**Shifting Patterns in the Interpretation of Phase III Clinical Trial Outcomes in the Treatment of Advanced NSCLC**

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**Introduction**: Advanced non-small cell lung cancer (NSCLC) continues to have a grim prognosis despite decades of trials involving novel agents. Over time, there appears to be an increasing willingness to study and adopt new treatments with very modest clinical benefit. We have sought to determine if the primary endpoint, outcome and interpretation of large scale clinical trials in advanced NSCLC are changing over time.

**Methods**: A literature search for all phase III randomized controlled trials of systemic therapy for advanced NSCLC was performed. Publication date, primary endpoint, clinical outcomes, statistical significance and conclusions of eligible trials were recorded. Aggregate data were compiled by 5-year intervals. Significant differences were determined using an unpaired Student's t-test.

**Results**: A total of 238 trials were reviewed and 207 were eligible for inclusion in this study. The primary endpoint of phase III trials shifted significantly from median survival in 1980-1990 (97% of trials) and 1991-2000 (96%) towards progression free survival in 2001-2010 (15% progression-free survival, 80% median survival; p=0.04 for 1980s vs. 2000s). A similar shift was noted in trial outcomes (positive vs. negative) from uncommonly positive in 1980-1990 (21% of trials) to frequently positive in 1991-2000 (65%) and 2001-2010 (78%; p=0.009 for 1980s vs. 2000s). A decrease in the magnitude of median survival gains in positive studies between 1980-1990 (4.3 months), 1991-2000 (2.6 months) and 2001-2010 (2.4 months) was observed (p=0.016 for 1980s vs. 2000s). Lastly, the period before 1990 was the only time in which studies were reported as negative due to insufficient magnitude of median survival benefit despite statistical significance.

**Conclusion**: A significant shift has occurred over the past 3 decades in the design and interpretation of phase III trials in advanced NSCLC. The use of median survival as the primary measure of benefit is declining alongside the magnitude of benefit deemed clinically relevant. This suggests a shift in the oncology community towards an increasing willingness to accept lesser benefit from new treatments.