NICE advice

AMBLor for identifying low-risk non-ulcerated early-stage cutaneous melanomas

Medtech innovation briefing
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Summary

- The **technology** described in this briefing is AMBLor. It is used for identifying low-risk non-ulcerated early-stage cutaneous melanomas in children and adults.
- The **innovative aspects** are the immunohistochemical method and detection antibodies in AMBLor. The company claims there is no other technology that can classify risk in non-ulcerated stage 1 to 2B melanomas.
- The intended **place in therapy** would be in addition to standard care in people with non-ulcerated stage 1, 2A or 2B melanomas. AMBLor can be run onsite in secondary or tertiary care.
- The **main points from the evidence** summarised in this briefing are from 3 retrospective validation studies including 1,025 people. They show that AMBLor can identify low risk of disease progression in non-ulcerated stage 1 and 2 melanomas. It is not suitable for identifying high-risk melanomas.

- **Key uncertainties** around the evidence or technology are that there is no evidence on the prospective use of AMBLor in clinical practice, its comparison with standard care, or its effect on treatment decisions, clinical outcomes or resource use.
- **Experts advised** that AMBLor may reduce the frequency of follow ups and the use of sentinel lymph node biopsy in low-risk melanoma. But evidence is needed on its effect on clinical decision making and resource use.
- The **cost** of AMBLor is £175 per test (excluding VAT). The company estimates additional processing costs of £20 per test for tests done in NHS settings. AMBLor would be an addition to standard care but costs may be offset if people with low-risk melanoma have fewer follow-up visits or sentinel lymph node biopsies.

The technology

AMBLor (AMLo Biosciences) is a prognostic risk stratification test for identifying low-risk non-ulcerated early-stage cutaneous melanoma in children and adults. This immunohistochemical assay uses 2 monoclonal antibodies that recognise the proteins AMBRA1 and loricrin in the epidermis covering the melanoma tumour. AMBRA1 is an autophagy protein that is involved in cell proliferation and differentiation and is a tumour suppressor. Loricrin is a marker of epidermal terminal differentiation. Melanomas with a lower risk of recurrence or spread retain the expression of AMBRA1 or loricrin, or both, in the tumoural epidermis. Tumours with higher risk lose the expression of both proteins.

AMBLor is used to qualitatively detect AMBRA1 and loricrin proteins by light microscopy in formalin-fixed paraffin-embedded sections of non-ulcerated primary cutaneous melanomas. It has been developed for use with the Ventana UltraView DAB immunohistochemistry (IHC) detection kit and Ventana BenchMark Ultra instrument. Positive and negative controls should be run with every test.

Innovations

The company claims that AMBLor uses a unique and patented immunohistochemical method and detection antibodies. It claims there is no other technology that can classify risk in non-ulcerated early-stage cutaneous melanoma.

Current care pathway

All pigmented skin lesions referred for assessment should be assessed using dermoscopy. Staging of melanoma is based on the American Joint Committee on Cancer (AJCC) cancer staging system. This considers the progression of the primary tumour and the spread of melanoma in the body. The initial staging of primary melanoma is based on the histopathological features of the tumour. The melanoma is staged as 0 to 2C based on factors such as thickness of the tumour and ulceration. A sentinel lymph node biopsy may also be done in stages 1B to 2C melanoma to detect secondary melanoma cells. If cancer cells are found in the sentinel nodes, the melanoma becomes stage 3. Stage 4 melanoma is when it has spread to distant parts of the body. Along with AJCC staging, other histopathological details may be used to assess risk of recurrence in melanoma by the multidisciplinary team.

Treating stages 1 to 2 melanoma involves excision to remove the melanoma and surrounding skin. After treatment, everyone is followed up in clinic for regular skin and lymph node examination. This aims to detect recurrence and other primary melanomas. Follow-up appointments are usually offered:

- Stage 1A: 2 to 4 times during the first year after treatment.
- Stages 1B to 2B: every 3 months for the first 3 years after treatment, then every 6 months for the next 2 years.

People would usually be discharged after completing these follow ups if no recurrence or new melanomas are found.

The following publications have been identified as relevant to this care pathway:

- NICE's guideline on melanoma: assessment and management
- NICE's guideline on suspected cancer: recognition and referral
- British Association of Dermatologists' Revised UK guidelines for the management of cutaneous melanoma 2010
- Royal College of Pathologists' Dataset for histopathological reporting of primary cutaneous malignant melanoma and regional lymph nodes.

