

**NIHR Innovation Observatory
Evidence Briefing: November 2017****IMCgp100 for the treatment of advanced or
metastatic uveal melanoma**

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LAY SUMMARY

Uveal melanoma is a very rare type of eye cancer, where a tumour grows in the middle of the eye. Symptoms include flashes of light, blurred vision or loss of vision. The middle of the eye has a lot of blood vessels, and it is common for cancer cells to be carried by the blood to other parts of the body, causing tumours to grow there (this is known as metastatic cancer). Uveal melanoma cancer cells often spread to the liver, but can also spread to the lungs and bones. Half of the people who have uveal melanoma die from metastatic cancer or associated liver problems, often living for only 2-12 months after the cancer has spread.

There are currently few effective treatments available for advanced or metastatic uveal melanoma, including surgery to remove the cancer, radiotherapy or chemotherapy. IMCgp100 is a drug under development that would enable the body's own immune system to recognise and specifically target and kill cancer cells. IMCgp100 is given by intravenous infusion and is currently being studied in patients with advanced/ metastatic uveal melanoma. It will offer a new treatment option if licenced.

This briefing is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.

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TARGET GROUP

Uveal melanoma, advanced or metastatic – first-line; monotherapy

TECHNOLOGY

DESCRIPTION

IMCgp100 is a first-in-class bi-specific biologic known as a “T cell redirector”. Based on the ImmTAC (Immune mobilising monoclonal T cell receptors (TCRs) Against Cancer) platform technology, IMCgp100 enables the immune system to recognise and kill cancer cells. It binds, with picomolar affinity, to a melanocyte-associated target peptide of gp100 presented on the surface of melanoma cells by Human Leukocyte Antigen (HLA) molecules; once bound IMCgp100 redirects CD-3 positive T cells, including non-cancer specific T cells, to kill the cancer cells.¹

IMCgp100 is a 2-part fusion protein with antineoplastic activity, comprising 1) an affinity enhanced human TCR, specific for binding gp100 peptide presented via (class I MHC) HLA-A*02*01 on the surface of cancer cells, fused to; 2) an anti-CD3 single-chain antibody fragment (ScFv), that binds circulatory T lymphocytes. Thereby, through specifically attaching to the HLA-A*02*01-peptide complex, the ImmTAC decorates the outside of the cancer cell and selectively cross-links T lymphocytes to the cancer cell, activating the cross-linked T cells to release proinflammatory cytokines, induce T cell proliferation and induce tumour cell death. This leads to further the recruitment of cytotoxic T lymphocytes (CTL) to the T lymphocyte/tumour cell aggregates resulting in widespread CTL-mediated death of gp100-expressing melanoma cancer cells.²

In studies with IMCgp100, delivery was initially investigated as an intra-tumoural administration and has subsequently been examined under various regimens of intravenous administration.² In the phase II trial NCT03070392, IMCgp100 concentrate for solution for infusion is administered to advanced uveal melanoma patients at a dose of 20mcg cycle-1 day-1, then 30mcg cycle-1 day-8, then 68mcg cycle-1 day-15 and weekly thereafter by intravenous infusion over 15 minutes until confirmed disease progression or unacceptable toxicity.³

IMCgp100 does not currently have Marketing Authorisation in the EU for any indication.

INNOVATION and/or ADVANTAGES

There is no proven standard of care for patients with uveal melanoma who develop metastatic disease, and there is considerable variation in treatments offered at specialist centre in England.⁴ A number of chemotherapeutic regimens and combinations have been investigated, with disappointing results to date.⁵

Results published from phase I trials showed that durable tumour responses were observed, and longer overall survival was observed compared with the standard of care in this disease setting.⁶

If licensed, IMCgp100 will offer a new treatment option for patients with advanced or metastatic uveal melanoma, who currently have few effective therapies available.

DEVELOPER

Immunocore Ltd

AVAILABILITY, LAUNCH or MARKETING

In January 2016, IMCgp100 received orphan drug designation for uveal melanoma in the USA.

IMCgp100 was accepted on the EMA's Adaptive Pathway pilot programme in September 2015.

