# Health Technology Briefing
# January 2022

# Bempegaldesleukin in combination with nivolumab for previously untreated unresectable or metastatic melanoma

| Company/Developer | Bristol Myers Squibb |
|---|---|

☒ New Active Substance ☐ Significant Licence Extension (SLE)

| NIHRIO ID: 31199 | NICE ID: 10654 | UKPS ID: 656994 |
|---|---|---|

## Licensing and Market Availability Plans

Currently in phase III clinical development.

## Summary

Bempegaldesleukin in combination with nivolumab is in clinical development as a treatment option for previously untreated unresectable or metastatic melanoma. Melanoma is a type of skin cancer that can occur anywhere on the body and spread to other vital organs. Unresectable melanoma refers to cancers that cannot removed with surgery while metastatic melanoma is one that has spread from the primary site to other parts of the body. Due to poor tumour response, not all patients respond to the standard of care treatment (immune checkpoint inhibitors such as nivolumab) in previously untreated, unresectable or metastatic melanoma. Therefore, there is an unmet need for novel therapies that can achieve durable responses without adding substantial toxicity.

Bempegaldesleukin is an IL-2 by receptor agonist that stimulates an antitumour immune response by increasing the infiltration of certain types of white blood cells that target specific antigens. It is administered via intravenous infusion in combination with nivolumab, which is an immune checkpoint inhibitor that has demonstrated prolonged benefit for patients with melanoma. If licensed, bempegaldesleukin in combination with nivolumab will offer a novel combination that modulates tumour expression and may address the limitations of the current first-line treatment.

## Proposed Indication

Treatment of Previously Untreated Inoperable or Metastatic Melanoma.

## Technology

### Description

Bempegaldesleukin (NEKTAR, BEMPEG, NKTR-214) is an IL-2 pathway agonist that provides sustained signalling through the IL-2**βγ** receptor and leverages the clinically validated IL-2 pathway to stimulate an antitumor immune response.[1,2] Bempegaldesleukin increases the proliferation and infiltration of CD8+ T-cells and natural killer cells into the tumour microenvironment, without expansion of regulatory T-cells. It also increases programmed death-1 (PD-1) expression on lymphocytes in the tumour microenvironment (a marker of CD8+ tumour-reactive T-cells) and PD-ligand 1 (PD-L1) expression on tumour cells. This is beneficial because a low amount of tumour infiltrating lymphocytes, low expression of PD-1 and the presence of partially exhausted $CD8^+$ T-cells in pretreatment biopsies are associated with poor response to PD-1 pathway blockades for cancer therapy.[2,3]

Bempegaldesleukin in combination with nivolumab is in development as treatment for untreated, unresectable or metastatic melanoma. In a phase III clinical trial (NCT03635983, PIVOT IO 001), bempegaldesleukin 0.006 mg/kg and nivolumab 360mg are administered sequentially via intravenous (IV) infusion every 3 weeks until disease progression or other discontinuation criteria is achieved.[1,4]

### Key Innovation

Immune checkpoint inhibitors (ICIs) such as nivolumab are a standard of care in the first line setting for metastatic melanoma, either as a single agent or in a combination with other therapies. However, not all patients respond to ICIs due to poor tumour response associated with factors such as low density of tumour-infiltrating lymphocytes, low PD-L1 expression, low tumour mutational burden and low interferon-gamma gene expression. Therefore, there is an unmet need for novel ICI combinations that can achieve durable and deep responses in a break population of patients with metastatic melanoma, without adding substantial toxicity. Combining an ICI (such as nivolumab) with an agent like bempegaldesleukin that modulates the tumour microenvironment may address some of the known limitations of the treatment.[2]

Bempegaldesleukin is a first-in-class, CD122-preferential IL-2 pathway agonist.[1,3] Safety and clinical activity of the combination of bempegaldesleukin plus nivolumab have been evaluated in PIVOT-02 (ClinicalTrials.gov: NCT02983045), a global, multicenter, Phase I/II study in multiple solid tumors [32]. Preliminary clinical data in patients with treatment-naive, metastatic melanoma (n = 38 efficacy-evaluable) in the Phase II dose expansion component of the PIVOT-02 trial (NCT02983045) showed that bempegaldesleukin plus nivolumab produced responses that were durable and deepened over time. The combination was well-tolerated and had a good safety profile.[1]

### Regulatory & Development Status

Bempegaldesleukin in combination with nivolumab does not currently have marketing authorization in the UK/EU for any indication.