Population, setting and intended user

Around 1 in 36 men and 1 in 47 women in the UK will be diagnosed with melanoma skin cancer in their lifetime, with about 16,700 new cases each year. In 2018, around 64% of people with melanoma were diagnosed at stage 1 and 19% at stage 2.

AMBLor is intended for use in non-ulcerated stage 1, 2A or 2B melanoma. It is only indicated for cutaneous melanoma that has been removed by excisional biopsy. It is not indicated for frozen biopsies and should not be used with:

- ulcerated stage 1 or 2 cutaneous melanomas
- stage 3 or above melanoma
- mucosal, acral, or uveal melanomas
- punch or shave biopsies
- melanoma that is in a psoriatic or eczemic lesion.

The AMBLor reagent kit can be run onsite in secondary or tertiary care settings. It uses the same biopsy sample used to diagnose melanoma. The assay should be read by a trained histopathologist along with the haematoxylin and eosin (H&E) slide of the same tissue used to diagnose melanoma. AMBLor may be used after initial staging of non-ulcerated stage 1 to 2B melanomas to identify people with low-risk disease. It may help healthcare professionals assess if a sentinel lymph node biopsy is needed. The company advises that the test should take no more than 20 minutes to complete when done in NHS settings.

Newcastle upon Tyne NHS Hospitals Trust also has UK Accreditation Service approval for a separate send-away service for NHS settings that do not have onsite testing. This service uses the AMBRA1 and loricrin antibodies used in AMBLor. The send-away service takes around 5 days from receiving samples to delivering the report.

Costs

Technology costs

AMBLor costs £175 per test (excluding VAT). Only 1 test is needed per biopsy analysis. The company estimates additional processing costs of £20 per test for tests done in NHS

settings. This includes costs associated with:

- preparing the sample and slides, including quality control staining, by a band 6 biomedical scientist
- scoring of the slides by a histopathologist
- writing the report.

Online training for pathologists is available through the company at no cost. The company estimates that the send-away service will cost £300 to £400 (excluding VAT).

Costs of standard care

AMBLor is an addition to standard care.

AMBLor is intended to enhance follow-up care and may reduce the frequency of follow-up appointments. The average cost of consultant led dermatology non-admitted face-to-face follow up (WF01A) is £123 per appointment (using the 2019/20 national schedule of NHS costs).

The company claims that AMBLor may also reduce the use of sentinel lymph node biopsies in people with AMBLor low-risk non-ulcerated stage 1B to 2B melanomas. There is currently no evidence of this.

NICE's guideline on melanoma: assessment and management (2015) estimated that the additional cost of sentinel lymph node biopsy alongside wide excision was £2,088 per person (using 2012/13 NHS reference costs). The company estimates this would be £2,309 when inflated to 2019/20 costs. There may also be additional costs for follow-up appointments and potential complications from the procedure.

Resource consequences

The antibodies that are used in the AMBLor test have been accredited by the UK Accreditation Service and are used in 1 NHS trust. The company states that the technology fits into the current care pathway with little change needed to existing processes. The AJCC staging system is limited by the heterogeneity of tumours. AMBLor may improve prognostic risk stratification for early-stage non-ulcerated primary cutaneous melanomas. It may better identify people with low risk who may benefit from more

conservative treatment. The company claims this could reduce the frequency of follow-up appointments, the need for sentinel lymph node biopsies, and may lessen the worries of patients.

AMBLor may be more cost effective and affordable than the current frequency of follow ups in standard care for stage 1 melanoma (Coughlan et al. 2019). A budget impact assessment by the company suggests that AMBLor could be cost saving when compared with standard care. Cost savings may range from £2 (stage 1A) to £245 (stage 2A) per person, with average savings of £175 per person.

Regulatory information

AMBLor is in the process of completing UK Conformity Assessed marking class IVDR for in vitro diagnostic devices. This is expected in mid-2022. Its component antibodies are approved by UK Accreditation Services for the send-away service with Newcastle upon Tyne NHS Hospital Trust.

Equality considerations

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

Melanoma is more common in older people, with incidence highest in people aged 85 to 89. It is increasing in younger people and is the second most common cancer in adults aged 25 to 49. In younger people, melanoma is more common in women, but it becomes more common in men over 55. Melanoma is more common in people with white skin because they have less of the protective pigment melanin. People with black or brown skin are more likely to be diagnosed with advanced melanoma. Late diagnosis of melanoma is associated with worse outcomes and higher risk of death. Age, sex, race, and disability are protected characteristics under the Equality Act 2010.

