Mixture-Cure Modelling of the Overall Survival of Patients with Metastatic Non-Small Cell Lung Cancer (NSCLC) Receiving Nivolumab + Ipilimumab in CheckMate 227

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Introduction

- Recent advances in immuno-oncology (I-O) have given rise to treatments which are associated with a marked heterogeneity of outcomes, whereby some patients derive long term benefits while others exhibit rapid progression. The former, based on their long-term survival and a risk of death close to that of the general population, can sometimes be considered "cured". However, the existence of a "cured" fraction is a challenge for standard models of survival analysis and extrapolation, and thus for healthcare decisions
- This study explores the potential for capturing the heterogeneity in life expectancy with I-O therapy using mixture cure models[1] (MCM), in which a study's population can be treated as a mixture of two groups, one "cured" and the other "not cured"
- The trial used in this research, CheckMate 227 (CM 227), has the longest survival follow-up reported yet (minimum 49.4 months; median 54.8 months) among phase 3 studies of 1st line dual I-O treatment for metastatic NSCLC in PD-L1 ≥1% and <1% patients. 1st line nivolumab + ipilimumab (NIVO + IPI) has demonstrated a significant OS improvement over chemotherapy in patients with PD-L1 ≥1%; descriptive analysis also showed a survival benefit of the combination in patients with PD-L1 <1%[2,3]

Objectives

- To model overall survival (OS) associated with dual I-O therapy in patients with metastatic non-small cell lung cancer (NSCLC) enrolled in the CM 227 trial, using MCM
- To investigate the inter-relationships (not always recognized) between three key elements of MCM: the fraction experiencing long-term survival (LTS, those with life expectancy similar to that of the general population), the parametric distribution applied to OS in those "not cured", and the mortality of the "cured" relative to general background mortality, or the standardized mortality ratio (SMR), where SMR of 1 indicates mortality equal to that of the general population

Methods

- Patient data were obtained from CM 227, an open-label, randomized phase 3 trial of NIVO + IPI versus platinum doublet chemotherapy (PDC). To provide a baseline which could be tested with longer term data, relative survival MCM were fitted by maximum likelihood to OS data, at a database lock (DBL) giving at least three years' follow-up, from all patients randomized to NIVO + IPI or chemotherapy in CM 227 (DBL: Feb 2020)
- Baseline hazard was informed by nationality, age and gender-specific WHO life tables matched to each patient. In the base case, long-term survival in the LTS fraction applied the matched general population's hazard of death; the complementary "uncured" fraction with shorter survival assumed a parametric hazard function above this baseline
- Dependencies between these models fitted to the trial data, the "uncured" distribution and SMR upon matched baseline hazard are reported

Results

- MCM were fitted successfully using a short-tailed distribution (Weibull) and a long-tailed distribution (lognormal), the latter tending to taper off more gradually than the former, for the "uncured" fraction
- In the base case scenario, assuming a general population baseline hazard (SMR=1), MCM gave the proportion in LTS as 0.291 (95% CI: 0.240, 0.340) for NIVO + IPI with excess hazard in the "uncured" described by a Weibull distribution (Table 1 and Figure 1); this compares with 0.173 (95% CI: 0.137, 0.21) for chemotherapy (Table 2 and Figure 2)
- In the sensitivity analyses, applying a lognormal distribution to the "uncured" gave a corresponding LTS fraction of 0.111 assuming SMR of 1 (95% CI: 0.001, 0.218) for NIVO + IPI (Table 1) compared with 0.052 (0.000, 0.122) for chemotherapy (Table 2)
- The plausibility and validity of the LTS estimates obtained in this research can be tested using longer term trial results, with further research planned applying MCM to 5-year CM 227 data

Table 1: LTS fractions and mean survival as the baseline hazard is varied: NIVO + IPI

Fit name	SMR	AIC	BIC	Long term survival fraction	Mean survival (months)
Weibull	1	3481.14	3494.24	**0.291** (0.251, 0.347)	**80.89** (70.78, 94.72)
	2	3476.09	3489.19	**0.320** (0.277, 0.378)	**68.87** (60.46, 79.98)
	5	3470.09	3483.19	**0.397** (0.349, 0.460)	**55.12** (48.94, 63.12)
	10	3482.42	3495.52	**0.501** (0.451, 0.571)	**45.97** (41.42, 51.91)
Lognormal	1	3479.46	3492.57	**0.111** (0.010, 0.228)	**56.76** (42.86, 75.21)
	2	3476.16	3489.26	**0.149** (0.051, 0.266)	**52.91** (42.90, 66.26)
	5	3473.99	3487.09	**0.250** (0.137, 0.366)	**47.52** (40.57, 56.03)
	10	3489.86	3502.97	**0.398** (0.285, 0.501)	**42.84** (38.07, 49.20)

FOOTNOTE SMR: standardized mortality ratio; AIC: Akaike information criterion; BIC: Bayesian information criterion

