Modeling survival to fully capture value

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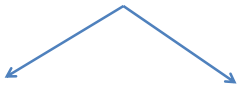
Heterogeneity of patient populations: a problem for survival modeling

Heterogeneous study populations comprise



Cured patients **Uncured** patients

- Some patients will be "**cured**" (eg, durable remissions, return to normality)
- Compared with uncured patients, cured patients will have
  - Longer survival, similar to a disease-free person
  - Greater healthcare costs (due to additional long-term follow-up/surveillance)
- **Standard approach for survival modeling:** assess the mean for all patients in each treatment arm
- **Issue: grouping** cured and uncured patients together and reporting one mean value = potential **bias**

Othus M, et al. *Value Health.* 2017;20:705-709

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Issues with the standard approach to survival modeling

- Mean OS for **cured** patients is much greater than mean OS for **uncured** patients
  - Mean OS for cured patients may exceed the observation period of the study
- **Grouping** cured and uncured patients together and reporting one mean value for OS **does not account for heterogeneity** in the population and results in
  - Incomplete assessment of a therapy that cures a proportion of patients
  - Biased assessments of OS

OS, overall survival

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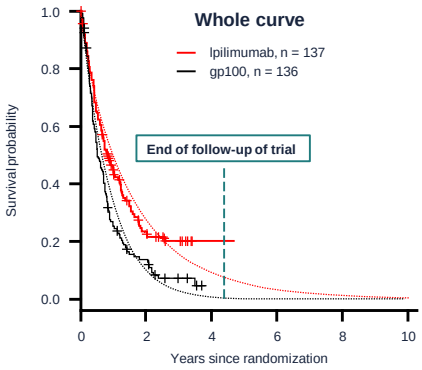
Estimating mean overall survival with survival plateau

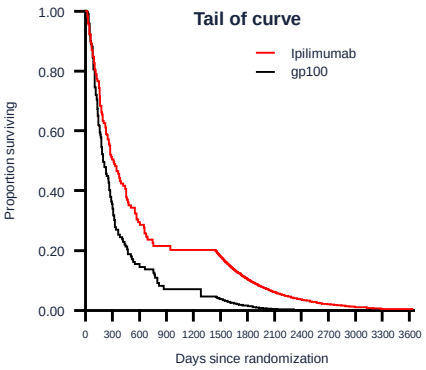
Survival curves plateau

- Mean OS cannot be estimated from an empirical curve



Standard approach and **previous work**

- Use **parametric models** to generate tail curve



OS, overall survival
Davies A, et al. *Health Outcomes Res Med.* 2012;3:e25–e36

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Mixture cure models: basic approach

- **General idea:** explicitly model the **mixture** of **"cured"** and **uncured** patients
- Use regression models to
  - Estimate the **probability** that a patient is **cured**
  - Predict the **survival** of patients who are **not cured**

Population survival = p_{cured} × $survival_{cured}$ + (1-p_{cured}) × $survival_{uncured}$

1. Berkson J, Gage RP. *Proc Staff Meet Mayo Clin.* 1950;25:270–288;
2. Kuk AYC, Chen CH. *Biometrika.* 1992;79:531–541;
3. Peng Y, Dear KB. *Biometrics.* 2000;56:237–243;
4. Sy JP, Taylor JM. *Biometrics.* 2000;56:227–236

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Example: applying the mixture cure model to the ZUMA-1 trial of CAR T-cell therapy for patients with relapsed or refractory large B-cell lymphoma

- ZUMA-1 trial
  - Phase 2, single-arm, registration study (N = 111) of axi-cel in patients with relapsed or refractory large B-cell lymphoma
  - 54% of the patients achieved a complete response to therapy
  - At 18 months, the Kaplan-Meier estimated rate of OS was 52%
  - Median follow-up was15.4 months
  - Responses were ongoing in 42% of the patients, including 40% with a complete response

axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; OS, overall survival
Neelapu SS, et al. *N Engl J Med.* 2017;28;377:2531–2544

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Methods for fitting Kaplan-Meier curves

- Weibull and lognormal distributions without a cure proportion
- Mixture cure: weighted average of cured and noncured

$$S(t,x) = S_B(t,x)[p(x) + (1 - p(x))S_E(t,x)$$

- Estimation of $\int_0^\infty S_B(t)dt$ and $\int_0^\infty S_B(t)S_E(t)dt$, respectively
- Percentile-based bootstrap 95% CIs calculated using 1000 bootstrap replicates