Clinical and technical evidence

A literature search was carried out for this briefing in accordance with the interim process and methods statement for medtech innovation briefings. This briefing includes the most

relevant or best available published evidence relating to the clinical effectiveness of the technology. Further information about how the evidence for this briefing was selected is available on request by contacting mibs@nice.org.uk.

Published evidence

Three studies are summarised in this briefing including a total of 1,025 people with stage 1, 2A or 2B melanoma. Two of the studies (Ewen et al. 2021 and Labus et al. 2020) appear to sample from the same centres. It is unclear if they both included the same sample of people with stage 2 melanomas.

All studies were retrospective validation studies, with 2 reported in abstracts and posters only. The clinical evidence and its strengths and limitations are summarised in the overall assessment of the evidence.

There are additional publications on AMBLor or the AMBRA1 and loricrin biomarkers that are not summarised in this briefing. Andrew et al. (2021) explored the use of artificial intelligence to quantify the expression of AMBRA1 and loricrin. This study was excluded because this algorithm is not included with the AMBLor kit described in this briefing. Cosgarea et al. (2021) used the biomarkers from the AMBLor kit to evaluate the impact of melanoma paracrine transforming growth factor beta2 signalling on the loss of AMBRA1. This study was excluded because it did not evaluate the AMBLor biomarkers but focused on the biology underlying epidermal loss.

Overall assessment of the evidence

The evidence on AMBLor consists of retrospective validation studies that were mostly reported in abstracts or posters. The company provided additional information on the design of these studies, which was not included in the abstracts. Based on this added information, the studies appear to be well-designed retrospective studies using prospective sampling from existing diagnostic specimens. Pathologists were blinded to patient outcomes when scoring slides with AMBLor, and data of clinical outcomes was only provided from sites once scoring was completed.

The evidence suggests that AMBLor risk classification of stage 1 or 2 melanomas may be associated with disease progression up to 12 years' follow up. AMBLor is reported to have good sensitivity and negative predictive value. The studies support the use of AMBLor as

a prognostic marker for identifying low risk of progression in stage 1, 2A or 2B melanoma. But it is not suitable for identifying high-risk melanoma because of its high rate of false positives. This is in line with AMBLor's intended use as a rule-out test.

More evidence is needed on the use and value of AMBLor in stratifying low-risk stage 1, 2A or 2B melanomas. This would ideally include prospective studies evaluating the effect of AMBLor on clinical decision making and outcomes for low-risk stage 1 to 2B melanomas. Evidence is also needed comparing AMBLor with standard care to determine the patient and system benefits of its addition to the care pathway. This should include outcomes related to resource use, including number of follow-up appointments and sentinel lymph node biopsies.

Ewen et al. (2021a)

Study size, design and location

Retrospective validation study in a mixed cohort of people with non-ulcerated stage 1 (n=334) or stage 2 (n=77) cutaneous melanomas.

People were recruited from centres in the US (n=241) and Australia (n=170). Clinical follow-up data ranged from 60 to 287 months. Cohorts were powered for metastasis rates of 10% for stage 1 and up to 20% for stage 2 melanoma.

Findings are reported in both abstract and poster (Ewen et al. 2021b) and both are summarised in the key outcomes.

Intervention

AMBLor.

Key outcomes

Retained expression of AMBRA1 and loricrin (n=70) was associated with 97% disease-free survival compared with 87% for people with loss of these protein markers (n=341; hazard ratio [HR] 0.20; 95% confidence interval [CI] 0.09 to 0.42; p=0.01). Within 5 years, 46 people had disease recurrence. Assay sensitivity was 96% with a negative predictive value of 97%. There were only 2 false-negative results. AMBLor returned 297 false positives, with low positive predictive value (11%) and specificity (19%). The authors

concluded that AMBLor is a marker to identify low-risk subsets of stage 1 or 2 melanomas, but it is not suitable for identifying high-risk melanomas.

Strengths and limitations

This study was reported in abstract and poster only. The poster included additional findings not reported in the abstract. The retrospective study design meant that AMBLor was not used in treatment decisions and its effect on clinical outcomes was not measured. The 5-year period for measuring disease recurrence and assay effectiveness aligns with the standard follow-up period in the NHS. The study included both stage 1 and 2 non-ulcerated melanomas. All stages were combined for analysis, with no results provided on stage 1 or stage 2 separately. The study reported a high rate of false positives. The company commented that the standard treatment for early-stage melanoma is a wide layer excision, which is curative in most cases. The company claims that this explains the high rate of false positives.

