Isatuximab (Sarclisa®) plus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (MM)

General information [1]

Drug description	Indication
Isatuximab is a monoclonal antibody that binds to a specific epitope on the human cell surface antigen CD38, which is widely and uniformly expressed on myeloma cells.	Patients with relapsed and refractory MM who received at least 2 previous lines of treatment, and had not responded to therapy with lenalidomide and a PI (bortezomib, carfilzomib, or ixazomib) given alone or in combination.

Current treatment [2]

- Despite recent progress, MM remains incurable and the majority of patients will progress and require treatment.
- Treatment options for relapsed and refractory MM which include the novel agents thalidomide, bortezomib and lenalidomide as single-agents or in combination with dexamethasone have shown significant activity in patients with relapsed MM and are generally well tolerated.
- These agents have set the stage for the development of the next-generation IMiDs and the PIs (i.e. pomalidomide and carfilzomib in relapsed and/or refractory disease).
- In general, doublet or triplet regimens are preferred above single agents for optimal effect.
- In instances of first relapse, current NICE guidelines recommend the use of:
  - Carfilzomib in combination with dexamethasone – only after one prior therapy, which did not include bortezomib
  - Bortezomib – only after one prior therapy and who have undergone, or are unsuitable for, bone marrow transplantation
  - Second ASCT– suitability determined by response to first transplant, number of prior treatments, overall health and fitness, and ranking on RISS system
- Subsequent relapse treatment may include:
  - Lenalidomide in combination with dexamethasone – two or more prior therapies
  - Ixazomib in combination with lenalidomide and dexamethasone, through the CDF after two or more prior therapies.
  - Panobinostat in combination with bortezomib and dexamethasone – relapsed and/or refractory, at least two prior therapies including bortezomib and an immunomodulatory agent
  - Pomalidomide in combination with low-dose dexamethasone – third or subsequent relapse; three previous treatments including both bortezomib and an immunomodulatory agent
  - Daratumumab monotherapy as 4th line therapy through the CDF
  - Bendamustine for relapsed disease where all other treatments contraindicated or inappropriate is available through the CDF.

Regulatory status

EMA [3]	FDA [4]
Approval status for this indication: On 26 March 2020, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for isatuximab UPDATE: **authorized** for use in the European Union (30/05/2020) **Other indications**: none ✓ **Medicine under additional monitoring**	**Approval status for this indication**: Isatuximab is indicated, in combination with pomalidomide and dexamethasone, for the treatment of adult patients with MM who have received at least two prior therapies including lenalidomide and a proteasome inhibitor. **Other indications**: none

Costs

Sarclisa® concentrate for solution for infusion 500 mg/25ml = € 3,320.00 (ex-factory price),
Sarclisa® concentrate for solution for infusion 100 mg/5ml = € 644.00 (ex-factory price) [5]

ICARIA-MM trial patients in the isatuximab–pomalidomide–dexamethasone group received isatuximab 10 mg/kg IV (on days 1, 8, 15, and 22 in the first 28-day cycle; and days 1 and 15 in subsequent cycles). Assuming an average **body weight of 70 kg → 1 dose = € 4,608**. Median treatment duration was **41 weeks** in the isatuximab–pomalidomide–dexamethasone group. Additionally, costs for pomalidomide and dexamethasone incur.

Posology [6]

- Premedication should be used prior to isatuximab infusion with the following medicinal products to reduce the risk and severity of infusion reactions:
  - Dexamethasone 40 mg oral or IV (or 20 mg oral or IV for patients ≥75 years of age
  - Acetaminophen 650 mg to 1000 mg oral (or equivalent)
  - H2 antagonists (ranitidine 50 mg intravenous or equivalent [e.g., cimetidine]), or oral proton pump inhibitors (e.g., omeprazole, esomeprazole)
  - Diphenhydramine 25 mg to 50 mg IV or oral (or equivalent)

- The above recommended dose of dexamethasone (oral or IV) corresponds to the total dose to be administered only once before the infusion, as part of the premedication and the backbone treatment, before isatuximab and pomalidomide administration.
- The recommended premedication agents should be administered 15-60 minutes prior to starting an isatuximab infusion. Patients who do not experience an infusion reaction upon their first 4 administrations of isatuximab may have their need for subsequent premedication reconsidered.

Study characteristics

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
ICARIA-MM NCT02990338 EFC14335	307	isatuximab–pomalidomide–dexamethasone	pomalidomide–dexamethasone	PFS	prospective, randomised, open-label, active-controlled, multicentre, multinational, phase 3 study	-	Sanofi	Link

Efficacy (I vs. C)

PFS: median PFS was 11.5 months (95% CI, 8.9–13.9) vs. 6.5 months (95% CI, 4.5–8.3); HR 0.596 (95% CI 0.44–0.81; p=0.001)
Partial response: 60% vs. 35%; p<0.0001
Very good partial response or better: 32% vs. 9%; p<0.0001
Overall response: 63% vs. 32%
Median duration of response: 13.3 months vs. 11.1 months
OS: At the PFS cut-off date, 99 deaths had occurred (43 vs. 56); an interim analysis of OS was done at that time: HR 0.687 (95% CI 0.461–1.023; p=0.0631). Median OS was not reached in either group.
HRQoL: no change from baseline in the Global Health score of the QLQ-C30 over time

Safety (I vs. C)

Any TEAE: n=151/152 (99.3%) vs. n=146/149 (98.0%)
Any drug-related grade ≥3 TEAEs: n=109/152 (71.7%) vs. n=71/149 (47.7%)

Any serious TEAEs: n=94/152 (61.8%) vs. n=80/149 (53.7%)
Any serious drug-related TEAEs: n=54/152 (35.5%) vs. n=24/149 (16.1%)

Any TEAE leading to definitive discontinuation: n=11/152 (7.2%) vs. n=19/149 (12.8%)
TEAE leading to death during treatment period: n=12/152 (7.9%) vs. n=14/149 (9.4%)

Risk of bias (study level)

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes	no	no (open-label)	unclear[1]	yes[2]	high-risk

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Abbreviations: ASCT=autologous stem cell transplant, C=comparator, CDF=Cancer Drug Fund, CHMP=Committee for Medicinal Products for Human Use, EMA=European Medicines Agency, FDA=Food and Drug Administration, HR=hazard ratio, HRQoL=health-related quality of life, I=intervention, ImiDs=immunomodulatory drugs, IV=intravenous, n=number, MM=multiple myeloma, TEAE=treatment-emergent adverse event, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PI=proteasome inhibitor.

[1] trial is ongoing hence partly interim analysis data
[2] industry-funded

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2. National Institute for Health Research (NIHR). Isatuximab in addition to pomalidomide and dexamethasone for relapsed and/or refractory multiple myeloma [Available from: http://www.io.nihr.ac.uk/wp-content/uploads/2018/06/13464-Isatuximab-for-Multiple-myeloma-V1.0-MAY2018-NON-CONF.pdf.
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