fig. 2**). The percentage of women was significantly different; 40% under traditional criteria versus 48% ($P < 0.001$) with broadened criteria. The percentage of patients aged 75+ years was significantly greater with broadened criteria (29% vs. 16%; $P < 0.001$). Comparing by stage, 59% of stage IV patients were included with traditional versus 72% ($P < 0.001$) using broadened criteria. Percentage of patients with ECOG PS 2+ was similar (18% vs. 20%; $P = 0.03$).

Discussion

Broadening three common eligibility criteria can potentially double the number of patients with aNSCLC eligible for trials. Prior analyses of eligibility of patients with aNSCLC demonstrated 60% were ineligible, with common exclusions being brain metastases and poor PS (25).

Support for expanding eligibility criteria examined also comes from analysis of Kaiser Permanente data, which showed 8% of patients would be excluded from trials because of another invasive cancer within 5 years (14). The analysis also revealed 28% of patients with lung, 20% with breast, 25% with colorectal, and 46% with bladder cancers would be excluded because of CrCl < 60 mL/minute. Renal function is of critical importance in aNSCLC, because carboplatin, pemetrexed, and cisplatin are renally cleared. Expanding CrCl eligibility to ≥30 mL/minute would substantially impact the eligible population, adding 20% of patients. It is important to recognize those instances when including patients with CrCl < 60 mL/minute should be avoided, specifically in studies of drugs cleared by the kidneys and without established dose adjustments where drugs cause direct renal toxicity. In other cases, the change to include those with CrCl > 30 mL/minute should be employed once safety is established (perhaps in an exploratory cohort in early development) and certainly in late-phase trials.

In this analysis, the population who met the broadened eligibility criteria are more representative of patients with aNSCLC than the traditional eligibility criteria population. The broadened population included more women, older patients, and/or patients with stage IV disease. Although broadened criteria resulted in a small increase in patients with PS 2+, analysis of PS was inconclusive. Most records (58.5%) lacked structured PS data. Translation of data from highly selected trial populations to patients seen in real-world practice identifies important knowledge gaps and increases confidence in applying trial results to typical patients.

While our analysis demonstrated an increase in the number of patients with aNSCLC potentially eligible for trials, their inclusion could also potentially affect interpretation of safety and efficacy data because of increased heterogeneity. Similar studies including broader populations, however, demonstrated similar safety and survival rates between restricted and broadened populations (9, 25). Our analysis is limited by characteristics of our data source. The population of patients included in CancerLinQ has not been compared with the U.S. cancer population, although CancerLinQ participating practices are geographically diverse and mostly outside academic settings. It was also difficult to match eligibility criteria to EHR data. We simplified the

Table 2. Characteristics of patients with aNSCLC according to eligibility criteria.

	(A) All patients with aNSCLC	(B) Patients excluded due to brain metastases	(C) Patients excluded due to other prior or concurrent malignancies	(D) Patients excluded due to CrCl ≤ 60 mL/minute	(E) Patients included by 3 traditional criteria	(F) Patients included by 3 broadened criteria	(G) Patients included by broadened and excluded from traditional	(H) Patients excluded by both broadened and traditional	*P*[a]
	10,500 (100)	2,226 (21)	1,509 (14)	2,254 (22)	5,495 (52)	10,346 (99)	4,851 (46)	154 (2)	
Age (median and IQR) at treatment index									
	68 (60–74)	65 (57–71)	69 (62–75)	76 (70–81)	66 (59–72)	68 (60–74)	69 (62–76)	78 (72–84)	
Age (at treatment index)									<0.001
≤49 years	426 (4)	140 (6)	48 (3)	7 (3)	254 (5)	425 (4)	171 (4)	1 (1)	
50–64 years	3,794 (36)	1010 (45)	484 (32)	246 (11)	2,268 (41)	3,781 (37)	1,513 (31)	13 (8)	
65–74 years	3,881 (37)	752 (34)	595 (39)	794 (35)	2,089 (38)	3,840 (37)	1,751 (36)	41 (27)	
75+ years	2,399 (23)	324 (15)	382 (25)	1,207 (54)	884 (16)	2,300 (22)	1,416 (29)	99 (64)	
Sex									<0.001
Female	4,647 (44)	1,086 (49)	624 (41)	1,203 (53)	2,216 (40)	4,550 (44)	2,334 (48)	97 (63)	
Male	5,853 (56)	1,140 (51)	885 (59)	1,051 (47)	3,279 (60)	5,796 (56)	2,517 (52)	57 (37)	
Race									0.49
White	6,813 (73)	1,365 (70)	1,009 (76)	1,505 (75)	3,567 (74)	6,716 (74)	3,149 (73)	97 (68)	
Black	1,255 (14)	241 (12)	163 (12)	320 (16)	660 (14)	1,223 (13)	563 (13)	32 (22)	
Other	1,206 (13)	357 (18)	158 (12)	180 (9)	615 (13)	1,192 (13)	577 (13)	14 (10)	
Unknown	1,226	263	179	249	653	1,215	562	11 (<1)	
Stage at index (closest to first-line advanced treatment)									<0.001
Stage IIIb/c	3,355 (35)	334 (16)	405 (30)	710 (34)	2,086 (41)	3,316 (35)	1,230 (28)	39 (27)	
Stage IV	6,354 (65)	1,714 (84)	965 (70)	1,352 (66)	3,039 (59)	6,251 (65)	3,212 (72)	103 (73)	
Unknown	791	178	139	192	370	779	409	12	
PS (on or ≤1 year prior to treatment index date; native ECOG or translated from Karnofsky)									0.06[b]
0	1,215 (28)	282 (29)	188 (30)	231 (22)	637 (29)	1,199 (28)	562 (27)	16 (18)	
1	2,121 (49)	490 (50)	289 (46)	495 (48)	1,058 (49)	2,079 (49)	1,021 (49)	42 (47)	
2	831 (19)	174 (18)	126 (20)	248 (24)	384 (18)	805 (19)	421 (20)	26 (29)	
3	182 (4)	37 (4)	27 (4)	59 (6)	83 (4)	178 (4)	95 (5)	4 (4)	
4	12 (<1)	1 (<1)	1 (<1)	2 (<1)	8 (<1)	11 (<1)	3 (<1)	1 (1)	
Unknown	6,139	1,242	878	1,219	3,325	6,074	2,749	65	
Smoking status (at treatment index)									<0.001
Never smoked	1,642 (16)	414 (19)	295 (21)	408 (19)	732 (14)	1,616 (16)	884 (19)	26 (17)	
Former smoker	5,225 (52)	978 (46)	708 (49)	1,195 (56)	2,802 (54)	5,145 (52)	2,343 (51)	80 (52)	
Current smoker	3,093 (31)	746 (35)	430 (30)	543 (25)	1,650 (32)	3,057 (31)	1,407 (30)	36 (23)	
Unknown	540	88	76	108	311	528	217	12	