Labus et al. (2020)

Study size, design and location

Retrospective analysis in 159 people with non-ulcerated stage 2A or 2B primary melanoma in the UK, Spain, or Australia.

This study is also reported in another abstract (Ellis et al. 2019a) and poster (Ellis et al. 2019b). All findings are summarised in the key outcomes.

Intervention

AMBLor.

Key outcomes

AMBLor high- and low-risk classifications were associated with differences in disease-free survival in people with non-ulcerated stage 2A or 2B melanomas. High-risk melanoma (n=138) was associated with 56% disease-free survival at 12 years compared with 89% for low-risk tumours (n=21; HR 4.83; 95% CI 2.29 to 10.14; p=0.015). Multivariate analysis of a subgroup of 80 people with non-ulcerated stage 2B melanoma also showed lower disease-free survival (68%) at 12 years in people with high-risk tumours (n=70) compared

with low-risk (83%, n=10). Assay sensitivity ranged from 95% to 96%, with negative predictive values ranging 90% to 91% and positive predictive values ranging 34% to 37%.

Further subgroup analysis of people with sentinel lymph node negative stage 2A or 2B melanomas found 36% disease-free survival at 10 years in people with high-risk melanoma (n=37) compared with 100% in low-risk (n=5). Assay sensitivity for this group was 100%, with a negative predictive value of 100% and a positive predictive value of 46%. Authors concluded that AMBLor can be used as a stratifying biomarker for adjuvant immunotherapy in people with non-ulcerated stage 2 sentinel lymph node negative melanomas.

Strengths and limitations

This study was reported in abstracts and a poster, with details of study design and findings missing from some of the publications. It was a multicentre study using cohorts across different countries. No demographic information was reported. AMBLor was assessed on previously collected diagnostic samples and was not used to guide treatment decisions.

Ellis et al. (2019c)

Study size, design and location

Retrospective validation study in 3 independent cohorts with a total of 455 people with stage 1 melanomas in the UK.

Peritumoral AMBRA1 expression was evaluated in an initial discovery cohort (n=76). Then, AMBRA1 and loricrin expression was correlated with clinical outcomes in 2 validation and qualification cohorts (n=379).

Intervention

Semi-quantitative immunohistochemistry analysis of AMBRA1 and loricrin.

Key outcomes

Initial analysis showed that people with peritumoral AMBRA1 expression loss (n=54) had 82% disease-free survival at 7 years compared with 100% in people with retained

expression (n=22; p=0.081). Sensitivity for identifying people at risk of disease progression was 100%, but specificity was 33%.

Analysis of the combined expression of AMBRA1 and loricrin found that people identified with low risk (n=239) had 98% disease-free survival compared with 85% for high-risk melanomas (n=140; p<0.001). This combined analysis had a sensitivity of 83%, negative predictive value of 98%, specificity of 66%, and positive predictive value of 14%. Subgroup analysis of stage 1B melanomas found AMBRA1 and loricrin expression was a stronger predictor of disease-free survival (HR 4.04; 95% CI 1.69 to 9.66; p=0.002) than Breslow depth (HR 2.97; 95% CI 0.93 to 9.56; p=0.07). Authors concluded that AMBRA1 and loricrin expression is a prognostic marker that can stratify risk better than American Joint Committee on Cancer (AJCC) staging alone.

Strengths and limitations

This was an earlier validation study of the immunohistochemical analysis of AMBRA1 and loricrin. Study design followed the Cancer Research UK prognostic biomarker roadmap, with methods and statistical analysis clearly reported. The cohorts were statistically powered to detect a HR of more than 4.0 at p=0.05. The study evaluated the use of antibodies to detect AMBRA1 and loricrin biomarkers. The company advises that these are used in the current AMBLor kit, but there have been changes to the earlier scoring methods used in the current technology and its instructions for use.

Sustainability

The company claims the technology could reduce the number of follow-up appointments, resulting in less travel and emissions. There is no published evidence to support these claims.

Recent and ongoing studies

The company reported that there is an ongoing clinical validation study on AMBLor in about 450 retrospective biopsies in Northern Ireland and Spain. The company is also planning a prospective observational study of 500 people with stage 1 or 2 melanoma. This is planned to start in October 2022 with a 5-year follow up.

