# The impact of long-term follow up on mean survival estimates from immuno-oncology clinical trials

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# Background

- Mean survival, estimated by extrapolation of incomplete data, is used by some HTA agencies in assessment of the value new oncology treatments.

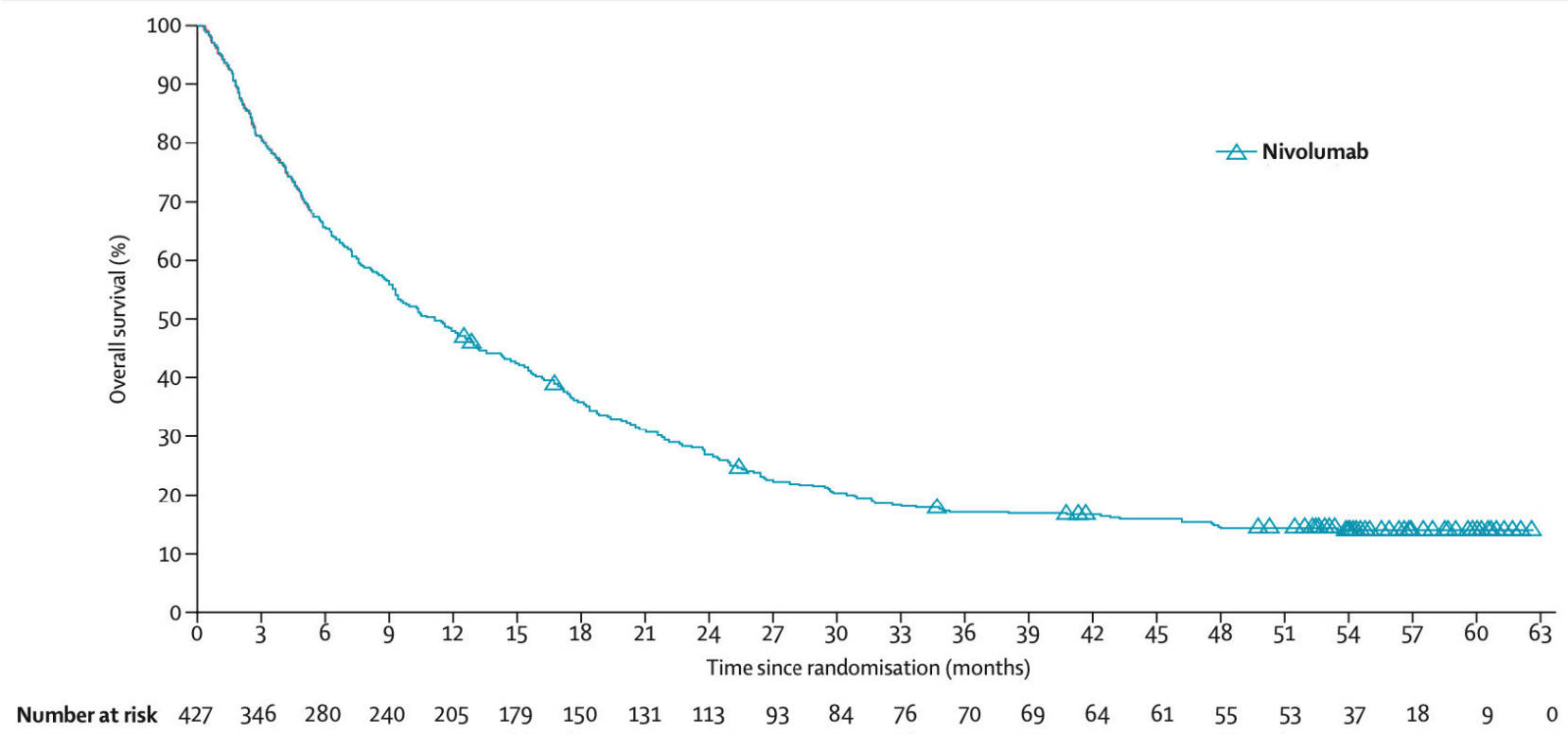
- A prolonged tail in the distribution of survival times, due to a subset of patients with durable response, increases population mean survival.

- However, if the proportion of durable responders is small or moderate, the potential for improved mean survival may only become apparent with longer follow-up.

- This research seeks to identify the impact of longer follow-up on estimates of mean survival from clinical trials of immuno-oncology (IO) therapies.

