Progression-Free Survival as a Surrogate for Overall Survival in Unresectable, Locally Advanced or Metastatic Non-Small Cell Lung Cancer: A Targeted Literature Review

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Introduction

Overall survival (OS) has historically been the 'gold standard' endpoint in oncology trials, but necessitates prolonged follow-up and may be confounded by subsequent therapies. In non-small cell lung cancer (NSCLC), the growing number of treatment options complicates the evaluation of novel treatments using OS as multiple efficacious lines of treatment are available when a patient's disease progresses. Furthermore, cross-over becomes an ethical necessity when new regimens display outstanding early efficacy, impacting the interpretation of OS data.[1]

To avoid delays in patient access, other endpoints are therefore often used by regulatory authorities and reimbursement agencies to inform decision-making. Progression-free survival (PFS) is one such endpoint that is often utilised as the primary measure of efficacy in advanced oncology trials. In addition to providing a direct measure of study treatment effect that is not confounded by subsequent treatment,[1] the clinical and patient-relevance of PFS makes it a valid standalone measure of therapeutic value.

This study aimed to summarise the available synthesised literature on PFS as a surrogate for OS in unresectable, locally advanced or metastatic NSCLC.

Methods

A targeted literature review (TLR) was conducted by searching MEDLINE, Embase, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects and preselected regulatory and health technology assessment (HTA) body websites from inception through May 2023.

Study abstracts, and subsequently full texts, were screened against eligibility criteria by two independent reviewers. Eligible records reported on a statistical assessment of the relationship of PFS to OS in patients with unresectable, locally advanced or metastatic NSCLC. Data from the included studies were extracted and summarised.

For analyses where authors had not categorised the strength of relationship, R^2 values (where reported) were categorised according to strength of relationship thresholds reported in Mauguen 2013[2] and Zhu 2021[3] (poor: ≤0.25; moderate: 0.25—0.50; good: 0.50—0.75; very good: 0.75—0.90; excellent: >0.90) as these were the only studies included in the TLR to report the thresholds utilised to categorise R^2 values.

Results

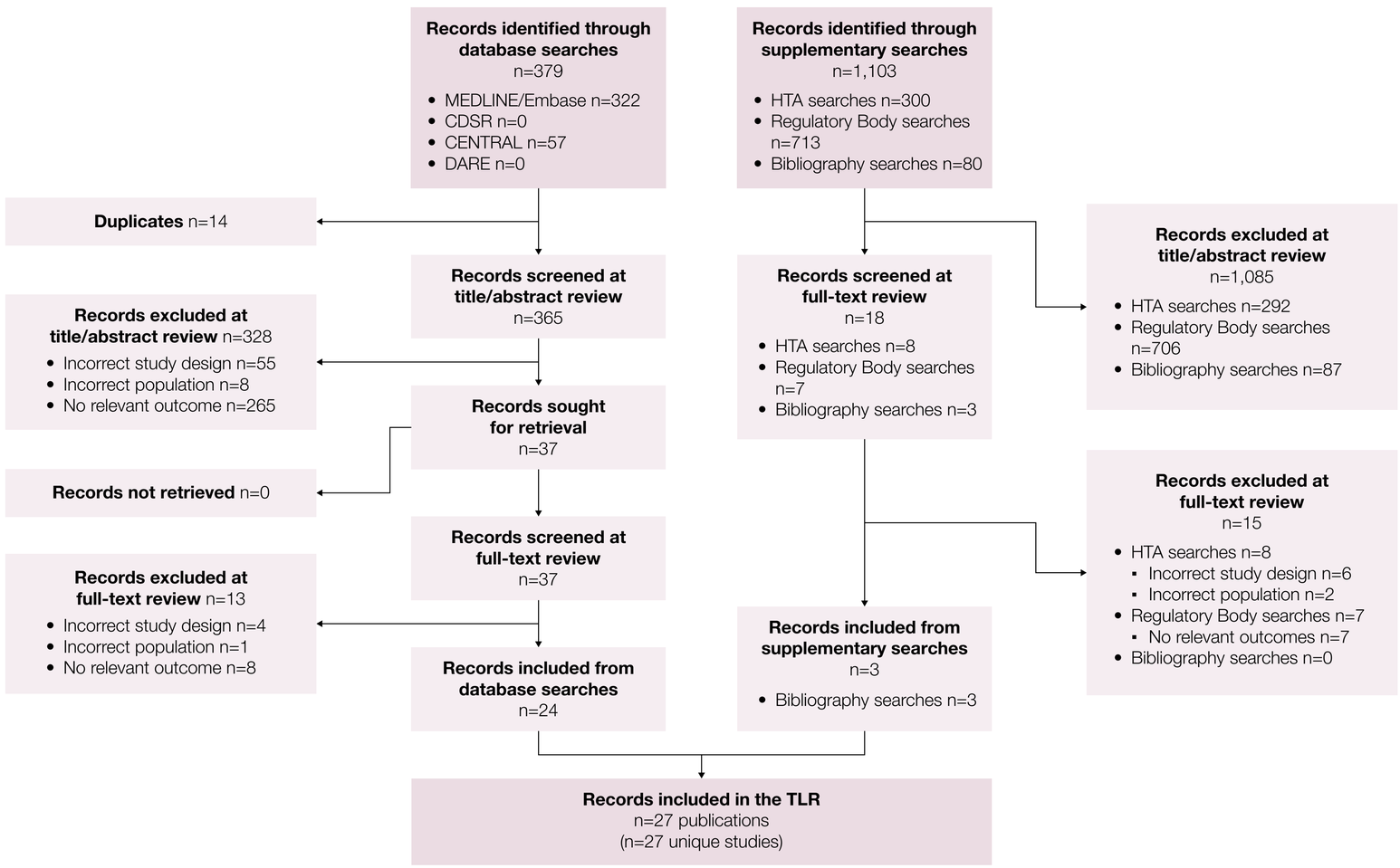
Of 1,482 records identified, 27 unique studies were included in the TLR (**Figure 1**). Of the 27 included studies, the majority drew on aggregate-level data (n=19), while several used patient-level data (n=3), or both patient and aggregate-level data (n=5). Studies varied in terms of patient eligibility criteria, disease stage, and included treatments. Included studies were predominantly multi-national (n=20) and had large sample sizes (median n=5,137 patients per analysis).

