



# Challenges in Network Meta-Analyses of Oncology

**Yingxin Xu, PharmD, PhD**  
Research Scientist, Meta Research, Evidera

**Ajibade Ashaye, MD, MPH**  
Research Scientist, Meta Research, Evidera

**Kyle Fahrbach, PhD**  
Principal Statistician, Meta Research, Evidera



**Yingxin Xu**



**Ajibade Ashaye**



**Kyle Fahrbach**

## Network Meta-Analyses (NMA) in Oncology

- Timing is key for pharmaceutical companies seeking global market access for immunotherapy agents.
- Phase II or early phase program for Breakthrough Therapy Designations Approval would have insufficient data to support generation of relative effectiveness evidence.
- Immunotherapy poses new challenges for comparable endpoints required for an NMA.

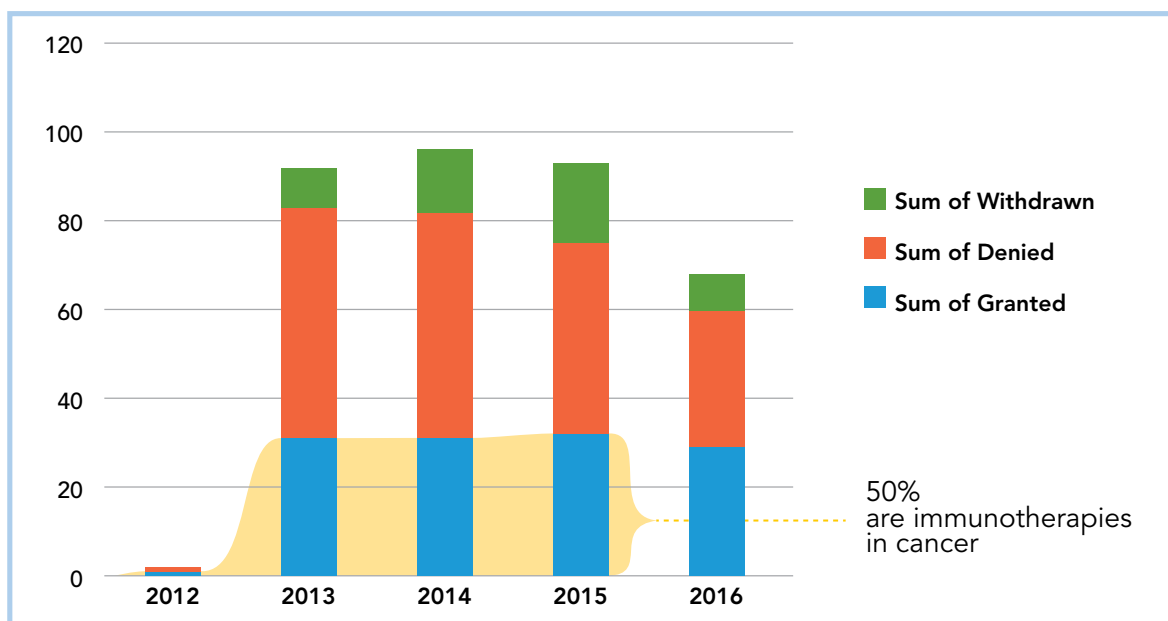
## Introduction

The era of the Tens has brought exciting and promising news for many patients with cancer. At the forefront is the growing possibility that “curing cancer,” rather than just “treating or managing cancer” may not be merely a dream — at least for some cancers and patient subtypes, if not for all. Part of the reason for this optimism is the growth of immunotherapy and immunochemotherapy, as these treatments have shown great promise in multiple clinical trials.

Research into immunotherapy has attracted a great deal of investment across the world. Since July 2012, when the U.S. Food and Drug Administration (FDA) created the Breakthrough Therapy Designation (BTD) as part of the FDA Safety and Innovation Act, they have received nearly 100 applications per year, and they have approved approximately one third of those.<sup>1</sup> As of June 30, 2016, 70% of the treatments approved as breakthrough therapies are immunotherapy or biologic agents to be applied in cancer treatment.<sup>2</sup> As at December 2015, 19 out of 38 BTD approvals were immunotherapy agents in cancer-related indications. Given these successes, timing is key for pharmaceutical companies seeking global market access for these newly approved molecules. Since demonstrating their relative effectiveness is still an important part of the evidence required by many reimbursement or health technology assessment authorities, the need for indirect treatment comparisons (ITC) or network meta-analyses (NMAs) has increased.