# Prolonged tail in overall survival

**Nivolumab in NSCLC: CheckMate 017 and 057 pooled 4-year follow-up**




Antonia *et al.* (2018)

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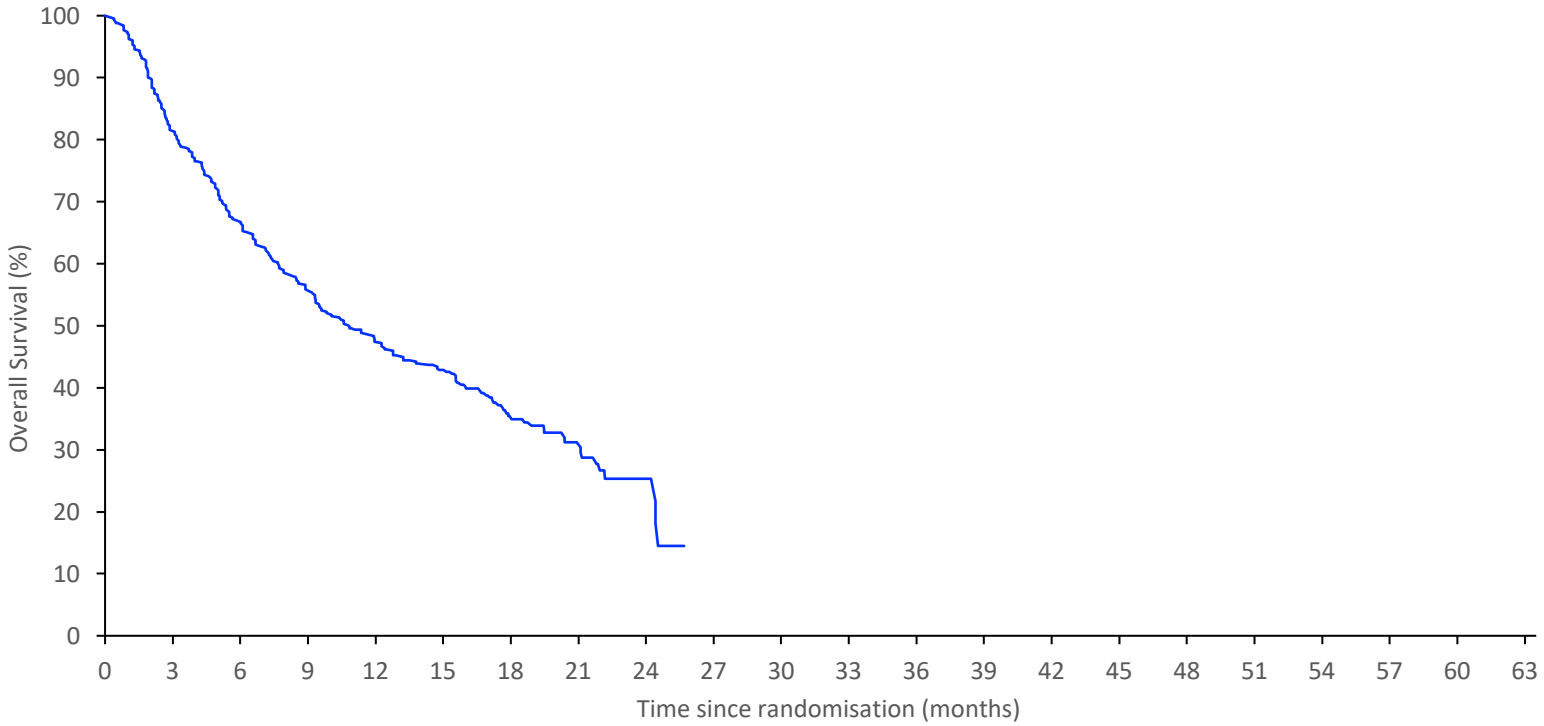
# Prolonged tail in overall survival?

## Nivolumab in NSCLC: CheckMate 017 and 057 pooled 1-year data




Borghaei *et al.* (2015), Brahmer *et al.* (2015)

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# Methods

**Targeted literature review**

- MEDLINE search, via PubMed:
  - Early IO indications: melanoma, NSCLC and RCC
  - Studies with published short-term results and long-term follow-up
  - Immune checkpoint inhibitor (ICI) monotherapies, to focus on IO effect only
  - Previously treated patients (2L+), to reduce potential impact of subsequent therapies.

