# Supplementary material: an overview of the evidence review conducted to identify patient characteristics and disease-related factors that may influence treatment decisions

# Methods

Factors that may affect first-line treatment decision-making were identified from three published sources: clinical trials, treatment guidelines, and technology appraisal (TA) reports from the UK National Institute for Health and Care Excellence (NICE). The factors were categorized as either patient characteristics or disease-related factors, although it was recognized that some could be considered to belong to both categories.

Published Phase 3 clinical trials comparing immunotherapies (pembrolizumab, ipilimumab, and nivolumab) or targeted therapies (vemurafenib, dabrafenib, and trametinib) with active comparators for patients with unresectable stage III or IV melanoma not previously treated with ipilimumab were identified from a systematic literature review conducted on 27 July 2015 (search terms are listed in supplementary tables 1 and 2). Long-term data from these trials published after the initial search were identified through additional searches of PubMed (19 October 2015) and Google Scholar (26 October 2015) using the NCT identifier [1-19]. Information on stratification factors, subgroups used in data analyses, and inclusion/exclusion criteria was extracted for each trial. Stratification factors were considered to represent potential prognostic indicators for advanced melanoma. Factors used in subgroup analyses represented potential treatment-effect modifiers. Inclusion/exclusion criteria could include disease-related factors and comorbidities that are important when considering the applicability of the results to patients in clinical practice.

Factors that may influence the choice of first-line therapy were also identified from European treatment guidelines published between January 2012 and October 2015, and from NICE TA reports for immunotherapies and targeted therapies published in the same period. NICE was chosen as a representative health technology assessment agency that applies a consistent, evidence-based approach to assessing new therapies and developing guidance for their use.

[Supplementary table 1]

[Supplementary table 2]

# Results

## Identification of patient characteristics and disease-related factors from clinical trials

### Sources of evidence

A total of 11 trials of immunotherapies and targeted therapies, used either as monotherapy or in combination, were identified within the systematic literature review. Five were studies of immunotherapy agents targeting programmed death ligand 1 (PD-L1) or cytotoxic T lymphocyte-associated protein 4 (CTLA-4) (see supplementary table 3), and six were studies of BRAF- or MEK-targeted agents (see supplementary table 4).

[Supplementary table 3]

[Supplementary table 4]

### Stratification factors

Nine stratification factors were identified from the clinical trials, the most commonly included being stage of disease and lactate dehydrogenase (LDH) level (see supplementary table 5).

[Supplementary table 5]

### Subgroups

Fifteen subgroups were analyzed in the trials (see supplementary table 6). The most common were sex, age, stage of disease, Eastern Cooperative Oncology group (ECOG) performance status, LDH level, PD-L1 status, BRAF status in trials of immunotherapies, and BRAF genotype in trials of targeted agents.

[Supplementary table 6]

### Inclusion/exclusion criteria

The factors identified were the number of measurable lesions according to Response Evaluation Criteria In Solid Tumors (RECIST) [20], location of metastases, comorbidities (e.g., HIV, hepatitis B/C, and lung disease), adequate organ function, history of prior malignancy, life expectancy, and blood test results.

## Identification of patient characteristics and disease-related factors in treatment guidelines and NICE technology assessments

### Sources of data

Seven European treatment guidelines were included [21-27]; the US National Comprehensive Cancer Network (NCCN) guidelines for melanoma were also included in our assessment as it was considered that clinicians from Europe were likely to consult them [28]. Five NICE TAs were reviewed (see supplementary table 7).

### Factors

The treatment guidelines refer to a number of factors in their recommendations for systemic treatment, such as stage of disease, line of therapy, and BRAF mutation status (see supplementary table 6). The guidelines of the NCCN and the German Association of the Scientific Medical Societies (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften, AWMF) were the most detailed in identifying factors that may influence treatment decisions, although often the terms used were poorly defined.

Tumor burden was specifically included in the AWMF guidelines and the NICE TA for ipilimumab for first-line treatment of advanced melanoma. The AWMF guidelines refer to “tumor load” in the algorithm for systemic therapy for stage IV and unresectable stage III disease, but the term was not defined. Similarly, the NICE TA 319 states that vemurafenib is likely to remain the standard of care for first-line treatment, particularly in patients with high disease burden, but does not explain how this is defined or assessed [29].

The presence of brain metastases, a component of tumor burden, was identified as a factor in all but one of the guidelines and in one NICE assessment [30].

