# Exploring Methodologies for Defining and Modeling Cure in Melanoma: Impacts on Estimating Cure Metrics

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## Background and objectives

- As therapeutic options for melanoma evolve, the concept of "cure" is increasingly emphasized in early-stage disease[1-4]
- However, definitions of "cure" vary widely among stakeholders, reflected in inconsistent terminology and diverse survival modeling approaches[3,5-11]
- This variability presents challenges for health technology assessment (HTA) bodies, which must estimate the lifetime impact of treatments based on limited clinical trial data. In early-stage melanoma, reliance on surrogate endpoints such as relapse-free survival (RFS), which may not always predict overall survival (OS), further complicates the measurement of cure[12]
- This study compares methodologies for defining and modeling cure in melanoma and evaluates their impact on cure rate estimates
- To illustrate how systematic literature reviews (SLR) can be applied in practice to inform HTA submissions, an HTA review for a single melanoma product is presented as a case example

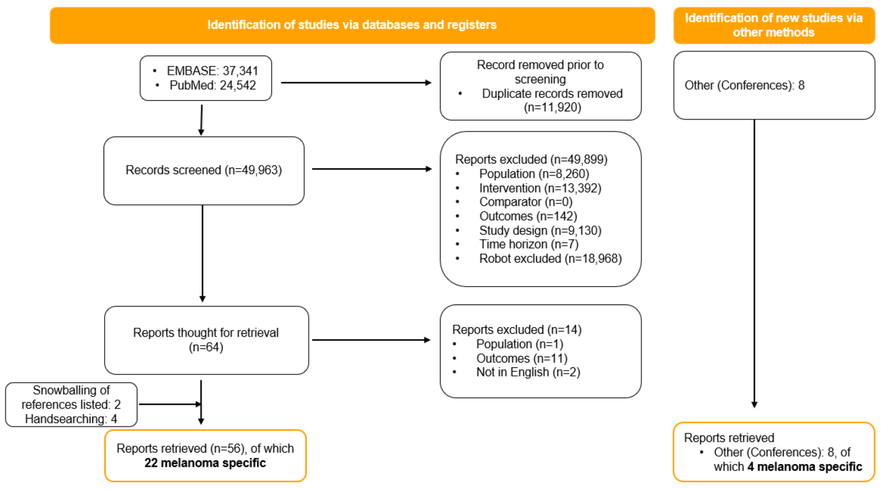
## Methods

- An SLR using PubMed and EMBASE was conducted from January 2014 to July 2024 for global English publications to analyze key factors influencing the definition of "cure", clinical criteria for determining cure, and cure/survival modeling approaches. We first developed a protocol of the search strategy based on PICOTS frameworks and according to systematic searching best practice guidance
- A 10-year timeline was applied to focus on the time period where the concept of "cure" began to emerge across the solid tumor literature, around the time of the first HTA appraisal decision report to reference "cure" in early-stage melanoma in the adjuvant setting, specifically, NICE TA544 (dabrafenib with trametinib for adjuvant treatment of resected BRAF V600 mutation-positive melanoma, 2018)
- Conference proceedings and abstract database/documents from ASCO, ESMO, and ISPOR were also electronically searched. These searches were limited to the previous 4 years (2020-2024), under the assumption that high-quality abstracts published before this time would have been subsequently published as full journal articles
- SLR inclusion criteria were necessarily broad to ensure no articles were missed, given that it was possible that articles mention "cure" in the discussion section rather than in the title or abstract. Clinical trials were not included as part of the title/abstract screening process. A pre-specified extraction template was developed based on the protocol
- The identified publications were screened at two levels: 1. title/abstract, 2. full text. Searches were managed, deduplicated, and screened using a bibliographic management software; Level 1 was conducted using an AI-assisted approach after being trained on 50 articles that had human decisions on their relevance. Following the title and abstract screening, a full-text screening was completed by two independent (human) reviewers according to the pre-defined inclusion criteria and exclusion criteria
- To categorize the definitions of cure, we thematically analyzed the descriptions and grouped them based on lexicon portrayal of subject matter, for example, if the definition was quality of life focused vs statistically focused. A group of two analysts named the lexicon groups, which was ratified by a third reviewer
- As an illustrative case example, HTA from 7 countries (Australia, Canada, France, England, Germany, Ireland, and Scotland) were reviewed to compare and contrast the approaches taken for estimating cure in the (neo)adjuvant setting and incorporating assumptions into cost-effectiveness models across the agencies
  - Scenarios were developed based upon European Medicines Agency (EMA) authorization dates of adjuvant therapy, the frequency of "cure" or similar words mentioned in the reports, the specific sections within the assessment/appraisal where "cure-like" discussions occur
- The results presented focus exclusively on melanoma-specific findings from both published literature and this selected HTA case example, providing insights into how definitions and modeling of "cure" are addressed within this disease context across published literature and international HTA submissions

