Validation of Long-Term Overall Survival Estimates in Non-Small-Cell Lung Cancer Using Registry Data from the Danish Cancer Registry and the Impact of Improvement of Survival Outcomes over Time

[RWD151]

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Background

- In Denmark, lung cancer is among the most common cancer types, with non-small cell lung cancer (NSCLC) being the most prevalent form. In 2021, a total of 4,973 new lung cancer cases were recorded, with approximately 80% of patients diagnosed with NSCLC.[1]
- Despite significant advancements in the treatment of NSCLC, overall survival rates for lung cancer remain low. Lung cancer remains the leading cause of cancer-related deaths, responsible for nearly 22% of all cancer fatalities in 2020.[2]
- CheckMate-816 (NCT02998528) is a phase III, randomized, open-label trial evaluating the efficacy and safety of three doses of nivolumab combined with chemotherapy versus chemotherapy alone as neoadjuvant (before surgery) treatment in patients with NSCLC stage IB-IIIA (TNM 7th edition).[3]
- The trial met its primary endpoints, showing significant improvements in event-free survival and pathological complete response. Additionally, a clinically important overall survival (OS) improvement trend was also observed.[4]
- While OS is a critical endpoint for evaluating the full impact of neoadjuvant therapies, the trial's OS data is still immature. Extrapolating long-term OS is further complicated by ongoing advancements in cancer treatment and patient care practices.
- Validating modeled OS against real-world data, such as from the Danish Lung Cancer Registry (DLCR), provides an opportunity to assess the external validity of survival projections from clinical trials.

Objectives

- This study aimed to validate the modeled OS for neoadjuvant chemotherapy from the CheckMate-816 trial using publicly available data from the DLCR. This comparison assesses the accuracy and real-world applicability of the model-predicted survival outcomes in clinical practice.

Methods

OS projection from CheckMate-816

- A three-state semi-Markov model with pre-progression, progressed, and death health states was developed to simulate the natural progression of resectable NSCLC and assess the long-term survival outcomes associated with neoadjuvant chemotherapy (**Figure 1**).
- The model tracks patients as they move between these health states over time, allowing for time-dependent survival analysis, where patients can remain in the pre-progression state, transition to progressed disease, or die at any point.
- Transition probabilities between the health states were derived by extrapolating the patient-level data from CheckMate-816. These extrapolations, extending up to 35 years (lifetime), were generated using parametric fitting methods, with the best-fit distributions chosen as the base case for the model.
- The log-normal distribution was selected to model time-to-progression for patients treated with neoadjuvant chemotherapy, based on data from the neoadjuvant chemotherapy arm of the CheckMate-816 trial (**Figure 2**).
- Mortality estimates for patients in the pre- and post-progression health states were derived from pooled data across both treatment arms in the CheckMate-816 trial and were capped by mortality from the general population, matched by age and sex. As there was no statistically significant difference in state-specific mortality between treatment arms, pooling data across arms was considered appropriate to increase the number of events, allowing for more reliable extrapolation. The best-fitting models for mortality were the exponential distribution for pre-progression (**Figure 3a**) and the lognormal distribution for post-progression (**Figure 3b**).
- The constructed OS was estimated by summing time spent in non-death health states (**Figure 4**).
- A key feature of the model was the implementation of a cure assumption. Given the curative intent of treatment for resectable NSCLC and input from clinical experts,[5,6] patients who remained progression-free and alive after 5 years were considered cured. Cured patients were no longer considered at risk of disease progression and were no longer subject to disease-specific mortality.

