swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Imjudo

International non-proprietary name: tremelimumab
Pharmaceutical form: concentrate for solution for infusion
Dosage strength(s): 25 mg/1.25 ml; 300 mg/15 ml
Route(s) of administration: intravenous
Marketing authorisation holder: AstraZeneca AG
Marketing authorisation no.: 68706
Decision and decision date: approved on 13 September 2023

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC_{ss}	Area under the plasma concentration-time curve at steady state
CI	Confidence interval
CL	Clearance
C_{max}	Maximum observed plasma/serum concentration of drug
CTLA-4	Cytotoxic T lymphocyte-associated antigen-4
CYP	Cytochrome P450
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ER	Exposure response
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
HCC	Hepatocellular carcinoma
HR	Hazard ratio
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
$IFN\gamma$	Interferon gamma
Ig	Immunoglobulin
IL	Interleukin
IV	Intravenous
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
NO(A)EL	No observed (adverse) effect level
OS	Overall survival
PFS	Progression-free survival
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
Q4W	once every 4 weeks
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
T75+D	Tremelimumab 75 mg plus durvalumab
T300+D	Tremelimumab 300 mg plus durvalumab
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
uHCC	Unresectable hepatocellular carcinoma
Vc	Central volume of distribution

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2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for tremelimumab in the above-mentioned medicinal product.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 a^{decies} no. 2 of the TPA.
Orphan drug status was granted on 15 November 2021.

2.2 Indication and dosage

2.2.1 Requested indication

Tremelimumab (TRADENAME) in combination with durvalumab is indicated for the treatment of patients with unresectable hepatocellular carcinoma (uHCC).

2.2.2 Approved indication

Hepatocellular Carcinoma (HCC)
IMJUDO in combination with durvalumab is indicated for the treatment of patients with unresectable hepatocellular carcinoma (uHCC) who have not received prior systemic therapy (see "Clinical efficacy").

2.2.3 Requested dosage

Summary of the requested standard dosage:
The proposed dosage is tremelimumab 300 mg as a single priming dose in combination with durvalumab 1500 mg at Cycle 1/Day 1, followed by durvalumab as monotherapy every 4 weeks.
Tremelimumab should be administered prior to durvalumab on the same day.
Patients with a body weight of 30 kg or less must receive weight-based dosing equivalent to tremelimumab 4 mg/kg and durvalumab 20 mg/kg until weight is greater than 30 kg.
Treatment should continue for as long as benefit is observed or until unacceptable toxicity is reached.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	22 April 2022
Formal control completed	12 May 2022
List of Questions (LoQ)	6 September 2022
Response to LoQ	5 December 2022
Preliminary decision	3 March 2023
Response to preliminary decision	1 May 2023
Labelling corrections	26 June 2023
Response to labelling corrections	3 August 2023
Final decision	13 September 2023
Decision	approval

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3 Medical context

Worldwide, hepatocellular carcinoma (HCC) represents the fifth most common cancer and the second most common cause of cancer-related death in men. HCC are aggressive tumours and frequently occur in the setting of chronic liver disease and cirrhosis. They are typically diagnosed late in the course of liver disease.

For patients with non-resectable HCC, approved systemic treatment options for first-line treatment of HCC in Switzerland are tyrosine kinase inhibitors or immune checkpoint inhibitors combined with the anti-angiogenesis agent bevacizumab.

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4 Quality aspects

4.1 Drug substance

Tremelimumab is a human monoclonal antibody from the immunoglobulin IgG2a subclass directed against cytotoxic T lymphocyte-associated antigen 4 (CTLA-4). Tremelimumab is a glycoprotein (molecular weight: approx. 149 kDa) composed of two heavy chains and two kappa light chains covalently linked with six interchain disulphide bonds.

Tremelimumab is produced in NS0 murine myeloma cells. A two-tiered cell banking system of Master Cell Bank (MCB) and Working Cell Bank (WCB) is in place. After thawing of the WCB vial, the cells are grown in suspension culture in a series of seed train bioreactors to generate sufficient cell mass to seed the production bioreactor. The cell culture fluid is harvested, and purification is performed with a series of chromatography steps, ultrafiltration/diafiltration steps, and viral inactivation and viral filtration steps.

The cell culture and purification processes for tremelimumab drug substance are both validated with several consecutive batches, and the data demonstrated a consistent production and an efficient removal of impurities.

Several changes were implemented during development of the manufacturing process for the drug substance, including changes to manufacturing site and production scale. However, comparability studies, including batch release data, extended characterisation data, and stress stability data, demonstrated comparability between the different processes.