Disease tempo, or a similar term describing disease pace or rate of progression, was discussed in two clinical guidelines and two NICE appraisals [23, 28, 30-31]. In the NCCN guidelines disease status, defined as the period of clinical stability (categorized as >12 weeks or ≤12 weeks), influences the recommendations for first-line treatment of metastatic or unresectable wild-type or BRAF-mutated melanoma [28]. The AWMF guidelines refer to the rate of progression (slow/fast) in the algorithm for decision-making [23].

Assessment of LDH levels was not discussed as a factor influencing treatment decisions in any of the guidelines or NICE appraisals reviewed, although it is discussed as a prognostic factor [28]. European Association of Dermato Oncology (EADO) guidelines from 2012 suggest that PD-L1 expression can be used to identify patients with superior response to anti-PD1 agents [22].

[Supplementary table 7]

## Summary of factors identified

A total of eight patient characteristics and 12 disease-related factors were identified across all sources.

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# Tables

Supplementary table 1 Search strategy for Embase and MEDLINE via Ovid

|  |  |  |
| --- | --- | --- |
| Line | Search term | Results |
| #1 | exp skin tumor/ or exp Skin Neoplasms/ | 388,115 |
| #2 | exp melanoma/ | 192,233 |
| #3 | ((skin adj neoplasm$) or (skin adj cancer$) or (skin adj tumour$) or (skin adj tumor$) or (skin adj carcinoma$) or (skin adj adenocarcinoma$) or (skin adj sarcoma$) or melanoma).ti,ab. | 228,184 |
| #4 | 1 or 2 or 3 | 573,787 |
| #5 | (advanced or metasta$ or recurr$ or unresect$ or non-resect$ or disseminated or stage 3 or (stage adj III) or (stage adj IIIC) or (stage adj 3C) or stage 4 or (stage adj IV)).ti,ab. | 2,388,796 |
| #6 | 4 and 5 | 151,087 |
| #7 | (pembrolizumab or lambrolizumab or MK3475 or MK-3475).ti,ab.  | 224 |
| #8 | (ipilimumab or Yervoy or CTLA-4 or CTLA4 or MDX-CTLA4 or MDX-010 or MDX-101).ti,ab. | 14,571 |
| #9 | (vemurafenib or Zelboraf or PLX4032 or PLX-4032 or 1029872-54-5 or RG7204).ti,ab. | 2,845 |
| #10 | (dabrafenib or Tafinlar or GSK2118436 or GSK-2118436 or GSK2118436A or GSK-2118436A or 1195765-45-7).ti,ab. | 856 |
| #11 | (nivolumab or anti-PD-1 or BMS-93655 or ONO-4538).ti,ab | 1,014 |
| #12 | (trametinib or Mekinist or GSK1120212 OR GSK-1120212).ti,ab. | 719 |
| #13 | (temozolomide or Temodar or Temodal or Temcad or ccrg 81045 or ccrg81045 or mb 39831 or mb39831 or nsc 362856 or nsc362856).ti,ab. | 11,711 |
| #14 | (dacarbazine or dacarbazin$ or DTIC or nsc 45388 or nsc45388 or deticene or imidazole carboxamide or 4342-03-4).ti,ab.  | 7,041 |
| #15 | (IL-2 or interleukin-2 or IL2 or interleukine 2 or Ro-23-6019 or Ro 23 6019 or Ro236019 or Ro-236019 or Ro 236019 or RU 49637 or RU-49637 or RU49637 or aldesleukin or Proleukin or Interking or denileukin diftitox or Ontak).ti,ab. | 135,655 |
| #16 | (Fotemustine or Muforan or Muphoran or Mustoforan or Mustophoran or S 10036 or S10036).ti,ab.  | 820 |
| #17 | or/7-16 | 169,940 |
| #18 | exp randomized controlled trial/ | 787,032 |
| #19 | (random\* or placebo\* or single blind\* or double blind\* or triple blind\*).ti,ab,kw.  | 1,993,976 |
| #20 | 18 or 19  | 2,154,542 |
| #21 | (animal$ not human$).sh,hw.  | 7,905,298 |
| #22 | ((comment or editorial or meta-analysis or practice-guideline or review or letter or journal correspondence) not "randomized controlled trial").pt.  | 6,987,719 |
| #23 | (random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not "randomized controlled trial".pt.  | 123,241 |
| #24 | or/21-23 | 14,688,992 |
| #25 | 20 not 24 | 1,631,295 |
| #26 | 6 and 17 and 25 | 1,086 |

