Health Technology Briefing
March 2023

BI 907828 for previously untreated advanced dedifferentiated liposarcoma

Company/Developer	Boehringer Ingelheim Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 34404	NICE TSID: 11860	UKPS ID: 668161

Licensing and Market Availability Plans

BI 907828 is currently in phase II/III clinical development.

Summary

BI 907828 is in clinical development for the first-line treatment of adults with advanced/metastatic dedifferentiated liposarcoma. Liposarcoma is a rare type of cancer that develops in the fatty tissues found all over the body. It can occur anywhere throughout the body but most commonly on the trunk, limbs and behind the abdomen. Dedifferentiated liposarcoma is an aggressive and high-grade form of liposarcoma. Advanced/metastatic cancer is cancer that has spread to the lymph nodes or other parts of the body and is not resectable (when the tumour cannot be removed by surgery). Liposarcoma occurs mainly in adults and is very rare in people under the age of 30. The current standard of care in the first-line treatment of patients with advanced dedifferentiated liposarcoma is associated with little efficacy and poor safety. There is need for more therapeutic options that will improve the lives of patients with advanced dedifferentiated liposarcoma.

BI 907828 is an orally available inhibitor of the interactions between two proteins called murine double minute 2 (MDM2) and p53. BI 907828 binds to MDM2 protein and prevents its binding to the tumour suppressor protein p53. By doing so, BI 907828 induces tumour cell death and causes the tumours to shrink while also promoting anti-tumour immune responses. If licenced, BI 907828 would offer a new molecular targeted first-line treatment option for adults with advanced and/or metastatic dedifferentiated liposarcoma.

Proposed Indication

First-line treatment of advanced/metastatic dedifferentiated liposarcoma.[1]

Technology

Description

BI 907828 is an oral, small-molecule inhibitor of the interaction between murine double minute 2 (MDM2) and p53 proteins. This effect can lead to direct action on tumour cells themselves by promoting p53-mediated cell-cycle arrest and apoptosis and activate the body's own immune response against the cancer. MDM2 is a negative regulator of the tumour suppressor p53. In non-malignant cells unexposed to stress signals, the auto-regulatory feedback loop between MDM2 and p53 is central to keeping p53 concentrations low and to limiting aberrant p53 activity. p53 can be activated in response to a wide variety of stress signals and can mediate downstream cellular responses, including cell-cycle arrest, DNA repair, senescence, and apoptosis. In human cancers, the *TP53* gene encoding p53 is frequently mutated or deleted or the function of wild-type p53 protein is inhibited by high MDM2 levels, leading to downregulation of the p53 pathway.[2]

BI 907828 is currently in clinical development for a variety of solid tumour indications, including the first-line treatment of advanced dedifferentiated liposarcoma. In the phase II/III clinical trial (Brightline-1, NCT05218499), patients are administered BI 907828 at 30mg or 45mg orally every 3 weeks.[1,3]

Key Innovation

The current standard of care in the first-line treatment of patients with unresectable/metastatic dedifferentiated liposarcoma is associated with poor efficacy and safety outcomes.[3] Patients impacted by dedifferentiated liposarcoma have had no new first-line treatment options in over 45 years.[4] Compared to currently available MDM2-p53 inhibitors, the pharmacokinetic properties of BI 907828 allow for more optimal dosing and dose schedules that may reduce myelosuppression, an on-target, dose-limiting toxicity for this class of inhibitors.[5] In phase 1 clinical trial (NCT03449381), BI 907828 demonstrated antitumour activity and a manageable safety profile in patients with advanced solid tumours, including dedifferentiated liposarcoma.[6]

If licensed, BI 907828 would offer a new, molecular targeted first-line treatment option for patients with advanced dedifferentiated liposarcoma who currently have limited treatment options.

Regulatory & Development Status

BI 907828 does not currently have Marketing Authorisation in the EU/UK for any indication.