The characterisation of the physicochemical and biological properties of the tremelimumab drug substance and its impurities was performed using state-of-the-art methods.

The specifications for release and stability of the drug substance include relevant tests and acceptance criteria, e.g. for identity, purity and impurities, quantity, and potency. Specifications are based on published limits, stability data, clinical experience, batch analysis data, and stability data, and are in conformance with current compendial or regulatory guidelines.

Batch analysis data for development, clinical, and process validation batches of tremelimumab drug substance were provided. All specific analytical methods are described and are fully validated.

No significant changes were observed during storage of tremelimumab drug substance under the proposed storage conditions.

4.2 Drug product

Tremelimumab drug product is a sterile, preservative-free, liquid dosage form intended for intravenous infusion after dilution. The drug product is provided in a 25 mg vial presentation and a 300 mg vial presentation. The 25 mg drug product is a single-dose vial that contains a label claim of 25 mg of tremelimumab in a 1.25 mL volume. The 300 mg drug product is a single-dose vial that contains a label claim of 300 mg of tremelimumab in a 15 mL volume. Prior to administration, the drug product must be diluted in 0.9% (w/v) saline or 5% (w/v) dextrose to the required target concentration.

All excipients (L-histidine, L-histidine hydrochloride monohydrate, α-trehalose dihydrate, disodium edetate dihydrate, polysorbate 80, water for injection), are of compendial grade and commonly used for the formulation of biopharmaceuticals. None of the excipients are of animal or human origin.

Several drug product dosage strengths, formulations, presentations, and filling facilities were used during clinical development. However, comparability studies, which included batch release data, extended characterisation data, and stress stability data, demonstrated comparability of the relevant quality attributes between the different processes.

Compatibility studies were conducted to establish the in-use stability of diluted drug product with the intended materials and conditions of use.

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The drug product manufacturing process consists of bioburden-reducing filtration of the formulated drug substance, sterile filtration and aseptic filling, crimping, visual inspection, labelling, and secondary packaging.

The drug product manufacturing process is validated with several consecutive batches. The data demonstrated a consistent production.

The specifications for release and stability of the drug product include relevant tests and acceptance criteria, e.g. for identity, purity and impurities, quantity, potency, appearance, pH, osmolality, visible and subvisible particles, bacterial endotoxins, and sterility. The drug product specifications comply with current compendial or regulatory guidelines.

Batch analysis data for several batches of the drug product, including development batches, clinical batches, and process validation batches were provided. All batch release data comply with the drug product specifications, which were valid at the time of batch release. All specific analytical methods are validated.

The 25 mg drug product is stored in a 2 mL clear glass vial, closed with an elastomeric stopper. The 300 mg drug product is stored in a 20 mL clear glass vial, closed with an elastomeric stopper. Stoppered drug product vials are capped with an aluminium seal and packaged in single-vial cartons. The materials of the type I glass vial and rubber stopper meet compendial requirements.

The vials are stored at 2°C to 8°C. The stability data support a shelf life of 48 months.

4.3 Quality conclusions

Satisfactory and consistent quality of drug substance and drug product has been demonstrated.

Safety of the product with regard to viral and non-viral contaminants is adequately addressed.

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5 Nonclinical aspects

For the nonclinical testing strategy, the applicant considered the recommendations outlined in ICH S9 and S6(R1).