Figure 1: OS curves fitted to the NIVO + IPI arm of CM 227 as the baseline hazard is varied (Weibull distribution)

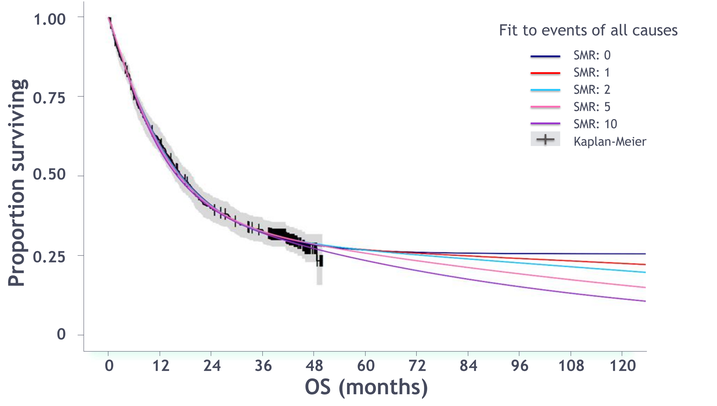
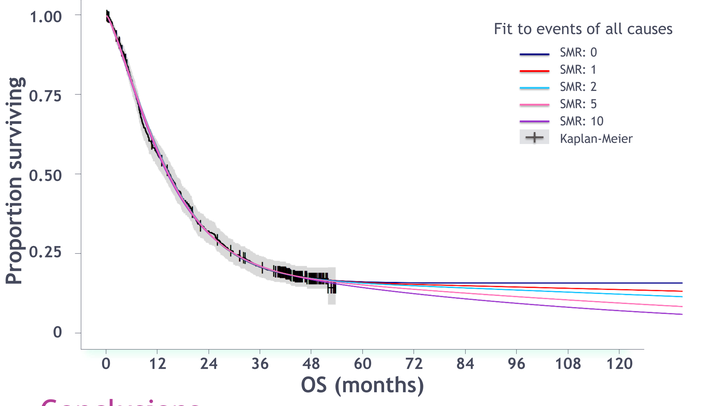


Table 2: LTS fractions and mean survival as the baseline hazard is varied: PDC

Fit name	SMR	AIC	BIC	Long term survival fraction	Mean survival (months)
Weibull	1	3773.09	3786.19	**0.173** (0.137, 0.214)	**52.81** (45.12, 61.79)
	2	3771.20	3784.30	**0.186** (0.148, 0.228)	**45.05** (39.06, 52.06)
	5	3769.75	3782.85	**0.224** (0.182, 0.271)	**36.67** (32.47, 41.42)
	10	3778.04	3791.14	**0.290** (0.242, 0.343)	**31.80** (28.65, 35.22)
Lognormal	1	3778.32	3791.43	**0.052** (0.000, 0.122)	**33.47** (24.31, 46.32)
	2	3775.95	3789.06	**0.066** (0.000, 0.143)	**32.08** (24.27, 41.89)
	5	3786.64	3786.64	**0.110** (0.005, 0.191)	**30.15** (24.49, 36.28)
	10	3794.06	379.06	**0.185** (0.057, 0.283)	**28.55** (24.56, 33.29)

FOOTNOTE SMR: standardized mortality ratio; AIC: Akaike information criterion; BIC: Bayesian information criterion

Figure 2: OS curves fitted to the PDC arm of CM 227 as the baseline hazard is varied (Weibull distribution)



Discussion

- The lowest Akaike Information Criterion (AIC) in both NIVO + IPI and chemotherapy arms was recorded with SMR=5 amongst the uncured. However, the validity of the long term extrapolation would need to be assessed
- Although the Weibull distribution provides a slightly better fit than the lognormal at SMR=5, the plausibility of the Weibull's LTS needs to be tested against the lower LTS of the lognormal distribution
- LTS was lower with chemotherapy but similarly sensitive to changes in SMR under the Weibull distribution; as the SMR was increased from 1 to 10, LTS increased by around 70% with NIVO + IPI (0.291 to 0.501) and chemotherapy (0.173 to 0.290)
- The impact of an increase in SMR from 1 to 10, using a Weibull distribution in the uncured, is that mean survival decreases from 81 to 46 months with NIVO + IPI and by a similar percentage (around 40%) with chemotherapy (53 to 32 months)

Conclusions

- Models of OS in CM 227 can be represented by MCM
- The LTS fraction varies according to the choice of OS parametric distribution for the uncured, with short-tailed distributions (e.g. exponential, Weibull) generating LTS fractions around 29% vs 17% (NIVO + IPI vs chemotherapy) with SMR=1 in the "cured". The LTS fraction also varied in response to changes in the SMR, demonstrating that parameters are specific to the baseline hazard assumptions made during fitting
- The responsiveness of the LTS fraction to changes in the SMR among the "cured" serves to highlight a limitation of the approach, namely the importance of validating long-term OS extrapolations; using external sources and longer follow-up can help to select appropriate parametric distributions and assess the plausibility of assumptions

References

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