Included studies reported on either absolute outcomes (e.g. median PFS or OS; n=12), relative treatment effects (e.g. treatment contrasts like hazard ratios; n=9) or both (n=6). Spearman's rank correlation test and R^2 were the most frequently reported tests and outcomes. Overall, 22 studies reported on strength of relationship between PFS and OS.

Where strength of relationship between PFS and OS was reported for absolute outcomes (39 analyses across 13 studies), the majority of analyses (82%) categorised the strength of this relationship as moderate-to-strong (32 analyses, 13 studies). These results stayed consistent when supplemented using reported R^2 values (moderate-to-strong relationship in 80% of analyses; **Figure 2A**).

Where strength of relationship between PFS and OS was reported for relative treatment effects (51 analyses, 12 studies), the majority of analyses (67%) categorised the strength of this relationship as moderate-to-strong (34 analyses, 10 studies). When supplemented using reported R^2 values, results were consistent (moderate-to-strong relationship in 69% of analyses; **Figure 2B**).

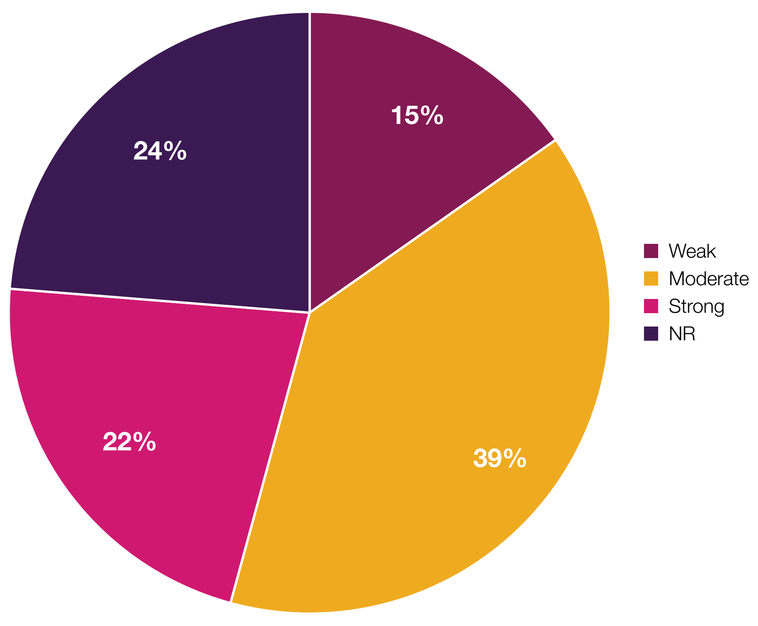
Figure 1. PRISMA flow diagram of included and excluded studies