## Results

- The SLR identified 64 publications, 26 of which included data on melanoma

### Figure 1. PRISMA chart




## SLR findings

Out of 26 publications that included data on melanoma: 13 were melanoma-specific, while the other 13 included cure data for different cancers, including melanoma

**Of the 13 melanoma-specific publications:**

- 5/13 defined "cure" in their wording (**Table 1**) and provided cure metrics specific to melanoma (ie, time to cure (TTC) or cure fraction (CF)) (**Table 2**)
- 5/13 define "cure" but did not report any cure metrics (**Table 1**)
- 3/13 did not define "cure" explicitly with a worded definition, but assessed cure on statistical modeling approaches, one of which also reported cure fraction (**Table 1**)

**For the 13 publications that included melanoma alongside other solid tumors:**

- These were assessed for the presence of cure metrics only, as any definitions provided may have been based on data from non-melanoma cancers. In total, 7/13 reported cure metrics (**Table 2**)

In the 13 melanoma-specific publications included in the review, the different cure concepts and definitions explored were generally based around three key categories, alone or in combination: **Lack of disease progression, Survival/statistical, Eradication**

Among these 13 publications:

- 15% (2/13) addressed "cure" as a **lack of disease progression** (avoiding the terms "cure" or "cured" and instead emphasizing absence of clinical events)
  - Both publications used the term "immune" in this context[14,15]
- 77% (10/13) "defined" "cure" as **survival/statistical cure**, using survival or statistical frameworks at the population level
  - This includes the 3 publications that specifically assessed "cure" based on statistical modeling approaches without reporting an explicit worded definition (**Table 1**)[3,13,16]
- 8% (1/13) discussed "cure" in terms of both **survival/statistical** and **eradication of cancerous cells** through medical or clinical means[11]

**Table 1** shows the definitions provided in the 13 melanoma-specific publications. While these definitions were identified in studies focused exclusively on melanoma, they are broadly applicable and reflect general concepts of cure.

### Table 1. Cure lexicon identified in studies that focused on melanoma alone

| Study | Cure lexicon category | Cure definition |
|---|---|---|
| Andersson, et al. 2014[1] | Survival/ statistical | **Cure proportion:** "Proportion of patients that do not experience excess mortality due to the disease." |
| Silversmit, et al. 2017[4] | | **Cure:** "Cumulative relative survival curves for many cancers reach a plateau several years after diagnosis, indicating that the cancer survivor group has reached "statistical" cure." |
| Harris, et al. 2022[13] | | This abstract did not explicitly provide a specific definition of "cure," but instead evaluates cure in terms of patients remaining recurrence-free, as estimated by mixture cure models. |
| Gomez, et al. 2021[3] | | This publication did not explicitly provide a specific definition of "cure," but instead evaluates cure in terms of overall survival as estimated by a flexible cure rate model. |
| Balakrishnan, et al. 2020[16] | | This publication did not explicitly provide a specific definition of "cure," but instead described the use of a statistical cure model to estimate cure rates and the probability of being cured over time, conditional on survival and nodal category. |
| Webb, et al. 2022[8] | | **TTC:** "Patients who are cured and will never experience the event of interest." |
| Su, et al. 2022[2] | | **CF:** "Proportion of subjects cured of disease." |
| Nicolaie, et al. 2019[9] | | **CF:** "Proportion of the population for which none of the competing events can occur"<br>**Cure:** "Patient not experiencing death due to the disease-related cause; therefore, the status of cure is observed only for individuals subjected to death not due to the cause of interest."<br>The presence of a sub-population that survived event-free was indicated by a plateau in the survival curve. |
| Ishak, et al. 2018[17] | | **Cure proportion:** "Flattening of curve suggests risk of cancer related deaths has become negligible, proportion cured aligned with observed plateau." |
| Zhang, et al. \|2023[18] | | **Cured patients:** "Patients enter the model in the recurrence-free state after having undergone complete resection of stage IIB–IIC melanoma." |
| Balakrishnan, et al. 2017[14] | Lack of disease progression | **Cured patients:** "Individuals completely cured from a certain disease and will not face any recurrence usually called cured or non-susceptibles or long-term survivors or immunes." |
| Calsavara, et al. 2020[15] | | "Individuals not susceptible to the event of interest, even if, accompanied by a sufficiently large time, which is so-called immune." |
| Brandao, et al. 2023[11] | Survival/ statistical Eradication | **CF:** "Proportion of patients responds favorably to a treatment, thus improving overall survival." |

CF, cure fraction; TTC, time to cure.