PATIENT GROUP

BACKGROUND

Uveal melanoma is a type of eye cancer, arising from blood-rich structures in the middle of the eye (iris, choroid or ciliary body). Biologically distinct to cutaneous (skin) melanoma, with different physiological, genetic, and epidemiology characteristics, uveal melanoma is often discovered via routine optometrist eye examination. If the tumour is in the ciliary body, it may not cause symptoms until it is quite large; tumours involving the macula are often spotted early as they cause symptoms, while tumours involving the iris are more easily seen due to their forward location. Symptoms include flashes of light, blurry vision, loss of vision, or floaters.⁷

Risk factors for uveal melanoma include light-coloured irides, congenital ocular melanocytosis, melanocytoma and neurofibromatosis. The role of sunlight is uncertain.⁸

Characteristically, the condition has two distinct disease states. Stage I-III when the tumour is contained to the eye (primary disease), and Stage IV when it has spread to distant organs (metastatic).⁷ Risk prediction of tumour spread is very important to uveal melanoma patients. The disease frequently spreads via the bloodstream, typically to the liver. Metastases in the liver are often numerous and can grow very quickly, with a doubling time of as little as four weeks. Other common sites of metastases include the lungs and bone.⁹ Patients can develop metastatic disease at any time from the initial diagnosis of the primary to several decades later.⁸

The prognosis for uveal melanoma depends on many factors, including the patient's age (poorer prognosis in older patients), where in the uvea the tumour grew, its size and thickness, whether it has spread outside of the eye, and the genetic make-up of the tumour (e.g. if monosomy 3 is detected that usually means the patients is at high risk of developing metastatic disease).⁷

CLINICAL NEED and BURDEN OF DISEASE

There are approximately 600 new cases of uveal melanoma in the UK each year.⁷

In England in 2015 there were 443 registrations of newly diagnosed cancer of the choroid (ICD-10 code C69.3) and 57 registrations of cancer of the ciliary body (ICD-10 code C69.4). The directly age-standardised rate per 100,000 population for newly diagnosed neoplasm of the eye and adnexa (ICD-10 code C69) was 1.4 for males and 1.1 for females. There were 94 registrations of death from neoplasm of the eye and adnexa in England in 2015.¹⁰

In England in 2016/17 there were 843 FCEs and 1,477 FCE bed days with primary diagnosis of ICD-10 codes C69.3 (malignant neoplasm of the choroid) or C69.4 (malignant neoplasm of the ciliary body). There were 783 hospital admissions, of which 250 were day cases.¹¹

Outcomes are poor once metastatic disease occurs, and close to 50% of uveal melanoma patients ultimately die of metastatic disease.⁹ The median survival from the time of the development of metastatic disease is 2-12 months and 1-year survival is reported to be 10-15%.⁸ Liver involvement is the cause of death in most patients with metastatic uveal melanoma. Most patients die from parenchymal liver failure, but obstructive jaundice may result from liver metastases compressing the common hepatic or intrahepatic ducts or, less commonly, from porta hepatis nodal disease compressing the extrahepatic duct.⁸

Based on recent published epidemiological data, the annual metastatic uveal melanoma population in England is estimated to <150 patients per year. Given that IMCgp100 is pharmacologically restricted to patients with a HLA-A*02*01 positive phenotype (approximately 50% of the UK population), half of these patients could be eligible to receive IMCgp100.¹²

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Talimogene laherparepvec for treating unresectable metastatic melanoma (TA410). September 2016.
- NICE technology appraisal. Nivolumab in combination with ipilimumab for treating advanced melanoma (TA400). July 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. Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma (TA319). July 2014.
- NICE technology appraisal. Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma (TA268). December 2012.
- NICE guideline. Melanoma: assessment and management (NG14). July 2015.
- NICE interventional procedure guidance. Chemosaturation via percutaneous hepatic artery perfusion and hepatic vein isolation for primary or metastatic liver cancer. (IP488). May 2014.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Ocular Oncology Service (Adults and Adolescents). D12/S(HSS)/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.
- NHS England. Clinical Commissioning Policy: The use of Stereotactic Ablative Radiotherapy (SABR) in the treatment of oligometastatic disease. 16032/P. July 2016.
- NHS England. Clinical Commissioning Policy: Chemosaturation for liver metastases from ocular melanomas. 16014/P. July 2016.