Figure 1. Three-state Markov model diagram

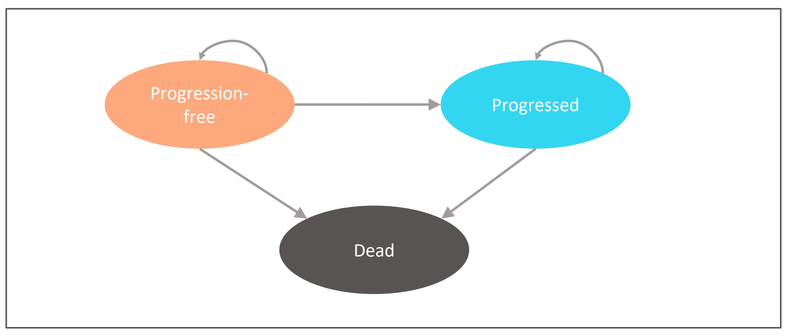
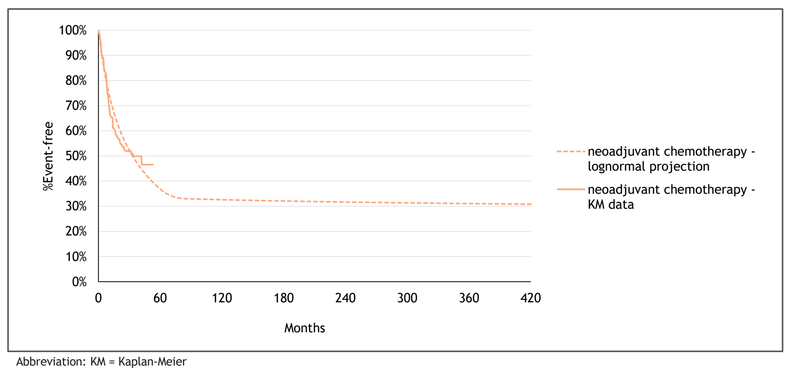
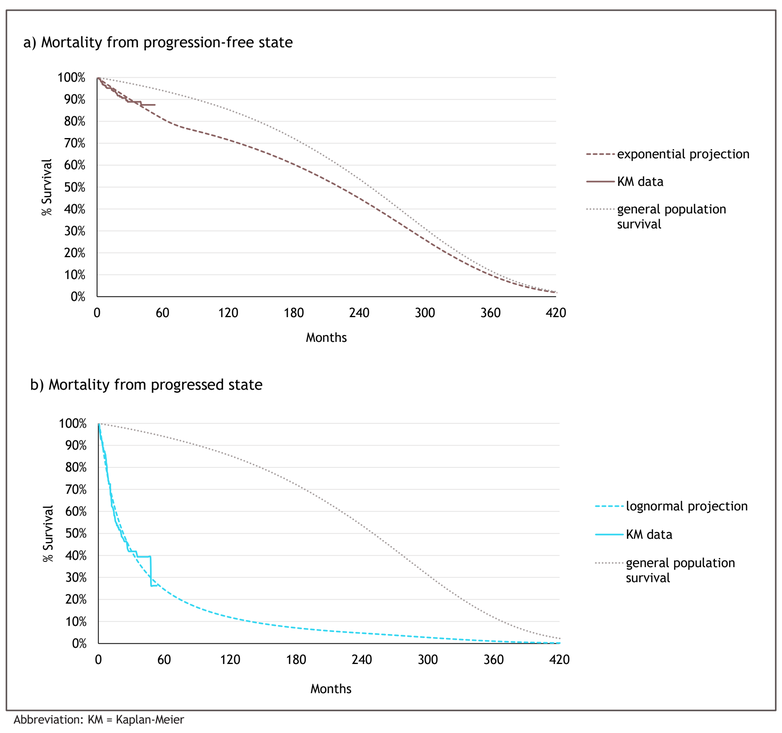


Figure 2. Modeled time-to-progression (cure at 5 years)



Abbreviation: KM = Kaplan-Meier

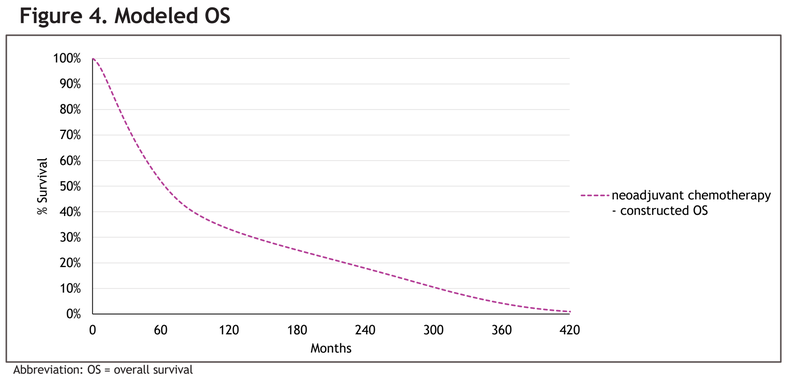
Figure 3. Modeled health state-specific mortality



Abbreviation: KM = Kaplan-Meier

Methods (cont.)