Search performed 27 July 2015

Supplementary table 2 Search strategy for Cochrane Register of Controlled Trials

|  |  |  |
| --- | --- | --- |
| Line | Search term | Results |
| #1 | MeSH descriptor: [Skin Neoplasms] explode all trees | 1,226 |
| #2 | melanoma | 2,594 |
| #3 | #1 or #2 | 3,152 |
| #4 | (ipilimumab or Yervoy or CTLA-4 or CTLA4 or MDX-CTLA4 or MDX-010 or MDX-101): ti,ab,kw | 183 |
| #5 | (pembrolizumab or lambrolizumab or MK3475 or MK-3475): ti,ab,kw | 11 |
| #6 | (vemurafenib or Zelboraf or PLX4032 or PLX-4032 or 1029872-54-5 or RG7204): ti,ab,kw | 36 |
| #7 | (dabrafenib or Tafinlar or GSK2118436 or GSK-2118436 or GSK2118436A or GSK-2118436A or 1195765-45-7): ti,ab,kw | 21 |
| #8 | (nivolumab or anti-PD-1 or BMS-93655 or ONO-4538): ti,ab,kw | 22 |
| #9 | (trametinib or Mekinist or GSK1120212 or GSK-1120212): ti,ab,kw | 22 |
| #10 | (temozolomide or Temodar or Temodal or Temcad or ccrg 81045 or ccrg81045 or mb 39831 or mb39831 or nsc 362856 or nsc362856): ti,ab,kw | 348 |
| #11 | (dacarbazine or dacarbazin$ or DTIC or nsc 45388 or nsc45388 or deticene or imidazole carboxamide or 4342-03-4): ti,ab,kw  | 810 |
| #12 | (IL-2 or interleukin-2 or IL2 or interleukine 2 or Ro-23-6019 or Ro 23 6019 or Ro236019 or Ro-236019 or Ro 236019 or RU 49637 or RU-49637 or RU49637 or aldesleukin or Proleukin or Interking or denileukin diftitox or Ontak): ti,ab,kw | 2,668 |
| #13 | (Fotemustine or Muforan or Muphoran or Mustoforan or Mustophoran or S 10036 or S10036):ti,ab,kw  | 29 |
| #14 | #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 | 3,828 |
| #15 | #3 and #14 | 682 |

Search performed July 27, 2015

Supplementary table 3 Clinical trials of immunotherapy agents (anti-PD-1 or anti-CTLA-4)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Trial | Treatment arms | Condition (stage) | Line of treatment | BRAF status |
| Pembrolizumab |
| Keynote 006NCT01866319 | Pembrolizumab 10 mg/kg q2w | Unresectablestage III, IV | First or secondIpilimumab + anti-PD-1-naive | WT and mutated |
| Pembrolizumab 10 mg/kg q3w |
| Ipilimumab 3 mg/kg q3w |
| Nivolumab |
| CheckMate 066NCT01721772 | Nivolumab 3 mg/kg q2w | Unresectablestage III, IV | First  | WT  |
| Dacarbazine 1,000 mg/m2 q3w |
| Nivolumab in combination with ipilimumab |
| CheckMate 067NCT01844505 | Nivolumab 3 mg/kg q2w | Unresectablestage III, IV | First | WT and mutated |
| Nivolumab 1 mg/kg q3w + ipilimumab 3 mg/kg q3w |
| Ipilimumab 3 mg/kg q3w |
| CheckMate 069NCT01927419 | Nivolumab 1 mg/kg q3w + ipilimumab 3 mg/kg q3wb | Unresectablestage III, IV | First | WT and mutated |
| Ipilimumab 3 mg/kg q3w |
| Ipilimumab |
| MDX010-20NCT00094653 | Ipilimumab 3 mg/kg q3w + gp100 q3w | Unresectablestage III, IV | Second  | Any |
|
| Ipilimumab 3 mg/kg q3w |
| gp100 q3w |

b For first four doses, followed by nivolumab 3 mg/kg q2w from cycle 3

q2w, every 2 weeks; q3w, every 3 weeks; WT, wild type

Source: Robert et al., 2015 [1];Robert et al., 2015 [2]; Long et al., 2015 [3]; Larkin et al., 2015 [4]; Postow et al., 2015 [5]; Hodi et al., 2010 [6]; McDermott et al., 2013 [7]