5.1 Pharmacology

Tremelimumab demonstrated *in vitro* high affinity to human and cynomolgus cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), with K_D values of 0.28 and 0.98 nM. The investigators studied binding of tremelimumab to CTLA-4 on activated T cells of various species such as human, cynomolgus and rhesus monkeys, mouse, rat, hamster, and rabbit. Overall, there was only binding to activated human, cynomolgus and rhesus monkey lymphocytes, which is consistent with sequence homology.
In a CTLA-4 competition binding assay, the antibody blocked the binding of the natural ligands CD80 and CD86 to CTLA-4 fusion protein, with IC_{50} values of 0.78 and 0.46 nM. This inhibition did not affect the function of CTLA-4 as such, as confirmed in a cell-based *in vitro* T-cell activation assay using the levels of interleukin-2 (IL-2) and interferon-γ (IFN-γ) as markers. The addition of tremelimumab significantly increased the levels of IL-2 and IFN-γ.
Using staphylococcal enterotoxin A (SEA) superantigen-stimulated human peripheral blood mononuclear cells or blood from healthy volunteers or cancer patients, the antibody also caused IL-2 enhancement. Tremelimumab did not trigger tumour necrosis factor-α (TNF-α), IL-6, or IL-1β release in the human whole blood assay.
Further on, the antibody did not affect the activity of human peripheral regulatory T cells to suppress IFN-γ production or the thymidine incorporation of stimulated human peripheral T responder cells. Exposure to tremelimumab did not significantly change the number of platelets isolated from healthy donors after a 25-hour incubation. The investigators also studied the binding of tremelimumab to Fc receptors using peripheral blood leukocytes from healthy human donors, prostate cancer patients and cynomolgus monkeys; they detected only minimal binding. Based on the available data, complement-dependent cytotoxicity or antibody-dependent cell-mediated cytotoxicity are not expected.
The applicant studied the anti-tumour activity of CTLA-4 inhibition alone and in combination with inhibition of programmed cell death protein 1 (PD-1) in murine tumour models using respective surrogate antibodies. In models with CT26 colon adenocarcinoma, EMT6 breast cancer as well as MCA205 soft tissue sarcoma cells, the antibody combination was superior to the individual agents regarding tumour growth inhibition.
No secondary pharmacodynamics studies were conducted with tremelimumab, which is acceptable considering the high specificity of the monoclonal antibody.
The repeat-dose toxicity studies in cynomolgus monkeys included safety pharmacology endpoints. The investigators did not identify any relevant effects on the cardiovascular, respiratory, and central nervous system function at clinically relevant exposure levels.
Pharmacodynamic drug interaction studies with tremelimumab were not conducted.

5.2 Pharmacokinetics

The applicant investigated the pharmacokinetic profile of tremelimumab in cynomolgus monkeys following single and repeated intravenous (IV) administration. The PK parameters are typical for a monoclonal antibody.
Serum exposure increased approximately proportional to dose and was comparable in male and female animals. The mean terminal half-life was greater than 9 days after a single dose. Clearance was low, as was the volume of distribution. Anti-drug antibodies were detected but had no impact on the exposure.
In line with ICH S6(R1), the applicant did not conduct studies on distribution, metabolism, and excretion.
As the release of cytokines can alter the expression of CYP enzymes, the applicant adequately discussed the potential impact of IL-2 and IFN-γ secretion on CYP450 expression and its consequences.

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5.3 Toxicology

The applicant provided two single-dose studies and two repeat-dose toxicity studies up to 6 months (recovery period up to 99 days) with weekly administrations, as well as an embryofetal development study and tissue cross-reactivity studies. The route of administration was IV as foreseen for clinical use. Dosing intervals were weekly and hence more frequent than requested. The presented pharmacology data supported the use of cynomolgus monkey as a pharmacologically relevant species. However, the affinity of tremelimumab to monkey CTLA-4 was approx. 3-fold lower, which might have had an impact on the activity in cynomolgus monkeys.
In the single-dose studies with doses up to 100 mg/kg, no mortality occurred. Tremelimumab caused loose stool at doses greater than 30 mg/kg, as well as reversible increases of lymphocyte or eosinophil counts. Other parameters, such as body weight gain and food consumption, were not affected. In one of the studies, the investigators confirmed IL-2 enhancement using the aforementioned superantigen assay. This was considered to be a pharmacological effect.
In the pivotal 6-month repeat-dose study (doses: 5, 15, and 50 mg/kg/week), adverse findings in high-dose animals resulted in treatment stop and early sacrifice of 7/12 animals after 6-7 weeks. Findings observed included persistent diarrhoea, decreased appetite, and weight loss and/or skin lesions. The surviving animals in this group were allocated to the recovery phase. Two animals in the low-dose group were either euthanised or found dead before the end of the study. This was not related to tremelimumab. No mortality occurred in the 1-month study.
In both studies, diarrhoea occurred in all treatment groups, including controls, but incidence and severity increased with dose and required supportive care in the high-dose group. Hence, the gastrointestinal tract is a target organ. Other targets were skin and liver. The investigators only recorded adverse skin lesions such as dry, cracked, scaly or crusted skin, or rash and enlarged lymph nodes in a dosing phase > 30 days. Treatment with tremelimumab also caused elevation of liver enzymes and an increase in organ weight in the 6-month study. Similar observations also occurred during clinical trials and are mentioned in the information for healthcare professionals.
Histology revealed mononuclear cell infiltration in multiple organs without a clear dose-response relationship in both studies. Mononuclear cell inflammation, defined as infiltration accompanied by necrosis, only occurred in the 6-month study – incidence and severity increased dose-dependently. Animals in both studies had lymphoid hyperplasia in spleen, mesenteric and axillary lymph nodes (6-month study only), and gut-associated lymphoid tissue (6-month study only), indicating that the lymphoid system is also a target organ. The NOAEL in the 1-month study was 5 mg/kg; there was no NOAEL in the 6-month study. The exposure at the highest non-severely toxic dose of 15 mg/kg was within the clinical exposure range, *i.e.* there is no safety margin.
In accordance with ICH S9 and S6(R1), the applicant did not perform genotoxicity or carcinogenicity studies with tremelimumab; this also applies to the conduct of fertility and peri/postnatal studies.
The investigators studied the potential impact on embryofoetal development in cynomolgus monkeys. The animals received up to 30 mg/kg tremelimumab IV on a weekly basis during gestation days 20 to 50. All dams, including controls, experienced diarrhoea. The number of affected days was higher in test item-treated animals, but there was no effect on body weight. Tremelimumab did not impact reproductive endpoints such as prenatal loss and foetal malformations or variations (safety margins 1.2 to 3.7).
Based on published literature, CTLA-4 activity is relevant for maintenance of pregnancy and embryofoetal development (EFD). The lack of effects of tremelimumab treatment in the EFD study in monkeys might be related to the lower affinity towards monkey CTLA-4. Therefore, use of tremelimumab during pregnancy is restricted. The applicant did not provide a stand-alone local tolerance study. This aspect was sufficiently addressed in the repeat-dose toxicity studies, revealing only mild injection site trauma.
In the tissue cross-reactivity studies with normal cynomolgus monkey and normal human tissues, the investigators identified a similar staining pattern between the species. Test item-reactive cells showed staining on the membrane and in the cytoplasm of lymphocytes.