**Generation of pseudo-IPD**

- Digitisation of published Kaplan-Meier curves using Enguage Digitizer
- Conversion to pseudo-IPD, using algorithm from Wei and Royston (2019)
- Quality check to original published Kaplan-Meier curves and numbers at risk.

**Extrapolation and comparison of short-term and long-term follow-up**

- Pseudo-IPD for short-term and long-term follow-up extrapolated and mean survival estimated, using 9 different models:
  - 6x parametric regression models
  - 3x flexible parametric models (restricted cubic splines).

# Data sources

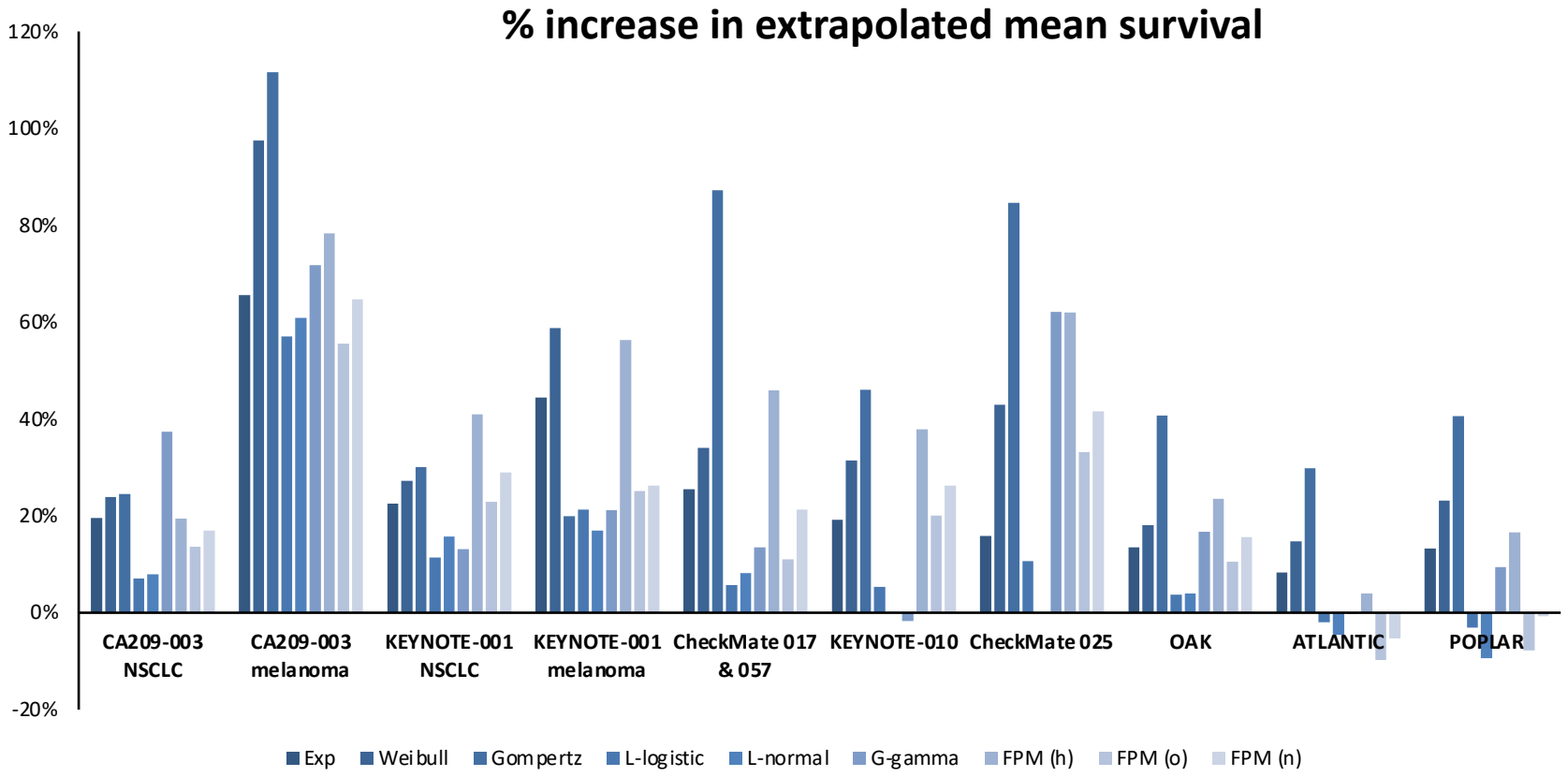
| Clinical trial | Disease | ICI drug | Line | Short-term data cut | Long-term follow up |
|---|---|---|---|---|---|
| **CA209-003** | Melanoma | Nivolumab | 2L+ | Topalian *et al.* (2014) | Topalian *et al.* (2019) |
| **KEYNOTE-001** | Melanoma | Pembrolizumab | 2L+ | Ribas *et al.* (2016) | Hamid *et al.* (2019) |
| **ATLANTIC** | NSCLC | Durvalumab | 3L+ | Garassino *et al.* (2018) | Garassino *et al.* (2020) |
| **CA209-003** | NSCLC | Nivolumab | 2L+ | Gettinger *et al.* (2015) | Gettinger *et al.* (2018) |
| **CheckMate 017 & 057** | NSCLC | Nivolumab | 2L+ | Borghaei *et al.* (2015)<br>Brahmer *et al.* (2015) | Antonia *et al.* (2019) |
| **KEYNOTE-001** | NSCLC | Pembrolizumab | 2L+ | Leighl *et al.* (2019) | Garon *et al.* (2019) |
| **KEYNOTE-010** | NSCLC | Pembrolizumab | 2L+ | Herbst *et al.* (2016) | Herbst *et al.* (2020) |
| **OAK** | NSCLC | Atezolizumab | 2L+ | Fehrenbacher *et al.* (2018) | Mazieres *et al.* (2020) |
| **POPLAR** | NSCLC | Atezolizumab | 2L+ | Fehrenbacher *et al*. (2016) | Mazieres et al. (2020) |
| **CheckMate 025** | RCC | Nivolumab | 2L+ | Motzer *et al.* (2015) | Motzer *et al.* (2020) |