Standard evidence generation through NMA is complex in its own right. The rapid evolution of these breakthrough immunotherapy agents presents new challenges in preparing for and conducting such analyses. These include maturity of data; definition of relevant comparators; comparability of outcome measures with those used with earlier, conventional chemotherapies; and non-standard patterns of survival data.

Figure 1. Trend of Breakthrough Therapy Approvals by the FDA (July 2012 through June 2016)



\* 2016 data include requests that are still pending a decision and are included in the total request received column; data in 2012 started from July 9, 2012.

### Maturity of Data Available for NMA

The rapid evolution in evidence related to immunotherapy means that many molecules have been evaluated in only Phase II or even Phase Ib trials when they receive their breakthrough designation. Data from Phase I or II trials are often not suitable for use in an NMA for various reasons, including low sample size, looser inclusion/exclusion criteria, and less stringent primary endpoints (e.g., response rather than survival). To proceed with an NMA, randomized controlled trials are required and are considered to be the gold-standard evidence for several countries or regions that require indirect treatment comparisons, such as Germany, France, the United Kingdom, and the European Union.

The evidence generation process involves conducting a systematic literature review; this includes identifying published evidence for all relevant comparators via public databases (e.g., PubMed, EMBASE, and conference proceedings). While the treatment (applicant) data are maturing, the comparator (competitor) data are also maturing. The comparator may have no results available in the public domain, thus precluding the feasibility of conducting an NMA, or perhaps only interim results may have been released, without sufficient follow-up on patient numbers or trial duration to support adequate comparisons. Often, interim data are available only in conference proceedings; these do not always require rigorous peer review processes, and often differ from the final results or expect to be updated/finalized at a later date. The quality of the data may be poor, and

relevant information on trial design, implementation, and outcome measurements are lacking. These issues prevent an adequate assessment of potential methodological variation and clinical differences; such deficiencies might preclude an NMA or seriously undermine the validity of some of its findings.

### Defining Relevant Comparators

Different immunotherapy agents could be effective for the same cancer, and the same immunotherapy agent may be effective for multiple cancer indications. The different mechanisms of action for these immunotherapy agents often further complicate the questions an NMA is designed to address. Would the control arm in the treatment (applicant) trial be the standard of care? Would that be sufficient to provide relative effectiveness for the application? If not, what are the appropriate, common, and relevant comparators to be considered in the NMA? Answers to those questions drive the approach of the systematic literature review (SLR) and thus the NMA.

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The commercialization strategy for immunotherapy agents will vary from company to company. A particular agent may be filed for approval for the same cancer indication at different therapeutic lines at a different time, while another agent could be submitted for the cancer indications, but at a different time for the same line of therapy. These permutations further complicate the process of defining the relevant comparators at each stage.

**Comparability of Outcome Measures**

Immunotherapies often have a slower onset of action but then show more durable responses and prolonged survival compared to conventional chemotherapy. This difference in the mechanisms of action between classical chemotherapy and the novel immunotherapies is now driving the ongoing evolution of outcomes measurement. The outcomes measurement processes are actively changing, and new trials for immunotherapy agents find new and different ways to examine and define treatment success. However, the problem remains: how to compare these new outcomes measures to the existing data from outcomes defined in older trials for conventional chemotherapy agents. Without immune-specific