- NHS England. Interim Clinical Commissioning Policy Statement: Stereotactic Radiosurgery / Radiotherapy for Ocular Melanoma and Pituitary Adenoma. D05/PS/a. September 2013.
- NHS England. Interim Clinical Commissioning Policy Statement: Selective Internal Radiotherapy (SIRT). B01/PS/a. June 2013.

OTHER GUIDANCE

European Journal of Cancer. Uveal Melanoma UK National Guidelines. November 2015.⁸

CURRENT TREATMENT OPTIONS

Uveal melanoma that is contained within the eye can be treated in a number of ways, depending on a number of factors including the size and position of the tumour.⁷

For treatment of the primary tumour, national guidelines for uveal melanoma recommend:

- Brachytherapy with iodine 125 or ruthenium 106
- Proton beam radiotherapy
- Stereotactic radiosurgery
- Transpupillary thermotherapy
- Photodynamic therapy
- Exoresection ± plaque
- Endoresection ± radiotherapy
- Enucleation
- Exenteteration⁸

The rarity of uveal melanoma and lack of close surveillance for secondary tumours have limited the evidence for treatment of metastases. There is currently no effective, systemic, cytotoxic chemotherapy for metastatic uveal melanoma. Resection of uveal melanoma liver metastases is proven to prolong survival when technically possible.⁹

In recent years there have been development in the use of liver-directed therapies, such as liver surgery, TACE (transcatheter arterial chemoembolisation), SIRT (selective internal radioembolisation) and PHP (percutaneous hepatic perfusion). Immunotherapy is also an option, although it must be given early enough to allow time for it to work (12 weeks to 1 year). The genetic mutations thought to initiate uveal melanoma (GNAQ and GNA11) are not currently therapeutically targetable. However, it is possible that biological therapies that target the same pathway, such as MEK inhibitors, could be useful in uveal melanoma.⁹

For metastatic disease, national guidelines for uveal melanoma recommend:

- Patients with systemic disease should be considered for clinical trials wherever possible, and should be offered systemic treatments if not placed in a clinical trial
- Patients with liver predominant disease should be considered for regional therapy

Loco-regional treatment for the management of oligometastatic disease (i.e. when metastases are limited to a single or limited number of organs) should be considered. This may include surgery, stereotactic treatment or other forms of ablation.

- Ipilimumab can be offered following NICE approval of this drug for use in melanoma generically
- For patients with technically resectable liver metastases, assessment for curative intent hepatic resection should be offered
- Regional or systemic treatments may be considered in patients with liver dominant disease where resection is not suitable⁸

A pilot study mapping the treatment pathway for patients in England with metastatic uveal melanoma found that there was considerable variation in treatments offered at specialist centres. This is turned to variation in whether patients received ongoing standard systemic treatments only at specialist centres or if they could be provided at centres more local to a patient's home.⁴

EFFICACY and SAFETY

Trial	NCT03070392, IMCgp100-202, EudraCT-2015-003153-18; IMCgp100 Vs. investigator choice (dacarbazine, pembrolizumab or ipilimumab)
Sponsor	Immunocore Ltd
Status	Ongoing
Source of Information	Trial registries ^{3,13}
Location	USA, Europe, Australia, Canada
Design	Randomised, active-controlled, parallel assignment
Participants	N=327 (planned); aged 18-99 yrs; uveal melanoma; metastatic or advanced; first-line
Schedule	Randomised to: Arm I: IMCgp100 concentrate for solution for infusion at a dose of 20mcg cycle-1 day-1, then 30mcg cycle-1 day-8, then 68mcg cycle-1 day-15 and weekly thereafter by intravenous infusion over 15 minutes until confirmed disease progression or unacceptable toxicity. Arm II (Investigator choice): dacarbazine powder for solution for injection/infusion at a dose of 1,000 mg/m ² of body surface area intravenous (IV) infusion every 3 wks until disease progression or unacceptable toxicity, OR ipilimumab concentrate for solution for infusion at a dose of 3mg/kg intravenous (IV) infusion over 90 mins for every 3 wks for a total of 4 treatments; OR pembrolizumab powder for concentrate for solution for infusion at a dose of 2mg/kg intravenous (IV) infusion over 30 mins for every 3 wks until confirmed disease progression or unacceptable toxicity.
Follow-up	Active treatment until confirmed disease progression or unacceptable toxicity. Overall follow-up period 40 mths.
Primary Outcomes	Overall survival defined as the time from patient inclusion to date of death due to any cause.
Secondary Outcomes	<ul style="list-style-type: none"> • Safety defined as the number of patients with treatment emergent adverse events, laboratory abnormalities, ECG changes, and/or