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Combination toxicology studies with durvalumab were not conducted as this is not a requirement according to ICH S9.
The EMA requested the conduct of a nonclinical biomarker study in paediatric tumour tissue in the PIP. The analysis suggests that, due to relatively low levels of mutations and the limited degree of immunogenicity and immune activation, the use of checkpoint inhibitors such as tremelimumab will not result in significant activity in these tumours. This is based on a limited set of samples but, according to the applicant, is in line with experience in this setting.
Since tremelimumab is a monoclonal antibody, there is no risk for the environment.
The summary of the key findings from the nonclinical studies in the RMP is acceptable.

5.4 Nonclinical conclusions

The submitted pharmacology studies showed that tremelimumab binds human CTLA-4 with high affinity and potently blocks the interaction with endogenous ligands. No unexpected safety concerns were identified in a set of toxicity studies in a pharmacologically relevant animal species. From a nonclinical point of view, the application is approvable.

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6 Clinical aspects

6.1 Clinical pharmacology

ADME

Absorption

Both durvalumab and tremelimumab are administered as intravenous infusions.

Dose Proportionality

The final popPK models for both durvalumab and tremelimumab included a linear and a time-dependent clearance component. The change of clearance over time was not regarded as clinically relevant. Overall, the PK of both monoclonal antibodies was linear over the dose range included in the analyses.

Pharmacokinetics after multiple Dosing

Tremelimumab reached its steady state after three Q4W doses, i.e. after 12 weeks. Accumulation ratios of tremelimumab ranged from 0.861 to 1.69 and from 1.50 to 1.87 for C_{max} and C_{trough}, respectively, following administration of 1 to 10 mg/kg tremelimumab Q4W.

Distribution

The durvalumab and tremelimumab Vc in HCC patients was 3.45 L and 3.59 L, respectively.

Metabolism

No studies regarding the metabolism of tremelimumab have been conducted, considering the biological nature of the molecule.

Elimination

The durvalumab and tremelimumab clearance in HCC patients was 0.277 L/D and 0.295 L/D, respectively.

Special Populations

The pharmacokinetics of tremelimumab and durvalumab in HCC patients was described in two separate popPK analyses.

The pivotal HCC study was Study D419CC00002 (HIMALAYA). Additional data in HCC patients were collected in Study D4190C00022 (“Study 22”). These data were added to existing popPK datasets for both MABs including patients with other cancer types.

Durvalumab

The durvalumab popPK dataset included 4,050 cancer patients. Of these, 2,827 (69.8%) came from previous studies and 1,223 (30.2%) were HCC patients from Studies “22” and HIMALAYA. The overall age range of the patients in the dataset was 18 – 96 years (HIMALAYA: 18 – 86 years). The overall weight range was 31.0 – 175 kg (HIMALAYA: 38.5 – 140 kg). The dataset included 1,379 (34.0%) patients between 65 and 75 years of age (HIMALAYA: 327/35.2%) and 451 (11.1%) patients ≥ 75 years (HIMALAYA: 133 (14.3%).