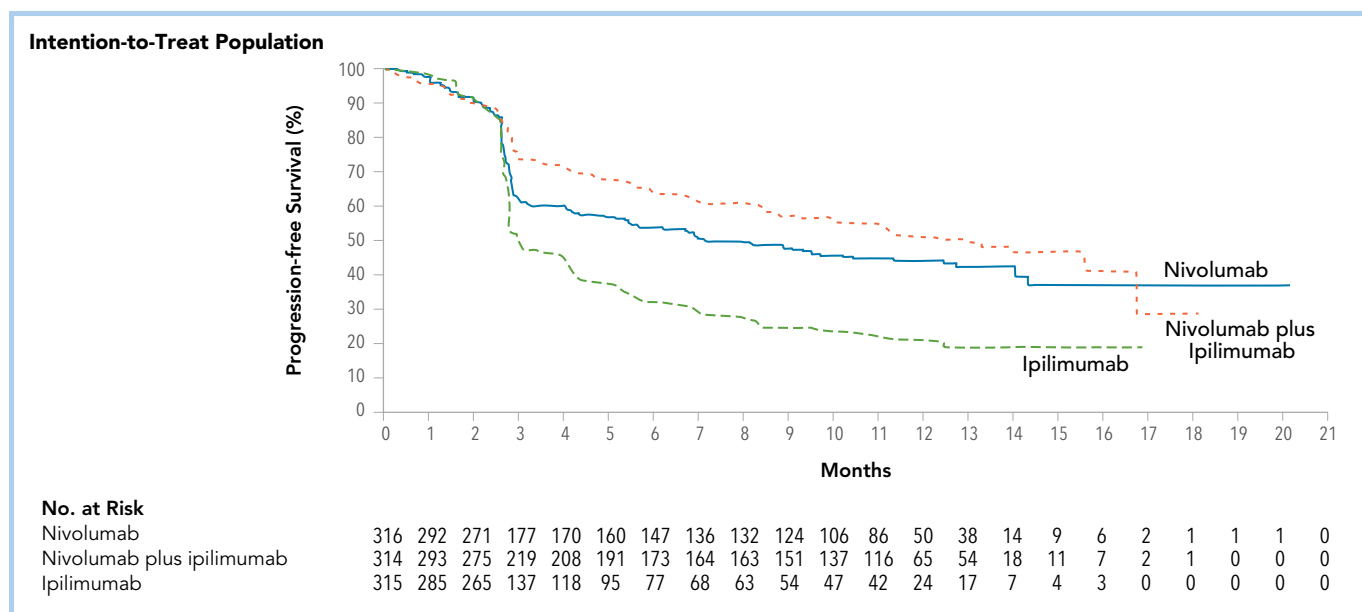
measures, it can be challenging for NMAs to accurately reflect the benefits of immunotherapy.

**Survival Outcome and the Assumption of Proportion Hazards**

It is common in oncology to measure relative treatment efficacy through the consideration of hazard ratios for progression-free and overall survival. A typical NMA makes a proportional hazards assumption hold across all the RCTs included in the network. However, since the “plateau of survival curve” in melanoma was first noted at the 2015 ASCO (American Society of Clinical Oncology) Annual Meeting, the plateauing mortality in immunotherapy has been recognized in various cancer indications.<sup>3</sup>

It also phrases a new challenge to the assumption required in the conventional NMA on survival outcomes: does a single hazard ratio (HR) capture the true benefit of immunotherapy? When an NMA involves both immunotherapy and classical chemotherapy, is it necessary to model survival in the NMA in a more sophisticated fashion, and are there any risks in doing so? It seems clear that in some instances, alternative approaches must be considered, such as applying analyses at different time points (i.e., before vs. after plateau as seen in Figure 2), or using more advanced techniques that attempt to model the time-dependent HRs or time-to-event distributions of treatment arms, e.g., a fractional polynomial approach. The implementations of these advanced methodologies are often threatened

**Figure 2. First Immunotherapy Plateau Survival Curve\***



\* Adapted from Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. *N Engl J Med.* 2015 July 2;373(1):23-34. doi: 10.1056/NEJMoa1504030.<sup>3</sup>

by gaps in the aggregated data on relevant comparators that has been derived from the literature. In some instances alternative approaches, such as matching adjusted indirect comparisons (MAIC) or simulated treatment comparisons (STC), can be employed as these techniques also offer the flexibility of directly estimating time-dependent effects.

## Conclusion

Most NMAs come with methodological challenges for which there are no right answers, or, more accurately, several possible right answers. The growing promise of immunological therapy comes with a need to address these challenges both accurately and swiftly in order to meet what can be accelerated timetables.

For more information, please contact [Yingxin.Xu@evidera.com](mailto:Yingxin.Xu@evidera.com), [Ajibade.Ashaye@evidera.com](mailto:Ajibade.Ashaye@evidera.com), or [Kyle.Fahrbach@evidera.com](mailto:Kyle.Fahrbach@evidera.com).

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