**Table 2** shows cure metrics specific to melanoma that were included in all publications identified that provided information on melanoma, including both the melanoma-specific articles and the articles that discussed a variety of cancers (including melanoma). The published data on cure metrics that included different cancer types showed that estimated cure fractions for melanoma were generally higher than those for other cancer types. However, based on the articles identified in the SLR, CF estimates for melanoma still varied across the publications, ranging from 28% to 98% (**Table 2**). Unlike Nicolaie et al. and Wang et al., who estimated time to cure using mixture cure survival models, Zhang et al. used a Markov cohort model to simulate transitions between health states and conduct a cost-effectiveness analysis.

### Table 2. Cure metrics specific to melanoma[a]

| | | | | Cure findings | |
|---|---|---|---|---|---|
| Authors | Methodology | Data source | Variable | TTC (years) | Fraction/proportion |
| Silversmit, et al. 2017[4] | Data analyses (cure model) | Belgian Cancer Registry | Not applicable | Not reported | 80.8% |
| Andersson, et al. 2014[1] | | Patient registers | Stage | | Stage IA: 98%, Stage IB: 88%, Stage II: 71%, Stage III-IV: 48% |
| Hubbel, et al. 2024[22] | | SEER database on 17 geographic regions of the US (timeframe of patient inclusion: 2006-2015) | | | Stage I: 95%, Stage II: 83%, Stage III: 67% |
| Dal Maso, et al. 2014[25] | | Italian cancer registries | Sex and age at diagnosis | Not reported | 15-44 yrs: 77% (M), 85% (W)<br>45-54 yrs: 67% (M), 78% (W)<br>55-64 yrs: 61% (M), 73% (W)<br>65-74 yrs: 54% (M), 68% (W) |
| Romain, et al. 2019[19] | | FRANCIM (the French network of cancer registries) | | 15-44 yrs: 5.1 (M), 3.8 (W)<br>45-54 yrs: 5.2 (M), 5.1 (W)<br>55-64 yrs: 4.9 (M), 6.4 (W)<br>65-74 yrs: 5.9 (M), 8.8 (W) | 15-44 yrs: 84% (M), 92% (W)<br>45-54 yrs: 83% (M), 90% (W)<br>55-64 yrs: 85% (M), 87% (W)<br>65-74 yrs: 79% (M), 80% (W) |
| Kou, et al. 2020[21] | | Australian Cancer Database by the Australian Institute of Health and Welfare (AIHW) | Sex | Not reported | 83.2% (M), 90.3% (W) |
| | | | Age | | 15-49 years: 92.1%, 50-69 years: 88%, 70-89 years: 83.6% |
| Hubbel, et al. 2024[22] | | SEER database on 17 geographic regions of the US (timeframe of patient inclusion: 2006-2015) | Age at diagnosis | | 40-54 yrs: 98% (Stage I), 85% (Stage II), 70% (Stage III)<br>55-64 yrs: 96% (Stage I), 83% (Stage II), 66% (Stage III)<br>65-74 yrs: 93% (Stage I), 81% (Stage II), 63% (Stage III)<br>75-84 yrs: 89% (Stage I), 70% (Stage II), 49% (Stage III) |
| Eloranta, et al. 2014[23] | Analytic approaches (cure model) | Swedish Cancer Registry | | | 50: 85%, 60: 83%, 70: 77%, 80: 70% |
| Xia, et al. 2022[23] | Data analyses (cure model) | SEER database | SEER summary stage | | Localized: 99.2%, Regional: 65.9%, Distant: 30% |
| Balakrishnan, et al. 2017[14] | Analytic approaches (cure model) | Dataset from Ibrahim, et al. 2005 | Nodule category | | 1: 65%, 2: 54%, 3: 43%, 4: 32% |
| Balakrishnan, et al. 2020[16] | | Phase III clinical trial conducted by the ECOG, E1690. | Nodal category | | 0: 62%, 1: 50%, 2: 39%, 3: 28% |
| Nicolaie, et al. 2019[9] | | Melanoma cancer data set | Not applicable | 10 years (plateau in survival curves) | Not reported |
| Wang, et al. 2020[24] | | Melanoma cancer dataset from University Hospital of Odense in Denmark | | 8 years (plateau at the tail after nearly 3000 days) | |
| Zhang, et al. 2023[18] | Data analyses (cure model) | 3 Retrospective studies in stage I-III | | 10 years (linearly increase from 0% at 7 years to 95% by 10 years onward) | |