	<p>physical examination findings (from consent to 90 days after end of treatment)</p> <ul style="list-style-type: none"> • Objective response rate (ORR) defined as the proportion of patients achieving an objective response (RECIST v1.1) (assessed every 3 mths from randomisation until disease progression, assessed up to 40 mths) • Duration of response (DOR) defined as the time from first documented objective response (RECIST v1.1) until the date of documented disease progression (assessed every 3 mths from randomisation until disease progression, assessed up to 40 mths) • Progression free survival (PFS) defined as the time from randomization to the date of progression (RECIST v1.1) or death due to any cause (assessed every 3 mths from randomisation until disease progression, assessed up to 40 mths) • Disease control rate (DCR) defined as the proportion of patients with either an objective response or stable disease (RECIST v1.1) (assessed every 3 mths from randomisation until disease progression, assessed up to 40 mths) • General health status will be assessed using the EQ-5D,5L questionnaire (assessed every 6 wks from randomisation for 24 wks and approx. 3 mths thereafter until death, assessed up to 40 mths) • Health related quality of life will be assessed using EORTC QLQ-C30 questionnaire (assessed every 6 wks from randomisation for 24 wks and approx. 3 mths thereafter until death, assessed up to 40 mths) <p>IMCgp100 arm only:</p> <ul style="list-style-type: none"> • Area under the plasma concentration-time curve (AUC) (assessed wkly for 3 wks and every 6 wks thereafter until end of treatment, assessed up to 40 mths) • The maximum observed plasma drug concentration after single dose administration (Cmax) (assessed wkly for 3 wks and every 6 wks thereafter until end of treatment, assessed up to 40 mths) • The time to reach maximum plasma concentration (Tmax) (assessed prior to and after the first 3 doses of IMCgp100, an average of 3 wks) • The elimination half-life (t1/2) (assessed prior to and after the first 3 doses of IMCgp100, an average of 3 wks) • The frequency of anti-IMCgp100 antibody formation (approx. 5 assessments performed between first dose of IMCgp100 and end of treatment, assessed up to 40 mths)
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date reported as July 2020.

ESTIMATED COST and IMPACT

COST

The cost of IMCgp100 is not yet known.

A study of hospital-related resource utilisation for metastatic uveal melanoma patients in England found that in the period April 2012-June 2017 the total cost to NHSE for metastatic uveal melanoma inpatient admissions was £3.1 million (mean:£6,451/patient; range:£118–65,947), and the cohort attended 5,056 outpatient appointments and had 899 A&E visits.¹⁴

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

- | | |
|------------------------------------------------------------------------------------|--------------------------------------------------------------------|
| <input checked="" type="checkbox"/> Reduced mortality/increased length of survival | <input checked="" type="checkbox"/> Reduced symptoms or disability |
| <input type="checkbox"/> Other | <input type="checkbox"/> No impact identified |

IMPACT ON HEALTH and SOCIAL CARE SERVICES

- | | |
|---------------------------------------------------------------|-------------------------------------------------------------|
| <input type="checkbox"/> Increased use of existing services | <input type="checkbox"/> Decreased use of existing services |
| <input type="checkbox"/> Re-organisation of existing services | <input type="checkbox"/> Need for new services |
| <input type="checkbox"/> Other | <input checked="" type="checkbox"/> None identified |

IMPACT ON COSTS and OTHER RESOURCE USE

- | | |
|--------------------------------------------------------------------|-------------------------------------------------------|
| <input checked="" type="checkbox"/> Increased drug treatment costs | <input type="checkbox"/> Reduced drug treatment costs |
| <input type="checkbox"/> Other increase in costs | <input type="checkbox"/> Other reduction in costs |
| <input type="checkbox"/> Other | <input type="checkbox"/> None identified |

OTHER ISSUES

- | | |
|-------------------------------------------------------------------------------------|-----------------------------------------------------|
| <input type="checkbox"/> Clinical uncertainty or other research question identified | <input checked="" type="checkbox"/> None identified |
|-------------------------------------------------------------------------------------|-----------------------------------------------------|

REFERENCES

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