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Predictive and Prognostic Value of *LK* ene Rearrangement in Non Small ell Lung ancer

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Abstract

Anaplastic Lymphoma Kinase ( ) is a relatively new as an oncogenic driver and a therapeutic target in Non-Small Cell Lung Cancer (NSCLC); the prognostic and predictive implications of -positivity in NSCLC is unclear and no large-scale studies have been reported to date. In the current review, we summarize published data examining the variation in prognostic and predictive effect of -positivity on clinical outcomes in NSCLC patients, based on the extent of control of or adjustment for known confounding factors such as smoking status, disease stage, and age by study design or analyses. rearrangement in NSCLC did not appear to be predictive of improved outcomes with chemotherapy but was predictive of poor response to EGFR TKI therapy. Overall, rearrangement was found to be a negative prognostic factor in NSCLC in studies controlling for known confounding factors. In addition to highlighting the importance of controlling for confounding factors in retrospective studies evaluating outcomes, our review also summarizes evidence of an unmet need in terms of poor response amongst -positive NSCLC patients to standard therapies that do not target .

Keywords: Anaplastic Lymphoma Kinase (*A*); Non-Small Cell Lung Cancer (NSCLC); Survival; Clinical Outcomes; Prognostic; Predictive; Review

Introduction

Anaplastic Lymphoma Kinase (ALK) is relatively new as an oncogenic driver an oncogenic driver and a drug target in Non-Small Cell Lung Cancer (NSCLC); however, little is known about the "natural history" of *A* -rearranged NSCLC. Some investigators have speculated that it may represent a more indolent disease [1,2] or be an independent positive prognostic factor [3]. Others have suggested that *A* rearrangement may be a negative prognostic factor when controlling for known factors such as age, sex, smoking status, stage/grade, and histology [4-6]. With the advent of *A* -speci c therapies and crossover in clinical trials, it is unlikely that the natural history of *A* -rearranged (*A* -positive) NSCLC can be examined in an unbiased manner moving forward. However, a handful of retrospective studies examining the outcomes with conventional therapy in *A* -positive NSCLC have been published or presented at scienti c meetings. Here we review data from these retrospective studies, exclusive of those involving *A* inhibitor therapy, with the goal to evaluate historical survival outcomes and treatment outcomes from chemotherapy, Tyrosine Kinase Inhibitor (TKI) therapy, surgical therapy, and thoracic radiotherapy in *A* -positive NSCLC.

Methods

We searched published literature in English in peer-reviewed journals indexed in Pub Med, Google Scholar, and presentations at conferences from July 2007 to Nov 2013 that had an observational study design assessing both the predictive and prognostic value of *A* in NSCLC, and that tested for *A* status using various diagnostic tests including uorescent in situ hybridization (FISH), Immunohistochemistry (IHC), or polymerase chain reaction (PCR). A total of 26 publications were identi ed and 8 were excluded, where two were reported from the same cohort [7,8]. Five studies reported only the outcome or gave a conclusion but did not have enough study description or data details [3,9-13]. Two studies had no con rmed *A* -negative comparator groups [1,14]. Aggregate data are summarized, comparing survival outcomes between *A* -positive versus *A* -negative NSCLC patients followed by an evaluation of responses with current non-*A* -targeted therapies (Figure 1). Clinical outcomes considered were Overall Survival (OS), Progression-Free Survival (PFS), Recurrence-Free Survival (RFS), Disease-Free Survival (DFS), Time to Progression (TTP), and Objective Response Rate (ORR). Studies were reviewed with a focus on the use of techniques within the study to control via study design and/or adjust with statistical methods for confounding factors that could impact the outcomes being investigated.