BI 907828 is currently in phase II clinical development for the following indications:[7]
Pancreatic neoplasms

- Biliary Tract cancer
- Solid tumours

BI 907828 was awarded the Innovation Passport by the MHRA for the treatment for de-differentiated liposarcoma in Dec 2022.[8]

Patient Group

Disease Area and Clinical Need

Sarcomas are cancers that can affect any part of the body, on the inside or outside, including the muscle, bone, tendons, blood vessels and fatty tissues.[9] Liposarcoma, which is a subtype of soft tissue sarcoma, develops from the fat cells found all over the body and can occur anywhere throughout the body but most commonly on the trunk, limbs and in the retroperitoneum. There are four main types of liposarcoma: well-differentiated liposarcoma, dedifferentiated liposarcoma, myxoid/round-cell liposarcoma, and pleomorphic liposarcoma.[10] Dedifferentiated liposarcoma is a fast-growing tumour that progresses from well-differentiated liposarcoma or can occur de novo.[11] Advanced/metastatic liposarcoma means the cancer is unresectable and/or has spread to the lymph nodes or other parts of the body.[12] Symptoms of dedifferentiated liposarcoma include a persistent growing lump, swelling or numbness in the area around the lump, weakness of the affected limb, stomach pain or cramping and gradually increasing abdomen. It most commonly occurs in adults over the age of 50 years.[11] There are a number of factors known to increase the risk of developing dedifferentiated liposarcoma including: age, certain genetic conditions, previous radiotherapy and exposure to certain chemicals.[13]

Soft tissue cancers are a rare type of cancer, accounting for approximately 1% of cancers diagnosed in the UK.[14] Liposarcomas account for approximately 10% of all soft tissue sarcomas diagnosed in England.[15] In England, 2021-22, there were 9,464 finished consultancy episodes (FCE) and 8,778 admissions for malignant neoplasms of other connective and soft tissues (ICD-10 code C49.0), which resulted in 20,926 FCE bed days and 5,490 day cases.[16]

Recommended Treatment Options

There are currently no National Institute for Health and Care Excellence (NICE) recommended treatment options specific for dedifferentiated liposarcoma.

Surgery with additional radiotherapy and chemotherapy are often used to treat de-differentiated liposarcoma.[11]

Clinical Trial Information

Trial	**Brightline-1**, NCT05218499, EudraCT2021-002392-20; A Phase II/III, Randomized, Open-label, Multi-centre Study of BI 907828 Compared to Doxorubicin as First Line Treatment of Patients With Advanced Dedifferentiated Liposarcoma. **Phase II/III:** Recruiting **Locations:** 13 EU countries, UK, USA, Canada and other countries. **Primary completion date:** March 2024
Trial Design	Randomised, parallel assignment, open-label
Population	N=390 (estimated); 18 years and older; all sexes; subjects with histologically proven locally advanced or metastatic, unresectable, progressive or recurrent dedifferentiated liposarcoma.
Intervention(s)	BI 907828 (oral) 30mg or 45mg every 3 weeks.[3]
Comparator(s)	Doxorubicin (IV) 75 mg/m^2 every 3 weeks to a maximum cumulative dose of 450 mg/m^2.[3]
Outcome(s)	Primary outcome measure:

	Progression-free survival [Time frame: Up to 30 months] See trial record for full lists of outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of BI 907828 is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Selinexor for treating unresectable de-differentiated advanced liposarcoma. (GID-TA10694). Expected date of issue to be confirmed.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2019 Service specifications: Sarcoma (all ages).
- NHS England. 2013/14 Standard Contract for Cancer: Soft Tissue Sarcoma (Adult). B12/S/a.
- NHS England. 2013/14 Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.

Other Guidance

- European Society for Medical Oncology (ESMO). Soft Tissue and Visceral Sarcomas: ESMO-EURACAN Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up. 2018. [17]
- Clinical Sarcoma Research. UK guidelines for the management of soft tissue sarcomas. 2016.[18]

Additional Information

References

1 Clinicaltrials.gov. *Brightline-1: A Study to Compare BI 907828 With Doxorubicin in People With a Type of Cancer Called Dedifferentiated Liposarcoma*. *Trial ID: NCT05218499*. 2022. Status: Recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT05218499 [Accessed 16 January 2023].

2 Boehringer Ingelheim. *MDM2-p53 Antagonist (BI 907828)*. 2022. Available from: https://pro.boehringer-ingelheim.com/inoncology/our-pipeline/mdm2-p53-antagonist [Accessed 07 March 2023].

3 Schöffski P, Schuetze S, Broto JM, Wagner AJ, Bauer S, Chen V, et al. A phase II/III, randomized, open-label, multicenter study of BI 907828 compared to doxorubicin in the

first-line treatment of patients with advanced dedifferentiated liposarcoma (DDLPS): Brightline-1. *Journal of Clinical Oncology*. 2022;40:TPS11586-TPS. Available from: https://doi.org/10.1200/JCO.2022.40.16_suppl.TPS11586.