Expert comments

Comments on this technology were invited from clinical experts working in the field and relevant patient organisations. The comments received are individual opinions and do not represent NICE's view.

Five experts commented on this briefing. Three were familiar with AMBLor, with 1 using it before.

Level of innovation

Two experts thought AMBLor is innovative, especially its potential to reduce follow up in people with low-risk melanomas. Three experts considered that AMBLor was a minor variation on an existing procedure. One expert advised that the Royal College of Pathologists dataset uses several histopathological details to gauge the risk of recurrence in melanoma, including tumour mitotic rate, perineural invasion, and perivascular invasion. Other tests are being investigated to stratify risk in early-stage melanoma, including gene expression profiling. These tests are not yet available in the NHS.

Potential patient impact

The classification of low risk in people with non-ulcerated stage 1 to 2B melanomas may provide reassurance that a tumour is less likely to recur or spread. One expert advised that this could be used to inform whether a person should have a sentinel lymph node biopsy. It could also reduce the number of follow-up appointments in this group of people.

The experts advised that a potential harm of AMBLor was possible false-positive or false-negative results. Incorrectly assigning lower risk could prevent people from having more frequent follow ups when needed, while false positives could cause unnecessary worry for patients. But because AMBLor is a rule-out test to identify low-risk melanomas, false positives would be less likely to have adverse effects. One expert commented that the technology is safe but clinical decision making using the results is not yet established. More prospective validation was recommended. Two experts expressed concern that reducing the frequency of follow ups could result in other primary melanomas being missed.

Potential system impact

All experts advised that AMBLor would be used alongside standard care. Reducing the frequency of follow ups and the use of sentinel lymph node biopsies could be cost saving. One expert considered that AMBLor would be much cheaper than other technologies currently under investigation in this area. Most experts agreed that no additional facilities would be needed to use AMBLor. It may result in more time needed for multidisciplinary teams to discuss the results. Additionally, histopathologists may need training to use the kit and to interpret the results. But 2 experts believed this would be minimal because NHS histopathological services are already familiar with the technique.

General comments

NICE's guideline on melanoma is being updated. Two experts advised that this could change the recommended frequency of follow ups, use of sentinel lymph node biopsy and imaging, and adjuvant therapy in stages 1 to 2B melanoma. One expert commented that there would need to be advice on how AMBLor would fit into this evolving patient pathway.

All experts thought that more research is needed, including prospective studies on the effect of AMBLor on clinical decision making and the number of sentinel lymph node biopsies and follow ups for people with low risk. One expert believed that AMBLor has great potential but needs more validation especially in stage 2A and 2B melanomas. Ideally, research would be prospective, but a large retrospective prospective series should also be considered.

Patient organisation comments

A representative from British Skin Foundation gave the following comments.

AMBLor is a new technology that has the potential to benefit patients and healthcare providers. It could assist with determining appropriate treatment paths for people with melanoma. AMBLor offers a notable change in prognostic tests for melanoma. It may lessen the worries of patients and could save the health service time and resources that can be used elsewhere.

Communication and advice on new technologies like AMBLor are important to raise awareness among healthcare providers and the public. Without this, there may be unequal

access to novel technologies in different locations.

Expert commentators

The following clinicians contributed to this briefing:

- Dr Victoria Akhras, consultant dermatologist, St George's University Hospitals NHS Foundation Trust. Did not declare any interests.
- Dr Paul Barrett, consultant cellular pathologist, County Durham and Darlington NHS Foundation Trust. Did not declare any interests.
- Mr Amer Durrani, consultant plastic and reconstructive surgeon, Cambridge University Hospitals NHS Foundation Trust. Did not declare any interests.
- Prof Paul Lorigan, professor of medical oncology, University of Manchester and Christie NHS Foundation Trust. Principle investigator on DETECTION study (NCT04901988) in people with stage 2B and 2C melanoma. Previously chair of Melanoma Focus, which awarded a scientific grant as part of a competitive application process to this team to try to develop this approach.
- Mr Amit Roshan, Cancer Research UK and Royal College of Surgeons clinician scientist and honorary consultant plastic surgeon, University of Cambridge. British Association of Plastic, Reconstructive and Aesthetic Surgeons Research Committee member.

A representative from British Skin Foundation also contributed to this briefing.

Development of this briefing

This briefing was developed by NICE. NICE's interim process and methods statement sets out the process NICE uses to select topics, and how the briefings are developed, quality-assured and approved for publication.

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