Results

ALK gene rearrangement as a prognostic biomarker in NSCLC

Summary of studies with no reported control of or adjustment for confounding factors: Six studies have examined OS in *A* -positive compared with *A* -negative, wild type (WT/WT) cases and two other studies examined OS in *A* -positive versus *A* -negative cases in which status was unknown. With a median follow-up time of 13 months at the time of analysis, Shaw et al reported a median OS of 20 months in *A* -positive cases and 16 months in WT/WT cases (=0.152; Table 1) [15]. In another study, which was an indirect comparison of OS between *A* -positive, crizotinib-naive

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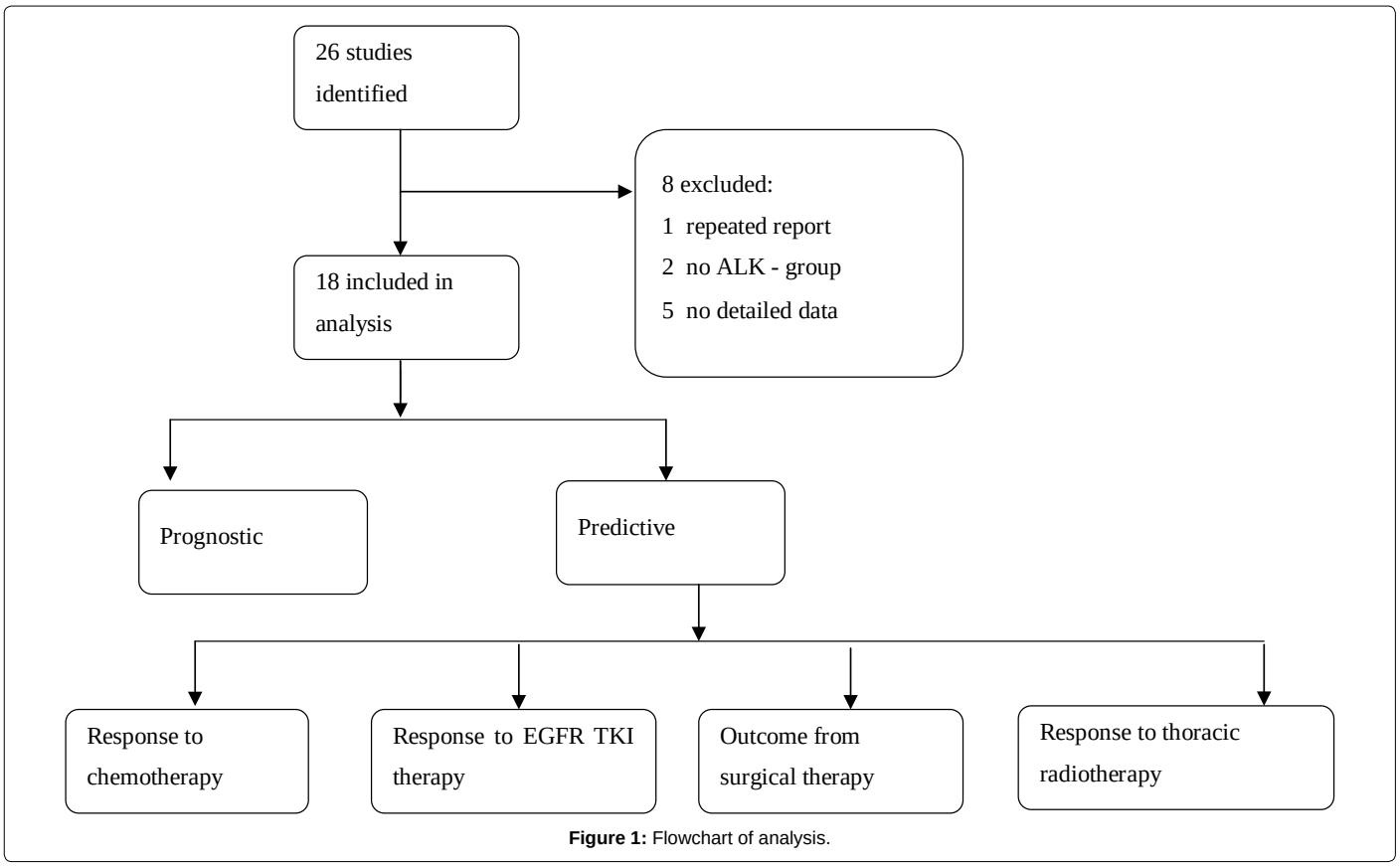

Figure 1: Flowchart of analysis.