Figure 4. Modeled OS



Abbreviation: OS = overall survival

OS from Danish Lung Cancer Registry

- Established in 2000, the Danish Lung Cancer Registry (DLCR) tracks interventions and outcomes for lung cancer patients in Denmark.
- Since 2003, the registry has utilized diagnostic codes aligned with the International Classification of Diseases, 10th Revision (ICD-10) to identify patients with lung cancer.
- The DLCR provides detailed data on patient demographics, diagnostic procedures, histology, tumor stage, lung function, performance status, comorbidities, treatments, treatment complications, and vital status.
- Survival data is reported as observed overall survival, based on yearly patient cohorts.

OS Comparison

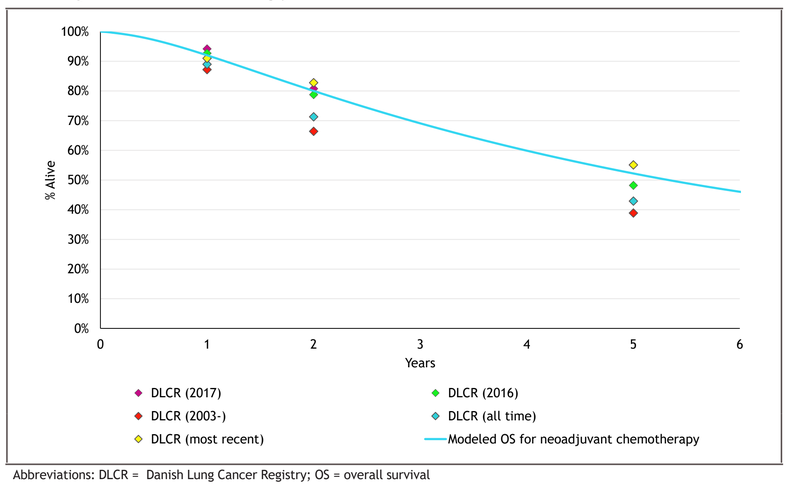
- The modeled OS for neoadjuvant chemotherapy was compared with two sets of outcomes from the 2022 DLCR report.[10] The comparison focused on:
  - **Absolute OS at Key Timepoints:** Compared the absolute difference in OS rates between patients treated with neoadjuvant chemotherapy (from the model) and those treated with adjuvant chemotherapy (from DLCR) at 1, 2, and 5 years.
    - Data from adjuvant chemotherapy was used due to very low numbers of patients treated with neoadjuvant chemotherapy in clinical practice.
    - Literature indicates that neoadjuvant and adjuvant chemotherapies have shown similar efficacy for resectable NSCLC, making neoadjuvant chemotherapy a valid proxy for comparing adjuvant chemotherapy outcomes.[7,8] This approach aligns with Danish treatment guidelines supporting this equivalency.[9]
    - The DLCR survival data for patients receiving adjuvant chemotherapy included 1-year survival (N = 4,643), 2-year survival (N = 4,380) patients, and 5-year survival (N = 3,593).
  - **Long-term Survival Time:** Compared the difference in mean survival times (measured in months) over 18 years between the modeled neoadjuvant chemotherapy OS and the DLCR Kaplan-Meier (KM) curve.
    - DLCR OS KM curves (N = 16,276) were stratified by pathological stage (pTNM), digitized, and weighted to match the baseline stage distribution of CheckMate-816 trial patients. Since the staging in the DLCR was based on the 8th edition of the TNM classification, while CheckMate-816 used the 7th edition, the staging from CheckMate-816 was adjusted to align with that of the DLCR. The resulting stage distribution is as follows: Stage IIA: 10.2%, Stage IIB: 25.5%, Stage IIIA: 47.4%, and Stage IIIB: 16.9%.
    - The mean survival time was estimated by calculating the area under the curve for both the modeled OS and the weighted KM curve from the DLCR.
    - The modeled OS was evaluated with and without incorporating the cure assumption.