The majority of the patients were male (70.4% overall, 82.4% HIMALAYA). In the overall dataset, the majority of the patients were White (60.9%). In the HIMALAYA dataset, the majority of the patients were Asians (51.7%). Both the overall and the HIMALAYA dataset included a relatively small number of anti-drug antibody (ADA) positive patients (3.33% overall, 2.59% HIMALAYA).

In the overall dataset, the majority of the patients (59.4%) received durvalumab alone, 32.5% durvalumab + tremelimumab or chemotherapy (Chemo) and 8.07% durvalumab + tremelimumab +

Chemo. In the HIMALAYA dataset, 41.8% of the patients received durvalumab alone and 58.2% durvalumab + tremelimumab or Chemo.

The overall dataset included a sufficient number of patients with mild, moderate or severe renal impairment, while only 3 patients with severe renal impairment were included in the HIMALAYA dataset. With regard to hepatic impairment, the overall dataset included only 1 patient with severe hepatic impairment, but a sufficient number of patients with mild or moderate hepatic impairment. This was also the case for the HIMALAYA dataset, which included no patients with severe hepatic impairment (National Cancer Institute (NCI) scale).

The final durvalumab popPK model was a two-compartment model with time-dependent clearance (same as the previous model). All covariate relationships included in the previous popPK model remained in the updated model. These were albumin, creatinine clearance, ECOG status, lactate dehydrogenase (LDH), sex, body weight and treatment combination as covariates of CL, as well as sex and body weight as covariates of V1. Newly added was tumour type (solid, lung, bladder, HCC) as covariate of CL. The model described the data reasonably well.

Serum albumin had the largest impact on durvalumab CL (21.6% ↑ at the 5^{th} percentile), followed by body weight (15.8% ↑ at the 95^{th} percentile compared to the reference patient). Body weight had the largest impact on durvalumab Vc (21.4% ↑ at the 95^{th} percentile).

The durvalumab AUC_{ss} was 28.1% lower in the HIMALAYA patients in the fourth weight quartile compared to the patients in the first weight quartile.

The effect of other covariates of clinical interest on durvalumab AUC in the HIMALAYA patients was comparable or less.

Tremelimumab

The tremelimumab popPK dataset included 2,406 cancer patients. Of these, 1,605 (66.7%) came from previous studies and 801 (33.3%) were HCC patients from Studies “22” and Himalaya. The overall age range of the patients in the dataset was 18 – 87 years (HIMALAYA: 18 – 86 years). The overall weight range was 34.0 – 149 kg (HIMALAYA: 40.5 – 140 kg. The dataset included 875 (36.4%) patients between 65 and 75 years of age (HIMALAYA: 197/36.5%) and 285 (11.8%) patients ≥ 75 years (HIMALAYA: 76 (14.1%).

The majority of the patients were male (71.6% overall, 82.0% HIMALAYA). In the overall dataset, the majority of the patients were White (61.7%). In the HIMALAYA dataset, the majority of the patients were Asians (50.1%). Both the overall and the HIMALAYA dataset included a relatively small number of ADA-positive patients (6.86% overall, 8.91% HIMALAYA).

In the overall dataset, the majority of the patients (65.5%) received tremelimumab + durvalumab, 20.9% tremelimumab alone and 13.5% tremelimumab + durvalumab + Chemo. In the HIMALAYA dataset, all patients received tremelimumab + durvalumab.

The overall dataset included a sufficient number of patients with mild, moderate or severe renal impairment, while only 3 patients with severe renal impairment were included in the HIMALAYA dataset. With regard to hepatic impairment, the overall dataset included no patients with severe hepatic impairment, but a sufficient number of patients with mild or moderate hepatic impairment. This was also the case for the HIMALAYA dataset (NCI scale).

The final tremelimumab popPK model was a two-compartment model with both linear and time-dependent clearance (same as the previous model). All covariate relationships included in the previous popPK model remained in the updated model. These were albumin, sex, body weight,

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primary indication and treatment combination as covariates of CL as well as sex and body weight as covariates of V1.
No other statistically significant covariate relationships were identified, i.e. the updated model was identical with the previous model. The model described the data reasonably well.

Serum albumin had the largest impact on tremelimumab CL (22% ↑ at the 5th percentile), followed by tumour type (14.6% ↓ in oesophageal carcinoma or biliary tract carcinoma compared to others) and body weight (14.7% ↑ at the 95th percentile compared to the reference patient). Body weight had the largest impact on tremelimumab Vc (18.1% ↑ at the 95th percentile).

