At first I was afraid, I was petrified... Issues and possible solutions to the problem of extrapolating survival curves from limited trial data

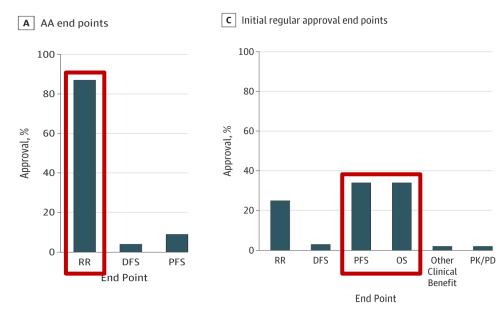
Victoria Federico Paly
Senior Principal, Health Economics
ICON, plc
Victoria.Paly@iconplc.com



Accelerated regulatory approvals for anti-cancer therapies

- Regulatory bodies have implemented accelerated approval schemes for licensing lifesaving therapies, based on interim analysis or surrogate outcomes
 - EMA approvals for oncology treatments based on immature OS data:
 - 19% (7 of 37) from 2009-2013
 - 39% (34 of 88) from 2014-2017 ¹

Clinical endpoints approvals informing FDA approval from 1992-2017²



Kordecka A, et al. Selection of Endpoints in Clinical Trials: Trends in European Marketing Authorization Practice in Oncological Indications. Value Health. 2019 Aug;22(8):884-890. Beaver JA, et al. A 25-Year Experience of US Food and Drug Administration Accelerated Approval of Malignant Hematology and Oncology Drugs and Biologics: A Review. JAMA 2 Oncol. 2018;4(6):849-856.

What does this mean for health technology assessment?

- Economic evaluation is an important part of health technology assessment (HTA)
- If new treatment impacts survival outcomes, economic evaluations often need to adopt a life time horizon
- Thus, HTA decisions for cancer treatments often need to be based on clinical trials with "immature" survival data – necessitating extrapolation of survival over a lifetime
- The plausibility of extrapolated portions of survival curves and the underlying assumptions of the methods used represent a key focus for HTA reviewers due to their potentially large impact on the uncertainty and reliability of cost-effectiveness results

Justifying model selections

A Review of Survival Analysis Methods Used in NICE Technology Appraisals of Cancer Treatments: Consistency, Limitations, and Areas for Improvement

Helen Bell Gorrod, Ben Kearns, John Stevens, Praveen Thokala, Alexander Labeit, Nicholas Latimer, David Tyas, and Ahmed Sowdani

ERG Critique

ERGs criticized the resulting extrapolated survival functions in 41 (71%) of the 58 STAs. The ERGs identified 23 cases in which the TSD had been misinterpreted or not followed. These included situations in which proportional

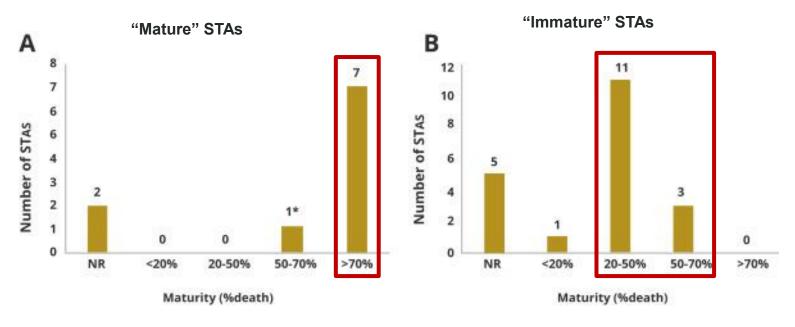


FAD Considerations

The FAD documents provided information on the issues of extrapolating hazard and survival functions that were raised during the appraisal committee discussions. Issues relating to the extrapolation of survival functions were discussed in 41 (71%) of the 58 STAs. The main areas of discussion were the suitability of proportional hazards assumptions $(n = 8)^{ii}$ use of the nonparametric Kaplan-Meier estimator rather than parametric survival functions (n = 6), 15,26,40,46,47,54 lack of validation with appropriate external data (n = 2), ^{28,45} clinical plausibility of the extrapolated hazard and survival functions (n = 19), iii structural uncertainty about the most plausible extrapolation (particularly when the duration of follow-up was short relative to patients' lifetime (n = 3), 21,42,65 and treatment switching (n = 5). Situations in which there was little or no discussion regarding the extrapolated survival functions occurred when the sensitivity of the ICER had been assessed for a range of plausible models,²⁴ when the survival function was mature, 15,26 or in cases in which the treatment was dominated. 20,43

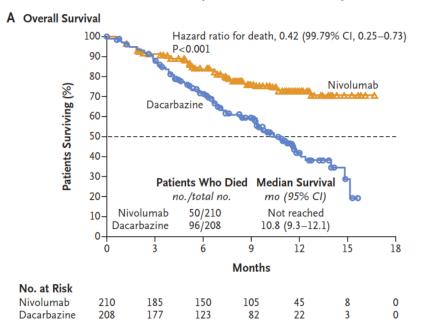
What does "immature" mean?