4 Boehringer Ingelheim. *Patients with a rare and aggressive form of liposarcoma need treatment advances*. 2021. Available from: https://www.boehringer-ingelheim.com/human-health/cancer/brightline-1-trial-launch-rare-sarcoma [Accessed 16 January 2023].

5 My Cancer Genome. *bi 907828*. 2018. Available from: https://www.mycancergenome.org/content/drugs/bi-907828/#:~:text=Upon%20oral%20administration%2C%20BI%20907828%20binds%20to%20MDM2,leads%20to%20p53-mediated%20induction%20of%20tumor%20cell%20apoptosis. [Accessed 16 January 2023].

6 Schoeffski P, Yamamoto N, Bauer T, Patel M, Gounder MM, Geng J, et al. 452O - A phase I dose-escalation and expansion study evaluating the safety and efficacy of the MDM2–p53 antagonist BI 907828 in patients (pts) with solid tumours. *Annals of Oncology*. 2022;33:S197-S224. https://oncologypro.esmo.org/meeting-resources/esmo-congress/a-phase-i-dose-escalation-and-expansion-study-evaluating-the-safety-and-efficacy-of-the-mdm2-p53-antagonist-bi-907828-in-patients-pts-with-solid.

7 clinicaltrials.gov. 2023. Available from: https://clinicaltrials.gov/ct2/results?term=BI+907828&recrs=b&recrs=a&recrs=f&recrs=d&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply [Accessed 23 March 2023].

8 Pharmiweb.com. *MHRA Innovation Passport awarded to Boehringer Ingelheim's investigational treatment in aggressive and rare cancer*. 2022. Available from: https://www.pharmiweb.com/press-release/2022-12-06/mhra-innovation-passport-awarded-to-boehringer-ingelheim-s-investigational-treatment-in-aggressive-and-rare-cancer [Accessed 23 March 2023].

9 Sarcoma.org. *About Sarcoma*. 2021. Available from: https://sarcoma.org.uk/about-sarcoma/ [Accessed 17 January 2023].

10 Sarcoma.org. *Liposarcoma*. 2021. Available from: https://sarcoma.org.uk/about-sarcoma/what-is-sarcoma/types-of-sarcoma/liposarcoma/ [Accessed 17 January 2023].

11 Sarcoma.org. *Dedifferentiated liposarcoma*. 2021. Available from: https://sarcoma.org.uk/about-sarcoma/what-is-sarcoma/types-of-sarcoma/liposarcoma/dedifferentiated-liposarcoma/#:~:text=Treatment%20Surgery%20is%20the%20main%20treatment%20used%20for,too%3B%20this%20is%20known%20as%20taking%20a%20margin. [Accessed 26 January 2023].

12 Cancer Research UK. *Stages and grades of soft tissue sarcoma*. 2021. Available from: https://www.cancerresearchuk.org/about-cancer/soft-tissue-sarcoma/stages-grades [Accessed 26 January 2023].

13 National Health Service. *Soft tissue sarcomas*. 2019. Available from: https://www.nhs.uk/conditions/soft-tissue-sarcoma/ [Accessed 17 January 2023].

14 National Health Service Inform. *Soft tissue sarcomas*. 2022. Available from: https://www.nhsinform.scot/illnesses-and-conditions/cancer/cancer-types-in-adults/soft-tissue-sarcomas [Accessed 17 January 2023].

15 National Cancer Registration and Analysis Service. *Liposarcoma: incidence and survival rates in England*. 2017. Available from: http://www.ncin.org.uk/publications/data_briefings/liposarcoma_incidence_and_survival_rates_in_england [Accessed 17 January 2023].

16 National Health Service Digital. *Hospital Admitted Patient Care Activity, 2021-22*. 2022. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2021-22 [Accessed 07 January 2023].

17 Casali PG, Abecassis N, Bauer S, Biagini R, Bielack S, Bonvalot S, et al. Soft tissue and visceral sarcomas: ESMO–EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up[†]. *Annals of Oncology*. 2018;29:iv51-iv67. Available from: https://doi.org/10.1093/annonc/mdy096.

18 Dangoor A, Seddon B, Gerrand C, Grimer R, Whelan J, Judson I. UK guidelines for the management of soft tissue sarcomas. *Clinical Sarcoma Research*. 2016;6(1):20. Available from: https://doi.org/10.1186/s13569-016-0060-4.

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