The tremelimumab AUC_{ss} was 13.4% lower in the HIMALAYA patients on tremelimumab 300 + durvalumab in the fourth weight quartile compared to the patients in the first weight quartile.

The effect of other covariates of clinical interest on tremelimumab AUC in the HIMALAYA tremelimumab 300 + durvalumab patients was comparable or less. No dose adjustments are required from a pharmacokinetic point of view.

Interactions

No *in vitro* or clinical interaction studies have been conducted with tremelimumab, considering the biological nature of the molecule.

Pharmacodynamics

Relationship between Plasma Concentration and Effect – Efficacy

The exposure response (ER) analyses indicated a statistically significant relationship between durvalumab exposure and OS/PFS, with a minor contribution of tremelimumab in HCC patients. Nevertheless, the hazard ratio (HR) was in favour of the combination treatment compared to durvalumab alone.

Relationship between Plasma Concentration and Effect - Safety

None of the durvalumab or tremelimumab exposure measures reached statistical significance according to the pre-specified criteria in the logistic regression analyses. The estimated slopes were negative, indicating a decreasing probability to experience AEs with increasing durvalumab or tremelimumab exposures. This is likely to be an artifact due to the narrow available exposure range and/or treatment interruptions due to the occurrence of AEs.

6.2 Dose finding and dose recommendation

No adequate clinical dose-finding studies were implemented. The selected flat doses of tremelimumab and durvalumab in the pivotal HIMALAYA study were mainly based on PK data and PK simulations with data from early phase studies.

6.3 Efficacy

The applicant submitted one pivotal open-label phase 3 study, HIMALAYA, which evaluated the combination of tremelimumab 300 mg or 75 mg + durvalumab (T300+D or T75+D) in comparison to sorafenib (S) and durvalumab (D) monotherapy in the first-line setting with a data cut-off August 2021 for final analysis.

Patients were randomly assigned, using an interactive web response system (IWRS) in a 1:1:1:1 ratio, to each of 4 treatment arms: D, T300+D, T75+D, and S. Recruitment in the T75+D treatment

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arm was prematurely closed due to non-meaningful differentiation in terms of efficacy from D in study 22.

Relevant inclusion criteria were age ≥ 18 years, body weight > 30 kg, confirmed HCC (tumour tissue), no prior systemic therapy, ineligible for locoregional therapy for unresectable HCC, Barcelona Clinic Liver Cancer (BCLC) stage B or C, Child-Pugh class A and ECOG score 0-1.

The primary endpoint of this study was OS in patients treated with T300+D vs. S (superiority).

The control arm of sorafenib is acceptable because, at the time of study initiation, the currently preferred treatment option of immune checkpoint inhibitors combined with anti-angiogenesis agent bevacizumab was not approved for HCC.

The open-label design is acceptable with respect to the hard endpoint of OS, which is an adequate endpoint in patients with advanced HCC.

For further details regarding study design, dosing/administration and included patient population, please refer to the attached information for healthcare professionals (chapter 8, appendix).

Of 1950 patients enrolled in the study, 1324 were randomised to one of the four original treatment arms. The treatment arms were balanced in terms of demographic and baseline characteristics, for details see information for healthcare professionals.

After a median follow-up of 33 months, the HIMALAYA study met its primary efficacy endpoint OS at the time of the final OS analysis. Treatment with T300+D demonstrated a statistically significant improvement in OS compared with S (HR: 0.78; 95% CI: 0.66, 0.92; p = 0.0035). The KM estimates for median OS were 16.4 months in the T300+D arm and 13.8 months in the S arm, an estimated 2.7-month difference in median values. The OS rates after 36 months were 30.7% in the T300+D arm and 20.2% in the S arm. According to the ESMO-Magnitude of Clinical Benefit Scale (MCBS, form 2A) a HR of 0.78 and a difference in median values of 2.7 months is rated as grade 2 (negligible benefit). The increase in 3-year survival alone was ≥ 10%, corresponding to a MCBS grade 4 classification. However, after 24 months the Kaplan Meier curves are extensively censored, limiting the interpretation of the results. The OS difference after 24 months in the mature part of the curve was 7.9%.

The applicant submitted follow-up analyses of HIMALAYA with a data cut-off date of January 2023 (78% OS data maturity for T300+D). The OS results were comparable to those in the OS final analysis, with an increase in the 3-year survival rate of 10.9% in the T300+D arm.

6.4 Safety

The most common adverse events (≥ 10%) in patients with HCC treated with tremelimumab in combination with durvalumab (including data from the pivotal HIMALAYA study and the supportive study 22) are diarrhoea, rash, pruritus, cough, pyrexia, abdominal pain, hypothyroidism, and AST/ALT increased.