Recent review of NICE STAs by Tai, et al.:

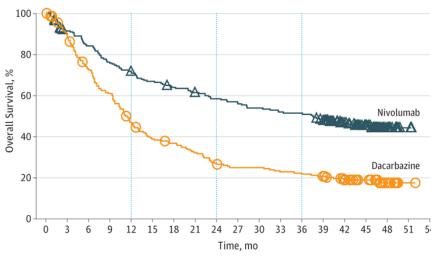


What does "immature" mean?

Minimum ~5 months (max 16 months) follow-up



Minimum 38 months follow-up



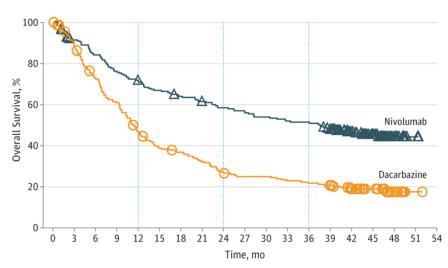
No. at risk
Nivolumab 210 186 171 154 143 135 128 122 116 111 107 103 102 92 72 53 16 2
Dacarbazine 208 179 146 122 92 76 71 62 51 47 47 43 41 38 26 19 7 1

Robert C, et al.. Nivolumab in previously untreated melanoma without BRAF mutation. New England journal of medicine. 2015 Jan 22;372(4):320-30.

Ascierto PA, et al. Survival Outcomes in Patients With Previously Untreated *BRAF* Wild-Type Advanced Melanoma Treated With Nivolumab Therapy: Three-Year Follow-up of a Randomized Phase 3 Trial. *JAMA Oncol.* 2019;5(2):187–194.

What does "immature" mean?

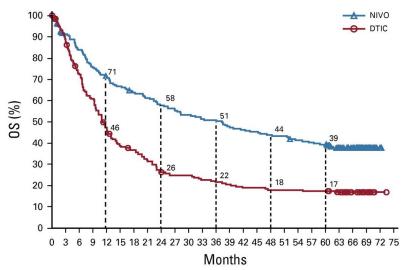
Minimum 38 months follow-up



No. at risk
Nivolumab 210 186 171 154 143 135 128 122 116 111 107 103 102 92 72 53 16 2
Dacarbazine 208 179 146 122 92 76 71 62 51 47 47 43 41 38 26 19 7 1

Ascierto PA, et al. Survival Outcomes in Patients With Previously Untreated *BRAF* Wild-Type Advanced Melanoma Treated With Nivolumab Therapy: Three-Year Follow-up of a Randomized Phase 3 Trial. *JAMA Oncol.* 2019:5(2):187–194.

Minimum 60 months follow-up



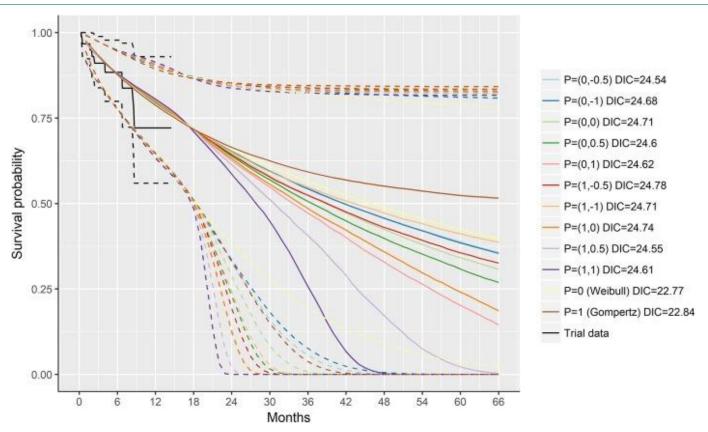
No. at risk

NIVO 210 186 171 154 143 135 128 123 116 111 107 103 102 95 93 91 88 87 82 80 78 62 50 18 3 0

DTIC 208 179 146 122 92 76 71 62 51 47 47 43 41 39 36 36 34 34 34 33 33 26 15 8 1 0

Robert C, et al.. Five-year outcomes with nivolumab in patients with wild-type BRAF advanced melanoma. Journal of Clinical Oncology. 2020 Nov 20.

Extrapolating based on immature data...



Cope S, et al. Integrating expert opinion with clinical trial data to extrapolate long-term survival: a case study of CAR-T therapy for children and young adults with relapsed or refractory acute lymphoblastic leukemia. BMC medical research methodology. 2019 Dec;19(1):1-1.

What can be done?