In August 2019, the FDA granted breakthrough therapy designation to bempegaldesleukin in combination with nivolumab for the treatment of advanced melanoma.[5]

Bempegaldesleukin in combination with nivolumab is also currently in phase III/II studies for multiple indications including:[6]

- Urinary bladder neoplasm
- Renal cell carcinoma
- Merkel cell carcinoma
- Breast cancer
- Non-small cell lung cancer
- Bladder cancer

## Patient Group

### Disease Area and Clinical Need

Melanoma is a type of skin cancer that can spread to other organs in the body. The most common sign of melanoma is the appearance of a new mole or a change in an existing mole. This can happen anywhere on the body, but the back, legs, arms and face are most commonly affected.[7] Melanoma starts in skin cells that are known as melanocytes. These cells are in the deep layer of the epidermis between the layer of basal cells. Melanocytes produce a pigment called melanin that gives skin its natural colour. The pigment helps to protect the body from ultraviolet light (UV radiation) from the sun. UV radiation can cause sunburn, which is a sign of damage to the genetic material (DNA) in skin cells. Over time, enough DNA damage can cause cells to develop abnormally and lead to cancer.[8] Certain things can increase chances of developing melanoma, such as having: lots of moles or freckles, pale skin that burns easily, red or blonde hair or a family member who has had melanoma.[7]Metastatic cancer is a cancer that has spread from the part of the body where it started (the primary site) to other parts of the body.[9] Similarly, unresectable cancer refers to inoperable cancers that cannot removed with surgery.[10]

Melanoma (ICD-10 code: C43) is the 5th most common cancer in the UK with around 16,700 new cases of melanoma diagnosed each year (2016-2018).[11] Superficial spreading melanoma are the most common type of melanoma in the UK.[7,12] More than a quarter of cases are diagnosed in people under 50, which is unusual compared to most other types of cancer. It's also becoming more common in the UK over time, thought to be caused by increased exposure to UV light from the sun and sunbeds. More than 2,000 people die every year in the UK from melanoma.[7]

### Recommended Treatment Options

NICE currently recommends the following systemic therapies for previously untreated advanced melanoma:[13]

- Nivolumab is recommended as an option for the adjuvant treatment
- Nivolumab in combination with ipilimumab is recommended
- Nivolumab as monotherapy
- Pembrolizumab
- Ipilimumab

## Clinical Trial Information

| | |
|---|---|
| Trial | **NKTR-214**, NCT03635983, 2018-001423-40, A Phase 3, Randomized, Open-label Study of NKTR-214 Combined With Nivolumab Versus Nivolumab in Participants With Previously Untreated Unresectable or Metastatic Melanoma<br>**Phase III:** recruiting<br>**Location(s):** 15 EU, UK, US, Canada and other countries<br>**Primary completion date:** April 2022 |
| Trial Design | Randomized, parallel assignment, open label |
| Population | N=764, 12 years and older, histologically confirmed stage III (unresectable) or stage IV melanoma, treatment-naive participants (ie, no prior systemic anticancer therapy for unresectable or metastatic melanoma) except for prior adjuvant and/or neoadjuvant treatment for melanoma with approved ages |
| Intervention(s) | Patients receive bempegaldesleukin 0.006 mg/kg plus nivolumab 360mg IV every 3 weeks (administered sequentially).[1] |
| Comparator(s) | Nivolumab 360mg IV administered every 3 weeks |
| Outcome(s) | Primary outcomes:<br>• Overall response rate (ORR) by Blinded Independent Central Review (BICR) [Time frame: Approximately 16 months]<br>• Progression-free survival (PFS) by BICR [Time frame: Approximately 22 months]<br>• Overall survival (OS) [Time frame: Up to 59 months]<br><br>See trial record for full list of other outcomes |
| Results (efficacy) | - |
| Results (safety) | - |

## Estimated Cost

The estimated cost of bempegaldesleukin is not yet known.

## Relevant Guidance

### NICE Guidance

- NICE Technology Appraisal. Nivolumab for adjuvant treatment of completely resected melanoma with lymph node involvement or metastatic disease (TA684). March 2021.
- NICE technology appraisal guidance. Encorafenib with binimetinib for unresectable or metastatic BRAF V600 mutation-positive melanoma (TA562). February 2019.
- NICE technology appraisal guidance. Cobimetinib in combination with vemurafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma (TA414). October 2016.
- NICE Technology Appraisal. Nivolumab in combination with ipilimumab for treating advanced melanoma (TA400). July 2016.

- NICE technology appraisal guidance. Trametinib in combination with dabrafenib for treating unresectable or metastatic melanoma (TA396). June 2016.
- NICE Technology Appraisal. Nivolumab for treating advanced (unresectable or metastatic) melanoma (TA384). February 2016.
- NICE Technology Appraisal. Pembrolizumab for advanced melanoma not previously treated with ipilimumab (TA366). November 2015.
- NICE technology appraisal guidance. Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma (TA269). December 2012. Updated January 2015.
- NICE technology appraisal guidance. Dabrafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma (TA321). October 2014.
- NICE Technology Appraisal. Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma (TA319). July 2014.
- NICE Technology Appraisal. Talimogene laherparepvec for treating unresectable metastatic melanoma (TA410). September 2016.
- NICE clinical guideline. Melanoma: assessment and management (NG14). July 2015.
- NICE quality standard. Skin cancer (QS130). September 2016.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Cancer: Skin (Adult). A12/s/b.