Results

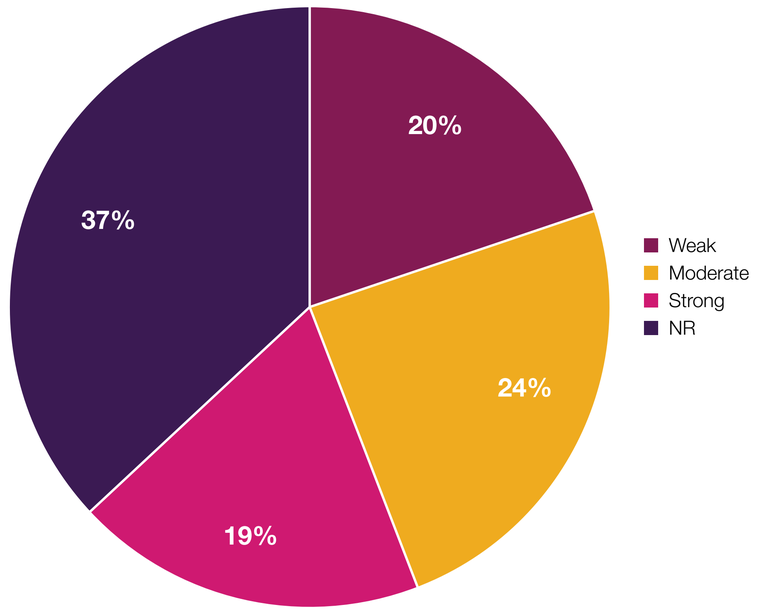
Figure 2. Strength of relationship across analyses (author categorisation supplemented with R^2 values)

A) Absolute Outcomes (45 analyses across 14 studies)



Footnotes: 9 analyses across 4 studies (including 2 analyses across 2 studies reporting only R^2) reported a weak or no relationship, defined as weak, low or no relationship; 23 analyses across 10 studies (including 3 analyses across 2 studies reporting only R^2) reported a moderate relationship, defined as moderate, moderate but not statistically significant, good, medium (undefined), good (undefined), and correlated; 13 analyses across 7 studies (including 0 analyses reporting only R^2) reported a strong relationship, defined as strong, high, excellent, or strong positive; 14 analyses across 8 studies did not report strength of the relationship or an R^2.

B) Relative Treatment Effects (70 analyses across 13 studies)



Footnotes: 22 analyses across 7 studies reported a weak relationship (including 5 analyses across 2 studies reporting only R^2), defined as weak, negligible, negligible-low, low, BSES poor, or no association; 27 analyses across 8 studies (including 9 analyses across 4 studies reporting only R^2) reported a moderate relationship, defined as moderate, IQWiG medium, BSES good, or some association; 21 analyses across 7 studies reported a strong relationship (including 5 analyses across 2 studies reporting only R^2), defined as strong, excellent, very good, high, very high, or strong positive; 41 analyses across 7 studies did not report strength of the relationship or an R^2.

Discussion

The majority of evidence shows a moderate-to-strong relationship between PFS and OS.

Notably, when focussing on associations of relative treatment effect, a key requirement for surrogacy assessment, there is a greater degree of heterogeneity in strength of relationship between PFS and OS observed across studies/analyses than for absolute outcomes. Difficulties in demonstrating strength of relationship using relative treatment effects have been documented previously.[4,5]

Surrogacy is specific to disease setting and class of intervention,[6] therefore the heterogeneity of study design of the included studies is a key limitation of this investigation. Further limitations include heterogeneity in statistical methodology and reporting thresholds for the strength of the relationship between PFS and OS, which limits granularity of final results and hinders comparability of outcomes. Finally, PFS is defined and measured variably across trials; therefore, formal determination of whether PFS is an acceptable surrogate endpoint would require a standardised definition and unbiased measurement of progression in trials as well as further validation studies.

Conclusion

Overall, the evidence is supportive of using PFS as a surrogate for OS in unresectable, locally advanced or metastatic NSCLC.

References: 1. Soria, J.C. et al. Should progression-free survival be the primary measure of efficacy for advanced NSCLC therapy? Annals of Oncology 2010;21(12):2324–2332. **2.** Mauguen, A. et al. Surrogate endpoints for overall survival in chemotherapy and radiotherapy trials in operable and locally advanced lung cancer: A re-analysis of meta-analyses of individual patients' data. The Lancet Oncology 2013;14(7):619–626. **3.** Zhu, G.L. et al. Progression-free survival assessed per immune-related or conventional response criteria, which is the better surrogate endpoint for overall survival in trials of immune-checkpoint inhibitors in lung cancer: A systematic review and meta-analysis. Cancer Medicine 2021;10(23):8272–8287. **4.** Buyse, M. et al. Individual-and trial-level surrogacy in colorectal cancer. Statistical Methods in Medical Research. 2008;17(5):467–475. **5.** Buyse, M. et al. Biomarkers and surrogate end points – the challenge of statistical validation. Nature Reviews Clinical Oncology 2010;7:309–317. **6.** Saad, E.D. et al. Progression-free survival as surrogate and as a true end point: insights from the breast and colorectal cancer literature. Annals of Oncology 2024;21(1):7–12.

Abbreviations: BSES, Biomarker Surrogacy Evaluation Schema; **CDSR**, Cochrane Database of Systematic Reviews; **CENTRAL**, The Cochrane Central Register of Controlled Trials; **DARE**, Database of Abstracts of Reviews of Effects; HTA, health technology assessment; **IQWiG,** Institute for Quality and Efficiency in Health Care; **NSCLC**, non-small cell lung cancer; **OS**, overall survival; **PFS**, progression-free survival; **PRISMA**, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **TLR**, targeted literature review.

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