Supplementary table 4 Clinical trials of targeted agents (BRAF or MEK inhibitors)

|  |  |  |  |
| --- | --- | --- | --- |
| Trial | Treatment arms | Condition (stage) | Line of treatment |
| Vemurafenib |
| BRIM-3NCT01006980 | Vemurafenib 960 mg bid | Unresectable stage IIIc, IV | First |
| Dacarbazine 1,000 mg/m2 q3w |
| Dabrafenib |
| BREAK-3NCT01227889 | Dabrafenib 150 mg bid | Unresectablestage III, IV | First (IL-2 allowed) |
| Dacarbazine 1,000 mg/m2 q3w |
|
| Trametinib |
| METRICNCT01245062 | Trametinib 2 mg qd | Unresectable stage IIIc, IV | First or second |
| Dacarbazine 1,000 mg/m2 or paclitaxel 175 mg/m2 |
| Dabrafenib in combination with trametinib |
| NCT01584648 | Dabrafenib 150 mg bid + trametinib 2 mg qd | Unresectable stage IIIc, IV | First |
| Dabrafenib 150 mg bid |
| NCT01072175 | Dabrafenib 150 mg bid | Metastatic melanoma | First (one previous chemo or IL-2 regimen or allowed) |
| Dabrafenib 150 mg bid + trametinib 1 mg qd |
| Dabrafenib 150 mg bid + trametinib 2 mg qd |
| NCT01597908 | Dabrafenib 150 mg bid + trametinib 2 mg qd | Unresectable stage IIIc, IV | First |
|
| Vemurafenib 960 mg bid |

bid, twice daily; IL-2, interleukin 2; qd, daily; q3w, every 3 weeks

Source: Chapman et al., 2011 [8]; McArthur et al., 2014 [9]; Hauschild et al.,2013 [10]; Hauschild et al., 2012 [11]; Hauschild et al., 2013 [12]; Hauschild et al., 2014 [13]; Grob et al., 2014 [14]; Flaherty et al., 2012 [15];Long et al., 2014 [16]; Long et al., 2015 [17];Flaherty et al., 2012 [18]; Robert et al., 2015 [19]

Supplementary table 5 Matrix of stratification factors identified in clinical trials

|  |  |  |  |
| --- | --- | --- | --- |
| Treatment | Trial | Patient characteristics | Disease-related factors |
| Region | Stage | ECOG PS | LDH | Previous treatment | Line | BRAF status | BRAF genotypea | PD-L1 status |
| Immunotherapy | Pembrolizumab | Keynote 006NCT01866319 | 🗶 | 🗶 | ✓ | 🗶 | 🗶 | ✓ | 🗶 | 🗶 | ✓ |
| Nivolumab | CheckMate 066NCT01721772 | 🗶 | ✓ | 🗶 | 🗶 | 🗶 | 🗶 | 🗶 | 🗶 | ✓ |
| Nivolumab + ipilimumab | CheckMate 067NCT01844505 | 🗶 | ✓ | 🗶 | 🗶 | 🗶 | 🗶 | ✓ | 🗶 | ✓ |
| CheckMate 069NCT01927419 | 🗶 | 🗶 | 🗶 | 🗶 | 🗶 | 🗶 | ✓ | 🗶 | 🗶 |
| Ipilimumab | NCT00094653 | 🗶 | ✓ | 🗶 | 🗶 | ✓ | 🗶 | 🗶 | 🗶 | 🗶 |
| BRAF/MEK inhibitors | Vemurafenib | BRIM-3NCT01006980 | ✓ | ✓ | ✓ | ✓ | 🗶 | 🗶 | 🗶 | 🗶 | 🗶 |
| Dabrafenib | BREAK-3NCT01227889 | 🗶 | ✓ | 🗶 | 🗶 | 🗶 | 🗶 | 🗶 | 🗶 | 🗶 |
| Trametinib | METRICNT01245062 | 🗶 | 🗶 | 🗶 | ✓ | ✓ | 🗶 | 🗶 | 🗶 | 🗶 |
| Dabrafenib + trametinib | NCT01584648 | 🗶 | 🗶 | 🗶 | ✓ | 🗶 | 🗶 | 🗶 | ✓ | 🗶 |
| NCT01072175 | 🗶 | 🗶 | 🗶 | 🗶 | 🗶 | 🗶 | 🗶 | 🗶 | 🗶 |
| NCT01597908 | 🗶 | 🗶 | 🗶 | ✓ | 🗶 | 🗶 | 🗶 | ✓ | 🗶 |

a V600 status

Four of the factors were characterized as patient characteristics and five as disease-related; however, some could be considered to belong to either category