Other Guidance

- National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Melanoma: Cutaneous, Version 2. 2022.[14]
- European Society for Medical Oncology (ESMO). Cutaneous Melanoma: ESMO Clinical Practice Guidelines. 2019.[15]

## Additional Information

## References

1 Khushalani NI, Diab A, Ascierto PA, Larkin J, Sandhu S, Sznol M, et al. Bempegaldesleukin plus nivolumab in untreated, unresectable or metastatic melanoma: Phase III PIVOT IO 001 study design. *Future Oncol*. 2020;16(28):2165-75. Available from: https://doi.org/10.2217/fon-2020-0351.

2 Diab A, Tykodi SS, Daniels GA, Maio M, Curti BD, Lewis KD, et al. Bempegaldesleukin Plus Nivolumab in First-Line Metastatic Melanoma. *Journal of Clinical Oncology*. 2021;39(26):2914-25. Available from: https://doi.org/10.1200/JCO.21.00675.

3 Electronic Medicines Compendium (eMC). *OPDIVO 10 mg/mL concentrate for solution for infusion*. Available from: https://www.medicines.org.uk/emc/product/6888

4 Clinicaltrials.gov. *Bempegaldesleukin Plus Nivolumab in First-Line Metastatic Melanoma Trial ID: NCT03635983*. 2021. Available from: https://clinicaltrials.gov/ct2/show/study/NCT03635983 [Accessed 14th December 2021].

5 Bristol Myers Squibb. *Nektar Therapeutics and Bristol-Myers Squibb Announce U.S. FDA Breakthrough Therapy Designation for Bempegaldesleukin (NKTR-214) in Combination with*

*Opdivo® (nivolumab) for the Treatment of Patients with Untreated Advanced Melanoma*. 2019. Available from: https://news.bms.com/news/partnering/2019/Nektar-Therapeutics-and-Bristol-Myers-Squibb-Announce-US-FDA-Breakthrough-Therapy-Designation-for-Bempegaldesleukin-NKTR-214-in-Combination-with-Opdivo-nivolumab-for-the-Treatment-of-Patients-with-Untreated-Advanced-Melanoma/default.aspx [Accessed 14th December 2021].

6 Clinicaltrials.gov. *Search of: Recruiting, Not yet recruiting, Active, not recruiting, Enrolling by invitation Studies | bempegaldesleukin | Phase 2,3 - List Results*. 2021. Available from: https://clinicaltrials.gov/ct2/results?intr=bempegaldesleukin&recrs=b&recrs=a&recrs=f&recrs=d&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply (login required) [Accessed 14th December 2021].

7 NHS Inform. *Skin Cancer (Melanoma)*. 2021. Available from: https://www.nhsinform.scot/illnesses-and-conditions/cancer/cancer-types-in-adults/skin-cancer-melanoma/ [Accessed 14th December 2021].

8 Cancer Research UK. *What is Melanoma?* 2020. Available from: https://www.cancerresearchuk.org/about-cancer/melanoma/about [Accessed 14th December 2021].

9 American Cancer Society. *Understanding Advanced and Metastatic Cancer*. 2020. Available from: https://www.cancer.org/treatment/understanding-your-diagnosis/advanced-cancer/what-is.html [Accessed 14th December 2021].

10 National Cancer Institute. *NCI Dictionary - Unresectable*. Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/unresectable [Accessed 14th December 2021].

11 Cancer Research UK. *Melanoma skin cancer statistics*. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/melanoma-skin-cancer#heading-Zero.

12 NHS UK. *Skin Cancer (Melanoma)*. 2020. Available from: https://www.nhs.uk/conditions/melanoma-skin-cancer/ [Accessed 14th December 2021].

13 National Institute of Health and Care Excellence (NICE). *Therapies for unresectable or metastatic stage III melanoma*. Available from: https://pathways.nice.org.uk/pathways/melanoma#path=view%3A/pathways/melanoma/therapies-for-unresectable-or-metastatic-stage-iii-melanoma.xml&content=view-index (login required) [Accessed 14th December 2021].

14 *NCCN Guidelines* National Comprehensive Cancer Network,. Available from: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1492 (login required).

15 European Society for Medical Oncology (ESMO). *Clinical Practice Guidelines - Cutaneous Melanoma* Available from: https://www.esmo.org/guidelines/melanoma/cutaneous-melanoma (login required)

***NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.***