Relevant safety concerns are haemorrhagic adverse events and immune-mediated adverse events that are already known for durvalumab and adequately labelled in the information for healthcare professionals for tremelimumab.
In the pivotal HIMALAYA study, treatment with T300+D was associated with a higher rate of serious adverse events (SAEs) (41.2% vs. 29.7%), immune-mediated AEs (35.8% vs. 8%), and grade 5 possibly related AEs (2.3% vs. 0.8%) compared to sorafenib.

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The increased toxicity of T300+D compared to S was analysed in a recently published article by Rizzo et al. (2023)[1], which evaluated the safety (only treatment-related AEs) of T300+D and other therapies compared to sorafenib in patients with HCC. This analysis showed that T300+D (HIMALAYA) was associated with a higher frequency of grade 5 treatment-related adverse events (TRAEs) and serious TRAEs compared to the same control of sorafenib (odds ratios of 3.02 and 2.03, respectively).

In the submitted safety analyses, the addition of tremelimumab to durvalumab is associated with relevant toxicity. Comparing the T300+D HCC pool (n=462) with the D mono HCC pool (n=492) and the D mono pan-tumour pool (n=4045), grade 3-4, SAEs and grade 5 events were more common in the T300+D pool.
A meta-analysis by Fahmy et al. (2022)[2] compared the tolerability of combined durvalumab and tremelimumab versus durvalumab alone in solid cancers. This analysis concluded that combined durvalumab and tremelimumab was associated with a higher risk of treatment discontinuation, mortality, fever, diarrhoea, rash, pruritus, and reduced appetite compared to durvalumab monotherapy.

Toxicity in special patient populations
Overall, 404/3781 patients in the tremelimumab+durvalumab pan-tumour pool were ≥ 75 years. The rate of grade 5 AEs was higher in patients ≥ 75 years (11.1%) compared to patients aged ≥ 65 to < 75 years (7.6%) and < 65 years (5.7%).

6.5 Final clinical benefit risk assessment

Conclusions: Clinical
The HIMALAYA study showed a positive effect on OS in patients treated with T300+D vs. S (superiority). The safety concerns are adequately described in the information for healthcare professionals. In summary, the benefit risk assessment is positive.

Conclusions: Clinical Pharmacology
The durvalumab and tremelimumab PK did not raise any concerns. No dose adjustments for covariates are required from a pharmacokinetic point of view.

The ER analyses, including all relevant treatment arms of the HIMALAYA study, indicated statistically significant relationships between durvalumab or tremelimumab exposures and efficacy endpoints in both indications. The contribution of durvalumab or tremelimumab to efficacy appeared to be variable, but the hazard ratios derived from the final Cox proportional hazard models were always in favour of the durvalumab+ tremelimumab treatment combination.
There was no statistically significant relationship between durvalumab or tremelimumab exposures and the probability of experiencing AEs in the ER analyses.

[1] Rizzo et al. Treatment-related adverse events of first-line immunotherapy versus sorafenib for advanced hepatocellular carcinoma: a meta-analysis. Expert Opin Drug Saf. 2023 Apr;22(4):323-329.
[2] Fahmy et al. Adverse Events and Tolerability of Combined Durvalumab and Tremelimumab versus Durvalumab Alone in Solid Cancers: A Systematic Review and Meta-Analysis. Biomedicines. 2022 May 10;10(5):1101

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7 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

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8 Appendix

Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Imjudo was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

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▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

IMJUDO®

Composition

Active substances

Tremelimumab (manufactured using recombinant DNA technology in murine myeloma cells).

Excipients

L-histidine, L-histidine hydrochloride monohydrate, α,α-Trehalose dihydrate, Disodium edetate dihydrate, Polysorbate 80, Water for Injection
Each vial contains 0.012 mg sodium/1.25 ml or 0.185 mg sodium /15 ml.

Pharmaceutical form and active substance quantity per unit

Concentrate for solution for infusion; 20 mg/mL in a single-dose vial for intravenous administration.
Each vial of 1.25 mL contains 25 mg of tremelimumab.
Each vial of 15 mL contains 300 mg of tremelimumab.
Sterile, preservative-free, clear to slightly opalescent, colourless to slightly yellow solution, free from or practically free from visible particles.

Indications/Uses

Hepatocellular Carcinoma (HCC)
IMJUDO in combination with durvalumab is indicated for the treatment of patients with unresectable hepatocellular carcinoma (uHCC), who have not received prior systemic therapy (see “Clinical efficacy”).