# Results: Summary

| Clinical trial | Disease | ICI drug | # models with increase in mean | Average change in mean estimates | Δ SD |
|---|---|---|---|---|---|
| **CA209-003** | Melanoma | Nivolumab | 9 of 9 | 73.6% | 18.29 |
| **KEYNOTE-001** | Melanoma | Pembrolizumab | 9 of 9 | 32.2% | -5.48 |
| **ATLANTIC** | NSCLC | Durvalumab | 4 of 9 | 3.9% | -6.6 |
| **CA209-003** | NSCLC | Nivolumab | 9 of 9 | 18.9% | 3.16 |
| **CheckMate 017 & 057** | NSCLC | Nivolumab | 9 of 9 | 28.0% | 2.74 |
| **KEYNOTE-001** | NSCLC | Pembrolizumab | 9 of 9 | 23.7% | 2.14 |
| **KEYNOTE-010** | NSCLC | Pembrolizumab | 8 of 9 | 20.5% | -2.46 |
| **OAK** | NSCLC | Atezolizumab | 9 of 9 | 16.3% | -2.02 |
| **POPLAR** | NSCLC | Atezolizumab | 5 of 9 | 9.1% | -10.82 |
| **CheckMate 025** | RCC | Nivolumab | 8 of 9 | 39.2% | -18.47 |

- For 8 out of the 10 trial populations, most or all extrapolation models produce higher estimates of mean survival with longer follow-up.
- The magnitude of increase is important.
- Variance across model estimates reduces with longer follow up in 6 out of 10 trials.