ECOG, Eastern Cooperative Oncology Group; FRANCIM, FRANce Cancers Incidence et Mortalité (French Cancer Incidence and Mortality); SEER, Surveillance, Epidemiology, and End Results; TTC, time to cure.

Notes: [a]Calsavara, et al. 2020 (27), Webb, et al. 2022 (28), Su, et al. 2022 (19), Gomez, et al. 2021 (29), Ishak, et al. 2018 (31), Brandao, et al. 2023 (20) did not report any cure metrics.

Several publications pointed to the fact that population heterogeneity influences the estimates of cure metrics. Highlighted key points summarized below:

- Disease stage: CF decreased with advancing stage[1,3,21,22,25]; identified as the most important determinant of cure.[1] Reduction ranging from 28% to 50% between Stage I and Stage III/IV[1,22]
- Tumor site: Along with disease stage, tumor site significantly influences cure estimates.[9] Having a tumor on the head and neck, the leg or the trunk instead of the arm significantly increased the risk of melanoma recurrence in one study,[8] and another study also confirmed that the cure rate for patients with melanoma in the head and neck region was lower than if the melanoma was in the extremities[1]
- Age: Higher CFs observed in younger patients[1-4,9,19-23], though impact is less than that of disease stage or site[9]
- Gender: Female patients generally had higher CFs than males,[3,4,9,19-21,23,25] but gender impact was less significant than stage or site[9]
- Other factors:
  - Increased tumor thickness associated with lower cure rates and higher recurrence risk[8,14]
  - Patients with prior surgery had better survival, but education level, prior radiotherapy, and prior chemotherapy did not have a substantial impact.[3] A further study found that prior surgery did impact cure rates in later-stage melanoma but there was little impact in early-stage disease[22]

## Case example: HTA findings for dabrafenib plus trametinib

### Table 3. Submissions reviewed for dabrafenib plus trametinib in melanoma across the seven countries in chronological order

| Drug (Indication) | NICE | SMC | G-BA | CDA | HAS | PBAC | NCPE |
|---|---|---|---|---|---|---|---|
| Dabrafenib + trametinib (adjuvant - melanoma) | Oct-18[29] | Feb-19[31] | Mar-19[32] | May-19[27] | Jun-19[28] | Jul-19[26] | Aug-20[30] |
| HTA/reimbursement outcome: | Recommended | | | Recommended with some restrictions | | | |

- In this case example, the HTA review of dabrafenib plus trametinib showed that while the same data cut was used for submissions across all HTA agencies, and majority of models were Markov, different approaches to survival modeling were noted
- There was an earlier submission for PBAC which was dated in March 2019. The outcome was not favorable in the earlier submission, which was not the case for the later submission in July 2019
- Additional data analyses with 10-month additional follow-up were mentioned in the SMC, CDA, HAS, PBAC, and NCPE submissions

### Table 4. Approaches to economic models for dabrafenib plus trametinib

| | |
|---|---|
| **Majority of models were Markov with similar 3-5 health states (depending on how granular post-recurrence was described) using RFS data** | |
| (PBAC)[26] | Manufacturer submitted an initial partitioned survival model, which was then restructured on resubmission |
| **Different approaches to survival modeling were noted, mostly reliant on mixture cure models** | |
| (CDA, HAS, NICE)[27-29] | Log-logistic cure model for comparator arm with HR for treatment effect applied |
| (NCPE)[30] | Unrestricted log-logistic cure model |
| (PBAC)[26] | Both RFS and OS curves were extrapolated using dependent parametric models (assumption of proportional hazards) |
| (SMC)[31] | Log-logistic unrestricted mixture model |
| **RFS extrapolation based on external study for comparator group with treatment effect applied for intervention group** | |