Note: *N* (%) are shown in table cells, except for age, which is presented as median and IQR. When calculating percentages, "unknown" cell counts were excluded.
[a]χ^2 tests were used to calculate *P* values with all categories included, except "unknown."
[b]Comparing PS < 2 versus PS ≥ 2, $P = 0.03$.

Table 3. Numbers of patients excluded by traditional versus broadened clinical trial eligibility criteria.

Original cohort	**10,500 (100%)**
Traditional criteria	
Pts excluded due to brain metastases	2,226 (21.2%)
Pts excluded due to prior/concurrent cancers	1,509 (14.4%)
Pts excluded because CrCl ≤ 60 mL/minute	2,254 (21.5%)
Pts excluded by one or more of 3 traditional criteria	5,005 (47.7%)
ASCO-*Friends*' broadened criteria	
Pts excluded by brain metastases and prior/concurrent cancers	0 (0%)
Pts excluded by CrCl ≤ 30 mL/minute cutoff	154 (1.5%)

Abbreviation: Pt, patient.

definition of brain metastases to present or absent, rather than using ASCO-*Friends*' recommendations' consideration of treated and/or stable metastases. Classification of diagnosis codes for another primary cancer at metastases sites as NSCLC metastases had a small impact (<1%). Record curation helped ensure very few patients were mischaracterized.

Conclusions

Broadening three common eligibility criteria would have allowed nearly twice as many patients (5,495 vs. 10,346) within this RWD analysis to meet eligibility criteria for clinical trials. With broadened eligibility, patients are more representative of the range of patients with aNSCLC, thus increasing the likelihood for definitive trials. Per ASCO and *Friends*' recommendations, eligibility criteria should be carefully selected and reflect safety concerns and compelling scientific rationale

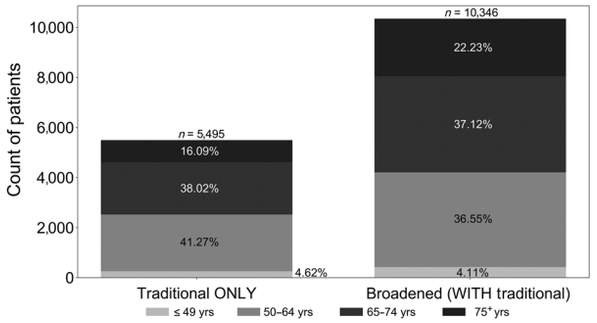

Figure 2.
Effect of traditional versus broadened eligibility criteria by ages represented ($N = 10,500$ patients with aNSCLC).

specific to the investigational therapy. Broadening eligibility criteria will enable improved equitable patient involvement in research and likely accelerate trial enrollment.

Authors' Disclosures

E. Stepanski reports employment with ConcertAI, a company that conducts research using real-world data. T.S. Uldrick reports other from Merck, Roche, and Celgene/BMS outside the submitted work, as well as a patent for US 10,001,483 B2 issued to Celgene and NCI. S. Khozin reports receiving salary from Johnson & Johnson outside the submitted work. R.S. Miller reports employment with American Society of Clinical Oncology. R.L. Schilsky reports grants from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Genentech, Lilly, Merck, and Pfizer outside the submitted work. E.S. Kim reports personal fees from AstraZeneca, Boehringer Ingelheim, and Genentech outside the submitted work. No disclosures were reported by the other authors.

Disclaimer

The opinions expressed in this article are those of the authors and do not necessarily reflect the views or policies of the authors' affiliated institutions. W.S. Rubinstein participated in this work prior to joining the FDA. This work and related conclusions reflect the independent work of study authors and do not necessarily represent the views of the FDA or U.S. government.

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