# Results: Increase in mean survival by clinical trial

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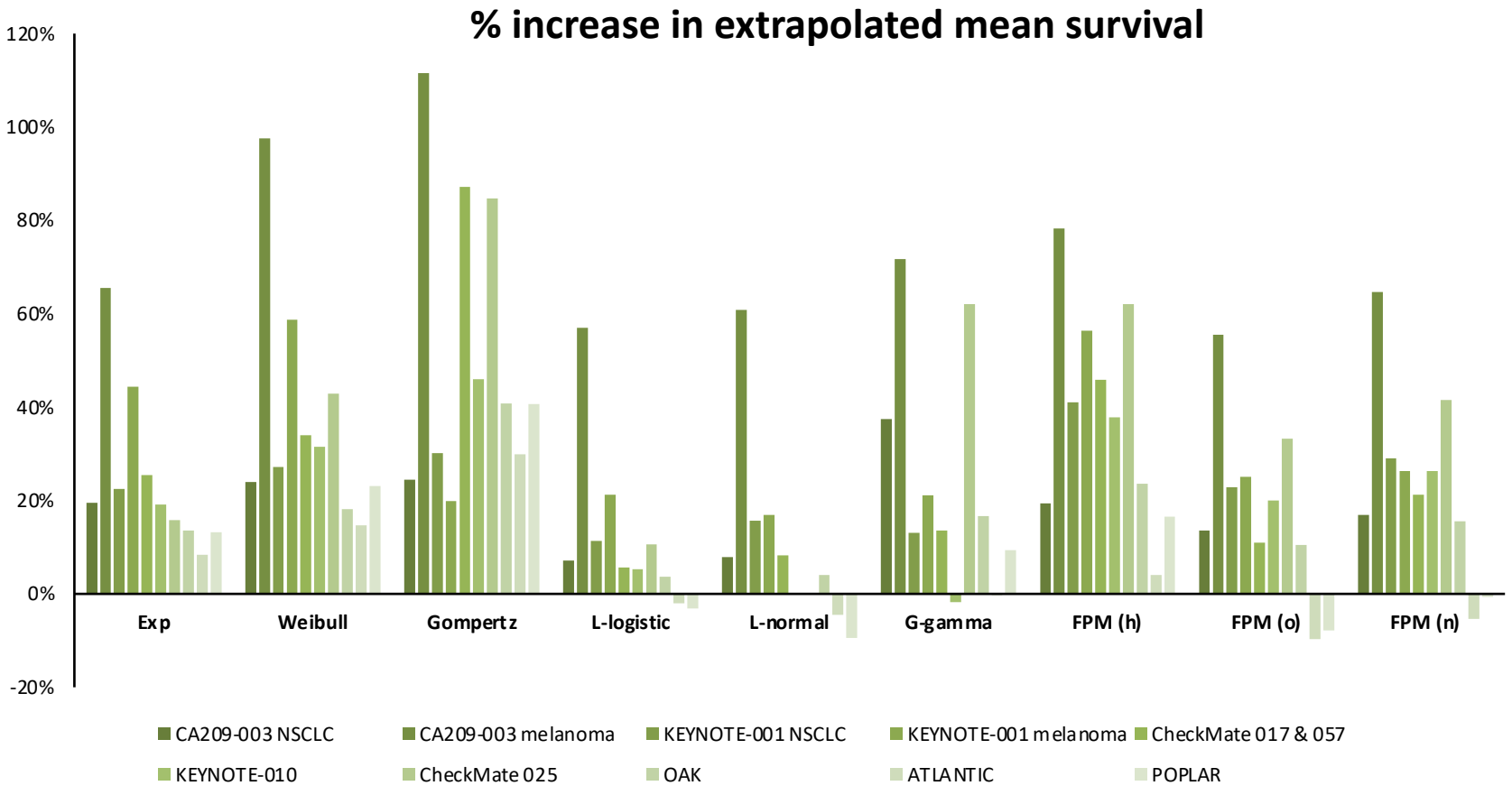
# Results: Increase in mean survival by function