- 1. Collect more data...AND
- 2. Leverage external information *available now* to inform extrapolations

Potential sources of external data

- General population mortality rates
- Earlier phase or older trials with longer follow-up
- Observational (e.g., registry) data
- Expert clinical opinion

How to leverage external data

Some considerations in selecting external data

- Leveraging general population mortality assumes they are appropriate for the mortality experience of patients who do not die from their disease
- Longer term observational data is commonly only available for control arm which may not provide insights on the extrapolation of treatment effect
- Evolving treatment patterns and first-in-class treatments limits generalizability of historical data
- Estimates from experts may be wide ranging; subject to bias

Indirect (retrospective) use

Use external sources of data to inform and validate model selection

Direct use

Formally incorporate external data to inform the extrapolation

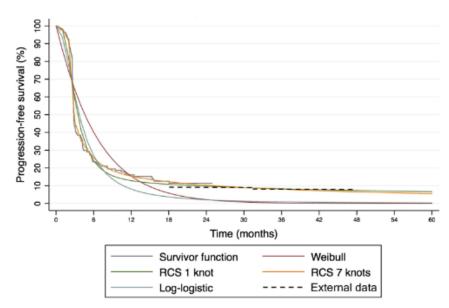
Poll question

How have you used external data to inform survival extrapolations your work?

- a) Indirectly (to inform & validate model selection)
- b) Directly (formally incorporate in extrapolation)
- c) Indirectly & directly used
- d) I have not yet used external data to inform my survival modeling

Examples of indirect use of external data

- Have clinical experts assess plausibility of extrapolations
- Compare landmark survival estimates to validate extrapolations from parametric models
 - Evaluate which models fall with in the 95% confidence interval of the summary estimates (or Kaplan-Meier data if available)
 - Can be from observational data or estimates elicited from clinical experts
 - Elicit plausible ranges of survival from experts without presenting extrapolations



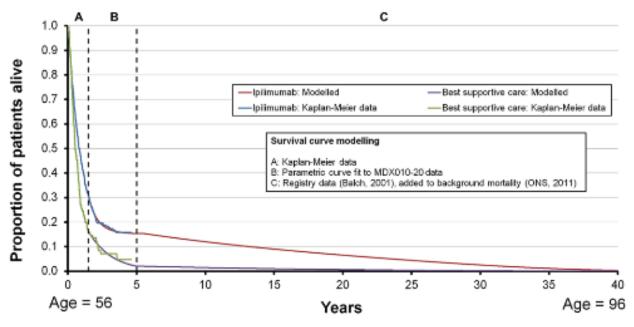
Gibson E, et al. Modelling the survival outcomes of immuno-oncology drugs in economic evaluations: a systematic approach to data analysis and extrapolation. Pharmacoeconomics. 2017 Dec;35(12):1257-70.

NICE DSU Technical Support Document 21:

"...retrospectively assessing the plausibility of extrapolations is inherently subjective and as a result may be prone to personal bias."

Examples of direct use of external data

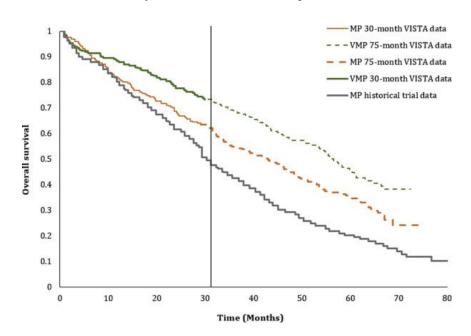
 Directly use patient-level data for a portion of the extrapolation (e.g. piecewise or hybrid approach)



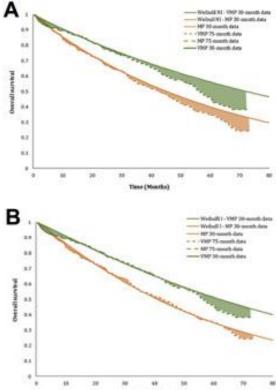
Examples of direct use of external data

Formally integrate external data into the extrapolations themselves as

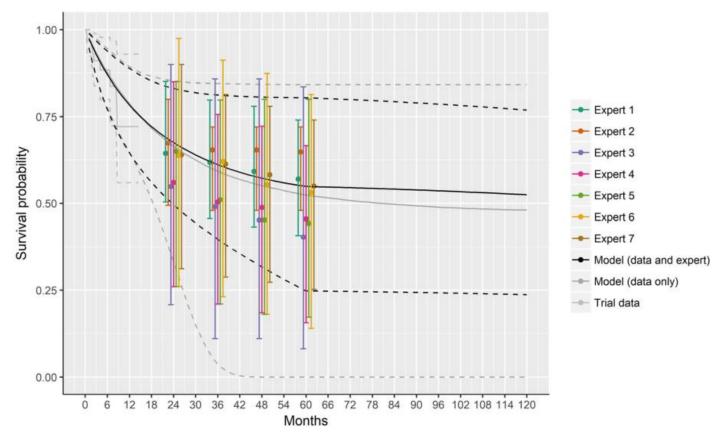
informative priors via a Bayesian framework



Soikkeli F, et al. Extrapolating Survival Data Using Historical Trial–Based a Priori Distributions. Value in Health. 2019 Sep 1;22(9):1012-7.



Examples of direct use of external data



Summary

- There is no magic bullet
- Increasingly robust methods are being developed
- Ultimately need to be prepared to test a (potentially long) list of plausible scenarios – leveraging both indirect & direct methods