cases and WT/WT controls, Shaw et al., reported the median OS from time of metastatic diagnosis as similar for the *A* -positive and WT/WT cases at 20 and 15 months, respectively (unadjusted HR 0.77; =0.244) [2]. Although an additional OS subset analysis conducted on cases ≤ 60 years old who were never- or light-smokers accounted to some degree for age and smoking status and showed median OS of 20 versus 24 months for *A* -positive and WT/WT cases, respectively (HR=1.01; p=0.978) [2], it was not formally controlled for all potential confounding variables including histology and treatment. With a median follow-up time of 10.8 months, Takeda et al., reported a median OS of 15.7 months in *A* -positive cases and 15.2 months in WT/WT cases (HR=0.83, =0.591; Table 1) [16]. Wang et al., reported a median OS of 19.27 months in 9 *A* -positive cases and 18.93 months in 45 WT/WT cases (=0.481, Table 1) [17]. Martinez et al., reported a median OS of 4.5 months for WT/WT cases (=65) versus a median OS not reached for 7 *A* -positive cases (=0.103) and 15.7 months in 13 mutant cases (=0.018) [8]. No statistically signi cant di erences were found in median OS between groups in all these studies.

Hayashi et al., reported a median OS in locally advanced adenocarcinoma patients of 7.7 months in 3 ALK-positive cases and 42.6 months in 23 WT/WT cases (=0.007; Table 1) [18]. Fukui et al., selected adenocarcinoma cases who underwent pulmonary resection and reported the 5-year OS rate for *A* -positive patients was 81%; whereas, the *A* -negative (status unknown) was 77% (=0.76) [19,20].

In early stage lung cancer patients, Paik et al., reported a median OS in stage I-III NSCLC patients of 97.7 months in *A* -positive cases and 78.9 months in *A* -negative (status unknown) cases (=0.10) [19].

Summary of studies with reported control of or adjustment for confounding factors: Four studies to date have, a priori, matched or controlled for important independent prognostic factors. ree of them suggest or clearly demonstrate a shorter OS or DFS for *A* -positive versus *A* -negative cases and one stated a prolonged OS in *A* -positive cases. e case-matched analysis by JK Lee et al., reported a median OS in stage IIIb-IV cases of 12.23 months in *A* -positive (=23), 29.63 months in mutant (=46) and 19.33 months in WT/WT (=46) cases (=0.001 versus mutant; =0.127 versus WT/WT) [6]. Yang et al., with selection of never-smoker, adenocarcinoma cases and control for age, sex, stage, and treatment, showed more than a 2-fold greater risk of recurrence or progression within 5 years of diagnosis in *A* -positive (=22) versus *A* -negative (status unknown) cases (=274; =0.004; Table 1) [4]. In the same study, a higher rate of extra-thoracic metastasis was observed among *A* -positive cases compared with *A* -negative cases, (HR=2.44, =0.03); albeit, the number of later stage patients in this analysis was limited (=13). With selection of never-smokers and comparator groups which were balanced in terms of age, sex, histology, stage and performance status (PS), Kim et al., reported a shorter median OS of 14.3 months in *A* -positive cases compared with 33.3 months in *A* -negative, WT and KRAS WT (triple WT), and 37.2 months in mutant (*A* -negative) cases (=0.016 for *A* -positive versus triple WT) [5]. In the same study, in a multivariate analysis, *A* -positivity was associated with a lower OS in patients with resected NSCLC (adjusted HR, 4.162; =0.005). e authors suggested that *A* -positivity may be a negative prognostic factor for early stage NSCLC. Wu et al., examined survival outcomes in lung adenocarcinoma patients with malignant pleural e usions and wild type in which *A* -positive and *A* -negative comparator groups were balanced in terms of age, sex, smoking history, PS, and treatment, and reported a longer median OS of 14.7

months in *A* -positive cases (=39) compared with 10.3 months in

based chemotherapy in the range of 8–10 months for patients with *A* -positive, mutant, and WT/WT disease [15]. e chemotherapy ORR in this study was 25% for *A* -positive and 35% for WT/WT cases with no statistically signi cant di erence between these groups (=0.723). is cohort was not balanced for age, sex, smoking history or exposure to *A* inhibitor therapy, which would have had an impact

PFS and ORR were reported as statistically non-signi cant. Similarly, this analysis was not balanced for age, with patients in the *A* -positive cohort being statistically signi cantly younger than WT/WT patients (median 46 versus 64 years, respectively; <0.001). e regimens were also not balanced between the comparator groups. e proportion of patients in *A*

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