Source: Roberts et al., 2015 [1]; Robert et al., 2015 [2]; Long et al., 2015 [3]; Larkin et al., 2015 [4]; Postow et al., 2015 [5]; Hodi et al., 2010 [6]; McDermott et al., 2013 [7]; Chapman et al., 2011 [8]; McArthur et al., 2014 [9]; Hauschild et al.,2013 [10]; Hauschild et al., 2012 [11]; Hauschild et al., 2013 [12]; Hauschild et al., 2014 [13]; Grob et al., 2014 [14]; Flaherty et al., 2012 [15]; Long et al., 2014 [16]; Long et al., 2015 [17]; Flaherty et al., 2012 [18]; Robert et al., 2015 [19]

ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; PD-L1, programmed death ligand 1

Supplementary table 6 Matrix of subgroups in clinical trials of immunotherapy and BRAF/MEK-targeted agents

|  |  |  |  |
| --- | --- | --- | --- |
| Treatment | Trial | Patient characteristics | Disease-related factors |
| Sex | Age | Race | Region | Stage | ECOG PS | LDH | Prior brain mets | Visceral disease | No. of disease sites | Previous treatment | Line | BRAF status | BRAF geno-type | PD-L1 status |
| Immunotherapy | Pembrolizumab | Keynote 006NCT01866319 | ✓ | ✓ | ✓ | ✓ | 🗶 | ✓ | 🗶 | 🗶 | 🗶 | 🗶 | ✓ | ✓ | ✓ | 🗶 | ✓ |
| Nivolumab | CheckMate 066NCT01721772 | ✓ | ✓ | 🗶 | ✓ | ✓ | ✓ | ✓ | ✓ | 🗶 | 🗶 | 🗶 | 🗶 | 🗶 | 🗶 | ✓ |
| Nivolumab + ipilimumab | CheckMate 067NCT01844505 | 🗶 | 🗶 | 🗶 | 🗶 | ✓ | 🗶 | 🗶 | 🗶 | 🗶 | 🗶 | 🗶 | 🗶 | ✓ | 🗶 | ✓ |
| CheckMate 069NCT01844505 | ✓ | ✓ | 🗶 | 🗶 | ✓ | ✓ | ✓ | ✓ | 🗶 | 🗶 | 🗶 | 🗶 | ✓ | 🗶 | ✓ |
| Ipilimumab | NCT00094653 | ✓ | ✓ | 🗶 | 🗶 | ✓ | 🗶 | ✓ | 🗶 | 🗶 | 🗶 | ✓ | 🗶 | 🗶 | 🗶 | 🗶 |
| BRAF/MEK inhibitors | Vemurafenib | BRIM-3NCT01006980 | ✓ | ✓ | 🗶 | ✓ | ✓ | ✓ | ✓ | 🗶 | 🗶 | 🗶 | 🗶 | 🗶 | 🗶 | ✓ | 🗶 |
| Dabrafenib | BREAK-3NCT01227889 | ✓ | ✓ | 🗶 | 🗶 | ✓ | ✓ | ✓ | 🗶 | ✓ | ✓ | 🗶 | 🗶 | 🗶 | 🗶 | 🗶 |
| Trametinib | METRICNT01245062 | ✓ | ✓ | 🗶 | 🗶 | ✓ | ✓ | ✓ | ✓ | 🗶 | 🗶 | ✓ | 🗶 | 🗶 | ✓ | 🗶 |
| Dabrafenib + trametinib | NCT01584648 | ✓ | ✓ | 🗶 | 🗶 | ✓ | ✓ | ✓ | 🗶 | ✓ | ✓ | 🗶 | 🗶 | 🗶 | ✓ | 🗶 |
| NCT01072175 | ✓ | ✓ | 🗶 | 🗶 | ✓ | ✓ | ✓ | 🗶 | 🗶 | 🗶 | 🗶 | 🗶 | 🗶 | ✓ | 🗶 |
| NCT01597908 | ✓ | ✓ | 🗶 | 🗶 | ✓ | ✓ | ✓ | 🗶 | 🗶 | ✓ | 🗶 | 🗶 | 🗶 | ✓ | 🗶 |