CI, confidence interval

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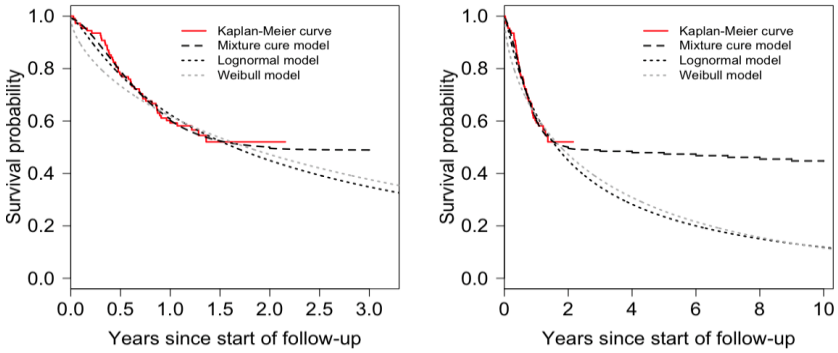
Lognormal, Weibull, and mixture cure models applied to the ZUMA-1 trial data vs a Kaplan-Meier curve



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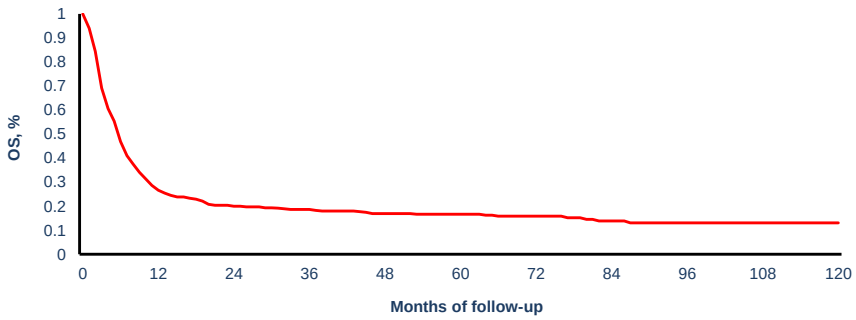
OS modeling in the SCHOLAR-1[1] cohort

- We assumed age-matched US general population mortality rates for patients alive at the conclusion of SCHOLAR-1 follow-up (10 years)



OS, overall survival

1. Crump M, et al. *Blood.* 2017;130:1800–1808

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Mean OS estimates for ZUMA-1

Summary statistic	Result
Lognormal analysis (without cure modeling)	
Mean (95% CI) OS, years	4.6 (2.3–10.3)
Weibull analysis (without cure modeling)	
Mean (95% CI) OS, years	2.0 (1.5–3.0)
Mixture cure model analysis	
Cure fraction (95% CI), %	50.2% (36.3–64.1)
Mean (95% CI) OS among cured patients, years	28.1 (26.0–30.1)
Mean (95% CI) OS among noncured patients, months	8.2 (7.1–9.9)

CI, confidence interval; OS, overall survival

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When to consider using mixture cure models vs standard models

- All survival curves have some degree of a tail
- Based on simulations, there needs to be
  - **The possibility of cure:** compared with standard models, mixture cure modeling is less efficient and can overestimate survival when there is no cure
  - **Sufficient follow-up:** Mixture cure modeling is likely to underestimate survival when the true-cure fraction is > 5% and follow-up is < 50% of the time at which 95% of events would have been observed
    - The smaller the true-cure fraction, the longer the necessary follow-up

Bansal A, Basu A. Unpublished data

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When to consider using mixture cure models in general

- Biological rationale
  - Is long-term remission (ie, “cure”) plausible?
- Shape of the Kaplan-Meier curve
  - What is the proportion of survivors at the end of the follow-up period?
- Duration of follow-up
  - Shorter follow-up = more uncertainty
  - Rules of thumb?
- Number of patients in each cohort

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Conclusions

- Mixture modeling offers advantages over traditional survival modeling for extrapolation, when treatments produce a clear fraction of patients with long-term remission (ie, “cure”)
  - Typically, mean survival estimates with mixture cure modeling are substantially greater than those achieved using standard parametric approaches
- The benefits of mixture cure modeling lessen and errors increase as the “cure fraction” decreases
- To avoid errors in estimation, it is critical to consider the biological rationale, shape of the Kaplan-Meier curve, and duration of follow-up before using mixture cure modeling

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