Use of data from the placebo arm of EORTC 18071 to estimate long-term survival[29,31]

- The majority of models had similar health states (ie, 3 to 5), depending on how granular post-recurrence was described using RFS data (**Table 4**)
- The submission for PBAC was the only one that initially included a partitioned survival model, but it was later restructured without providing further details about the new model.[26] Across all submissions, a time horizon greater than 35 years (ie, a lifetime horizon) was reported, except for the PBAC submission, where the time horizon was not specified (**Table 4**)[26-31]
- The structure of the models submitted to HAS, CDA, and NICE was similar, despite the time lag between submissions

HTA opinions varied on the acceptance of cure assumptions, which were primarily driven by the uncertainty on estimating treatment benefit. Variation of treatment effect over time was often preferred.

- PBAC and NCPE expressed skepticism about cure assumptions due to immature OS data (median follow-up: 2.8 years primary analysis with an additional 10-month follow-up), questioning whether the treatment truly cures or delays recurrence, with NCPE considering an alternative extrapolation that allows the treatment effect waning.[26,30] CDA also questions cure assumptions, citing discrepancies between observed and modeled OS curves, and noted that the OS curves were converging, resulting in overestimation of treatment benefit.[27]
- On the other hand, NICE aligned with clinical experts' opinions on cure assumptions despite the uncertainties provided in the model structure.[29] HAS accepted cure assumptions aligned with clinical pathology but did not specify timepoints or proportions.[28]
- There was no clear evidence that learnings from earlier HTA submissions influenced the approach to cure assumptions in subsequent submissions. The acceptance and critique of cure assumptions varied across HTA bodies, with no observable evolution or adaptation of methods or assumptions over time.

### Table 5. Key HTA commentary on approaches to economic models and cure proportion/timepoint assumptions

| HTA market | Key HTA commentary |
|---|---|
| (NICE)[29] | Committee aligned with company clinical experts' opinion on cure assumptions.<br>Accepted clinical experts' first preference for the log-logistic unrestricted mixture cure model and then the flexible parametric fit model to address the uncertainty on the choice of curves for modeling RFS, which can have a substantial effect on cost-effectiveness estimates. |
| (SMC)[31] | No HTA commentary was provided. Cure assumption unclear in the submission. |
| (G-BA)[32] | The prevention of recurrences is a significant therapeutic goal in view of the present curative therapeutic goal. Remaining tumor cells can cause a future recurrence, meaning that the aim of curing disease was unsuccessful. Occurrence of a recurrence is considered to be patient-relevant. |
| (CDA)[27] | Questioned cure assumption, since observed OS curves were converging (but modeled curves diverging), resulting in overestimation of treatment benefit.<br>Uncertainty resulted from modeling OS indirectly from RFS curves. The variation of the treatment effect over time was preferred. |
| (HAS)[28] | Cure assumptions considered consistent with the clinical pathology: majority of recurrence during the 1st year, risk gradually decreases to <5% after 3 years.<br>No correlation has been established between RFS and OS. The variation of the treatment effect over time was preferred. |
| (PBAC)[26] | Given immaturity of the OS data, insufficient data to conclude that dabrafenib + trametinib cures patients, as opposed to delaying recurrence. |
| (NCPE)[30] | Not supportive of concept of cure due to immature OS data; and consider an alternative extrapolation that allows the treatment effect waning.[5] Model approach considered optimistic due to assumption of a lifelong treatment benefit from dabrafenib + trametinib. Revised model by NCPE assumed treatment effect waning. |

- HTA commentary supporting cure assumption
- HTA commentary questioning cure assumptions (moderate importance)
- HTA critiques on the acceptance of cure assumptions (high importance)

## Conclusions

- There is currently not an agreement on the definition of "cure" in melanoma, highlighting the need to account for population heterogeneity when assessing cure potential
- The variability in data types and analytic techniques further complicates this assessment. For HTA submissions, the absence of mature OS data remains a significant challenge, highlighting the value of long-term follow-up and the need to correlate surrogate endpoints with OS to strengthen confidence in model estimations.
- Expert commentary is essential for robust model validation, and future economic modeling strategies should use flexible approaches that capture variations in treatment effects and address uncertainties in estimating treatment benefit
- Comprehensive HTA comparisons across products and solid tumors are needed to better understand the relationship between cost-effectiveness and clinical effectiveness



https://bit.ly/3VXmVhX

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