Results

OS Difference at Key Timepoints (Figure 5, Table 1):

- 1-Year and 2-Year OS: The difference between modeled OS for neoadjuvant chemotherapy and the DLCR data for adjuvant chemotherapy is relatively small, with an absolute difference of 0.1%-6% for patients diagnosed after 2014. In earlier cohorts (2003-2014), the difference was larger, reaching up to 13.5%.
- 5-Year OS: For cohorts diagnosed after 2015, the difference in 5-year OS between the two groups was between 2%-4%. In cohorts prior to 2015, this difference was more pronounced, reaching up to 13.3%.
- A key observation was the difference in survival outcomes between patients diagnosed after 2014 versus those diagnosed in 2003 to 2014. The smaller gap between modeled OS and registry data in most recent cohorts suggests that improvements in treatment over time are reflected in real-world outcomes, aligning more closely with clinical trial results.

Figure 5. Comparison with historical 1,2- and 5-year OS in patients treated with adjuvant chemotherapy



Abbreviations: DLCR = Danish Lung Cancer Registry; OS = overall survival

Table 1. Comparison with historical 1,2- and 5-year OS in patients treated with adjuvant chemotherapy

1-Year Survival (Model estimate = 92.3%)								
DLCR cohort (by year of diagnosis)	2021	2020	2019	2018	2017	2016	2003-2015	Overall
1-Year OS from DLCR	91.0 %	92.2 %	93.7 %	90.5 %	94.2 %	92.7 %	87.2 %	89.0 %
Difference vs. Modeled OS	-1.3%	-0.1%	1.4%	-1.8%	1.9%	0.4%	-5.1%	-3.3%
2-Year Survival (Model estimate = 79.9%)								
DLCR cohort (by year of diagnosis)	2020	2019	2018	2017	2016	2015	2003-2014	Overall
2-Year OS from DLCR	82.8 %	82.2 %	77.7 %	80.8 %	78.8 %	73.9 %	66.4 %	71.3 %
Difference vs. Modeled OS	2.9%	2.3%	-2.2%	0.9%	-1.1%	-6.0%	-13.5%	-8.6%
5-Year Survival (Model estimate = 52.2%)								
DLCR cohort (by year of diagnosis)	2017	2016	2015	2014	2013	2012	2003-2011	Overall
5-Year OS from DLCR	55.1 %	48.2 %	50.2 %	45.2 %	38.9 %	44.7 %	38.9 %	42.9 %
Difference vs. Modeled OS	2.9%	-4.0%	-2.0%	-7.0%	-13.3%	-7.5%	-13.3%	-9.3%

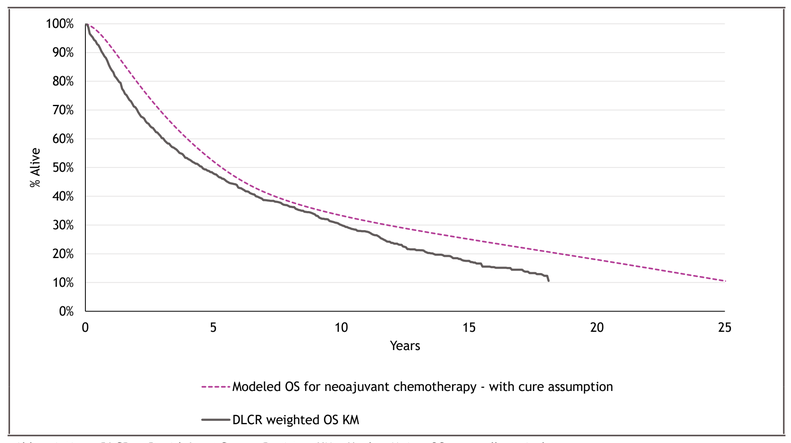
Abbreviations: DLCR = Danish Lung Cancer Registry; OS = overall survival

Results (cont.)