Seven of the factors were characterized as patient characteristics and seven as disease-related; however, some could be considered to belong to either category

Source: Roberts et al., 2015 [1]; Robert et al., 2015 [2]; Long et al., 2015 [3]; Larkin et al., 2015 [4]; Postow et al., 2015 [5]; Hodi et al., 2010 [6]; McDermott et al., 2013 [7]; Chapman et al., 2011 [8]; McArthur et al., 2014 [9]; Hauschild et al.,2013 [10]; Hauschild et al., 2012 [11]; Hauschild et al., 2013 [12]; Hauschild et al., 2014 [13]; Grob et al., 2014 [14]; Flaherty et al., 2012 [15]; Long et al., 2014 [16]; Long et al., 2015 [17]; Flaherty et al., 2012 [18]; Robert et al., 2015 [19]

ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; PD-L1, programmed death ligand 1

Supplementary table 7 Matrix of factors affecting treatment decisions in treatment guidelines and NICE TAs

|  |  |  |
| --- | --- | --- |
| Source | Patient characteristics | Disease-related factors |
| Disease stage | PS (ECOG, WHO) | Brain metastases | Disease tempo and prognosis | Tumor burden | Line of therapy | BRAF mutation  | Other mutations (N-ras, c-Kit) | PD-L1 expression |
| Guidelines | ESMO, 2015 | ✓ | 🗶 | ✓ | 🗶 | 🗶 | ✓ | ✓ | ✓ | ✓ |
| EADO, 2012 | ✓ | 🗶 | ✓ | 🗶 | 🗶 | ✓ | ✓ | ✓ | ✓ |
| AWMF, 2013 | ✓ | 🗶 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 🗶 |
| AIOM, 2013 | ✓ | 🗶 | 🗶 | 🗶 | 🗶 | ✓ | ✓ | ✓ | 🗶 |
| IKNL, 2012 | ✓ | 🗶 | ✓ | 🗶 | 🗶 | ✓ | ✓ | 🗶 | 🗶 |
| SEOM, 2015 | ✓ | 🗶 | ✓ | 🗶 | 🗶 | ✓ | ✓ | 🗶 | 🗶 |
| Sweden, 2014 | ✓ | ✓ | ✓ | 🗶 | 🗶 | ✓ | ✓ | 🗶 | 🗶 |
| NCCN, 2015/2016 | ✓ | ✓ | ✓ | ✓ | 🗶 | ✓ | ✓ | ✓ | 🗶 |
| NICE TA | Ipilimumab, 2nd line (TA268) | ✓ | 🗶 | 🗶 | 🗶 | 🗶 | ✓ | 🗶 | 🗶 | 🗶 |
| Vemurafenib (TA269) | ✓ | 🗶 | 🗶 | 🗶 | 🗶 | ✓ | ✓ | 🗶 | 🗶 |
| Dabrafenib (TA321)  | ✓ | ✓ | ✓ | ✓ | 🗶 | ✓ | ✓ | 🗶 | 🗶 |
| Ipilimumab, 1st line (TA319) | ✓ | 🗶 | 🗶 | 🗶 | ✓ | ✓ | ✓ | 🗶 | 🗶 |
| Pembrolizumab, 2nd line (TA357) | ✓ | 🗶 | 🗶 | ✓ | 🗶 | ✓ | ✓ | 🗶 | 🗶 |

ESMO, European Society for Medical Oncology [21]; EADO, European Association of Dermato Oncology [22]; AWMF, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (Association of the Scientific Medical Societies in Germany) [23]; AIOM, Associazione Italiana di Oncologia Medica (Italian Association for Medical Oncology) [24]; IKNL, Integraal Kankercentrum Nederland (Netherlands Comprehensive Cancer Organisation) [25]; SEOM, Sociedad Española de Oncología Médica (Spanish Society for Medical Oncology) [26]; Swedish Association of Regional Cancer Registries (Regionala Cancercentrum i Samverkan) [27]; NCCN, National Comprehensive Cancer Network [28]; NICE TA documents: https://www.nice.org.uk/, accessed 19 October 2015

ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; PD-L1, programmed death ligand 1; WHO, World Health Organization