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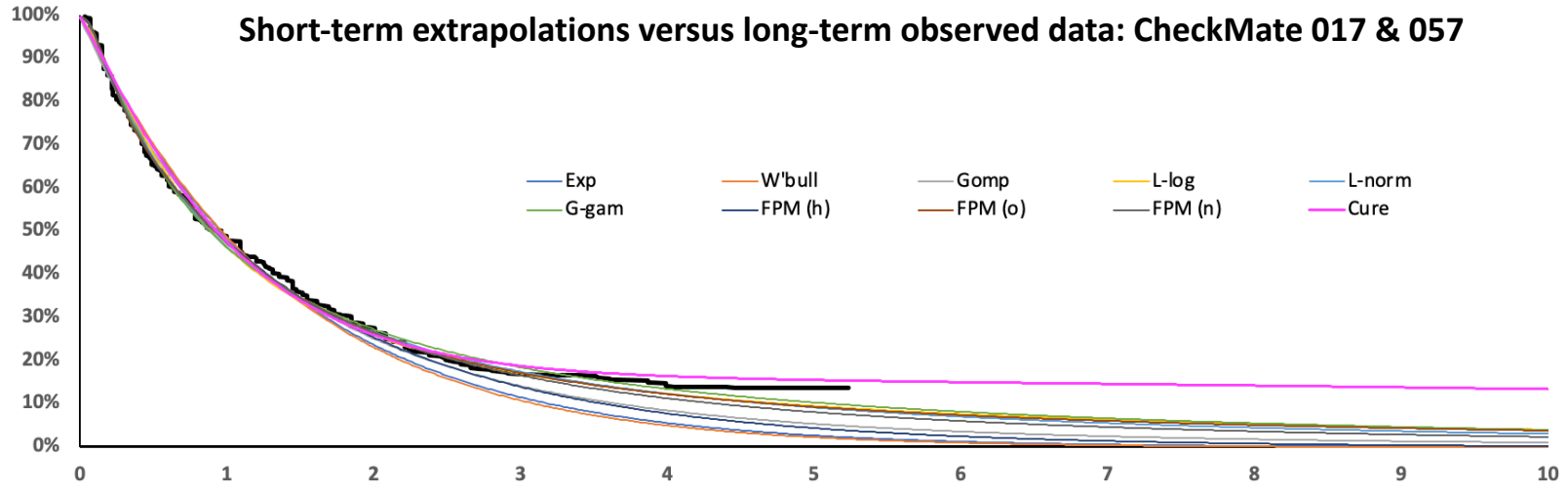
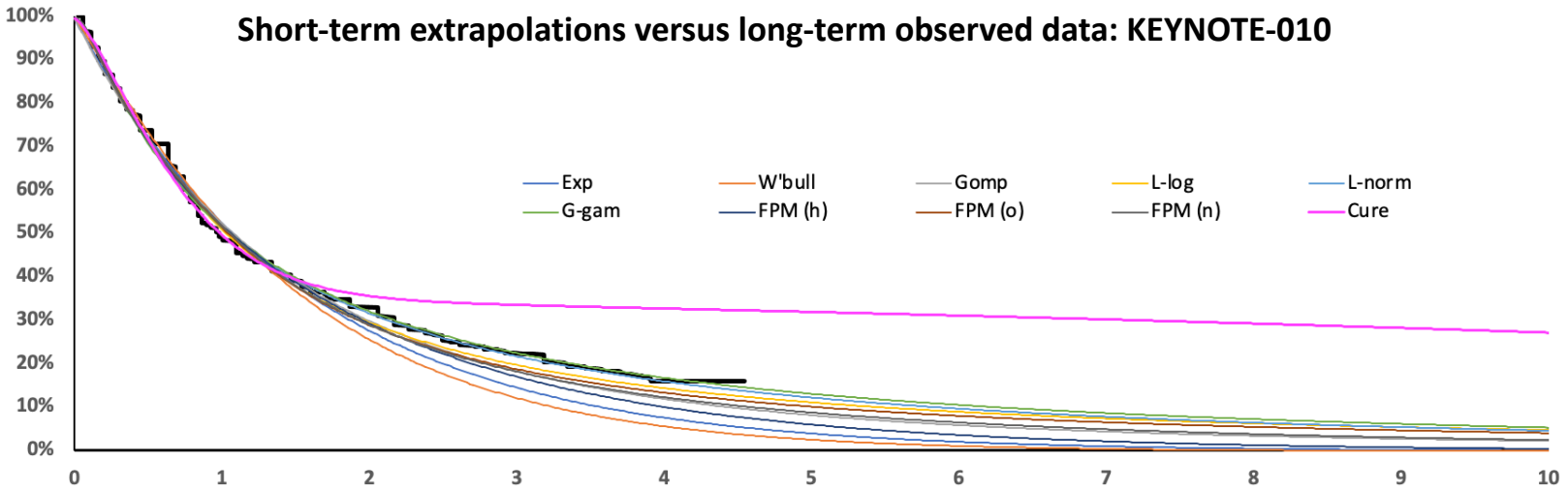
# What about a cure model?

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# Conclusions

- Estimates of mean survival systematically increased with longer follow-up in clinical trials of immune checkpoint inhibitors.
- Variability in mean estimates across extrapolation models reduced with longer follow-up.
- Mean survival estimates increased regardless of extrapolation model:
  - Exponential, weibull and gompertz models had the largest increases
  - Log-normal and log-logistic produced smaller increases
  - Flexible parametric models produced larger than expected increases
  - Goodness of fit of short-term extrapolations (measured by AIC/BIC) is not a guide to the extent of increase.

- **Developers of innovative IO therapies should plan for and publish long-term follow-up from clinical trials wherever feasible:**
  - Longer follow-up will improve mean survival estimates and reduce the range of uncertainty over the value of IO therapies in HTA
  - Greater availability of long-term data will increase understanding of IO survival and support research to improve methods for extrapolation from incomplete data.

# Q&A

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