Difference in Long-term Survival Time

- The OS predicted by the Markov model aligns closely with the weighted DLCR KM data over the long term, showing less than a 10% deviation in absolute OS estimates over 18 years (**Figure 6**).
- The derived mean survival times for years 0-5 and 5-10 show strong consistency, with a difference of up to 4.4 months. For the full 0-18-year period, the mean survival time difference reaches 12.5 months (**Table 2**).
- When the cure assumption was excluded from the model, the alignment with the DLCR KM data improved even further. Between years 5 and 18, the absolute OS estimates from the model and the registry data nearly overlap (**Figure 7**).
- The mean survival time difference between the model without the cure assumption and registry data was reduced to just 4.5 months, indicating a high degree of alignment over the long term (**Table 3**).
- This improved alignment without the cure assumption suggests that earlier patient cohorts, tracked over 18 years, likely received less effective treatments and disease management, making cure less achievable in the past. As treatments have advanced, patients are now achieving better outcomes, as reflected in the model's predictions based on clinical trial results.

Figure 6. Comparison of long-term mean survival times (with cure assumption)



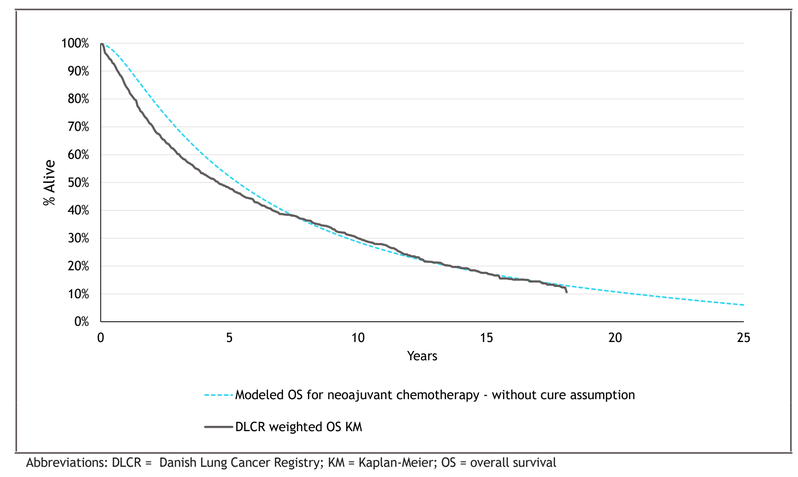
Abbreviations: DLCR = Danish Lung Cancer Registry; KM = Kaplan-Meier; OS = overall survival

Table 2. Comparison of long-term mean survival times (with cure assumption)

Mean Survival Times (in Months) with Cure Assumption	0 - 5 Years	5 - 10 Years	0 - 18 Years
Derived from Modeled OS	45.8	24.4	96.0
Derived from the KM from DLCR	41.5	22.9	83.6
Difference	**4.4**	**1.5**	**12.5**

Abbreviations: DLCR = Danish Lung Cancer Registry; OS = overall survival

Figure 7. Comparison of long-term mean survival times (without cure assumption)



Abbreviations: DLCR = Danish Lung Cancer Registry; KM = Kaplan-Meier; OS = overall survival

Table 3. Comparison of long-term mean survival times (without cure assumption)

Mean Survival Times (in Months) without Cure Assumption	0 - 5 Years	5 - 10 Years	0 - 18 Years
Derived from Modeled OS	45.8	23.2	88.1
Derived from the KM from DLCR	41.5	22.9	83.6
Difference	**4.4**	**0.4**	**4.5**

Abbreviations: DLCR = Danish Lung Cancer Registry; OS = overall survival

Conclusion

- This study highlights the value of publicly available cancer registry data for validating cost-effectiveness models and long-term survival projections.
- The comparison of modeled overall survival from the CheckMate-816 trial with real-world data from the DLCR supports the validity of the OS projections for patients treated with neoadjuvant chemotherapy.
- Advances in treatment over time have led to better survival outcomes in more recent patient cohorts within the registry data, which now align more closely with clinical trial results.
- Harmonizing OS outcome reporting across cancer registries would facilitate more robust cross-country comparisons. It is recommended that Nordic Registries adopt standardized reporting of OS outcomes based on TNM stage at diagnosis and other relevant clinical variables.

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