Dosage/Administration

Treatment must be initiated and supervised by a physician experienced in the treatment of cancer.
To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

Usual dosage

The recommended dose of IMJUDO is presented in Table 1.
IMJUDO is administered as an intravenous infusion over 1 hour.

Table 1: Recommended dosage of IMJUDO

Indication	Recommended IMJUDO dosage	Duration of Therapy
uHCC	Patients with a body weight ≥ 30 kg IMJUDO 300 mg is administered as a single dose in combination with durvalumab 1500 mg[a] in cycle 1 day 1, followed by durvalumab monotherapy (1500 mg) every 4 weeks. Patients with a body weight < 30 kg IMJUDO is administered as weight-based dosing, equivalent to IMJUDO 4 mg/kg and durvalumab 20 mg/kg, given in cycle 1 day 1, followed by durvalumab monotherapy (20 mg/kg) every 4 weeks until weight is greater than 30 kg.	Durvalumab should be given until disease progression or unacceptable toxicity

[a] Administer IMJUDO prior to durvalumab on the same day. Refer to the Prescribing Information for durvalumab dosing information.

Dose adjustment following undesirable effects/interactions

No durvalumab dose reduction for treatment is recommended. In general, withhold treatment regimen for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue treatment regimen for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating corticosteroids.

For suspected immune-mediated adverse reactions, adequate evaluation should be performed to confirm etiology or exclude alternate etiologies.

For non-immune-mediated adverse reactions, withhold durvalumab for Grade 2 and 3 adverse reactions until ≤ Grade 1 or return to baseline. Durvalumab should be discontinued for Grade 4 adverse reactions

Recommended treatment modifications are summarized in Table 2. Refer to section “Warnings and precautions” for further monitoring and evaluation information.

Table 2. Treatment modifications and management recommendations for immune-mediated undesirable effects**

Adverse Reactions	**Severity**[a]	**Treatment Modification**	**Corticosteroid Treatment Unless Otherwise Specified**[b]
Immune-mediated pneumonitis/interstitial lung disease	Grade 2	Withhold dose[c]	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 or 4	Permanently discontinue	
Immune-mediated hepatitis without tumour involvement of the liver	ALT or AST > 3 ≤ 5 x ULN or total bilirubin > 1.5 ≤ 3 x ULN	Withhold dose[c]	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	ALT or AST > 5- ≤ 10 x ULN	Withhold dose[c]	
	Concurrent ALT or AST > 3 x ULN and total bilirubin > 2 x ULN[d]	Permanently discontinue	
Immune-mediated hepatitis in HCC (or secondary tumour involvement of the liver with abnormal baseline values)[e,]	ALT or AST > 2.5- ≤ 5 x BLV and ≤ 20 x ULN	Withhold dose[c]	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	ALT or AST >5-7 x BLV and ≤ 20 x ULN OR concurrent 2.5- 5 x BLV and ≤ 20 x ULN AND total bilirubin > 1.5 - < 2 x ULN[d]	Withhold dose[c]	
	ALT or AST > 7 x BLV OR >	Permanently discontinue	

Adverse Reactions	Severity[a]	Treatment Modification	Corticosteroid Treatment Unless Otherwise Specified[b]
	20 ULN whichever occurs first OR bilirubin > 3 x ULN		
Immune-mediated colitis or diarrhoea	Grade 2	Withhold dose[c]	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 or 4	Permanently discontinue	
	Intestinal perforation of ANY grade	Permanently discontinue	Consult a surgeon immediately if an intestinal perforation is suspected
Immune-mediated hyperthyroidism, thyroiditis	Grade 2-4	Withhold dose until clinically stable	Symptomatic management
Immune-mediated hypothyroidism	Grade 2-4	No changes	Initiate thyroid hormone replacement as clinically indicated
Immune-mediated adrenal insufficiency, hypophysitis/hypopituitarism	Grade 2-4	Withhold dose until clinically stable	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper and hormone replacement as clinically indicated
Immune-mediated Type 1 diabetes mellitus	Grade 2-4	Withhold dose until clinically stable	Initiate treatment with insulin as clinically indicated
Immune-mediated nephritis	Grade 2 with serum creatinine > 1.5-3 x (ULN or baseline)	Withhold dose[c]	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper

Adverse Reactions	Severity[a]	Treatment Modification	Corticosteroid Treatment Unless Otherwise Specified[b]
	Grade 3 with serum creatinine > 3 x baseline or > 3-6 x ULN; Grade 4 with serum creatinine > 6 x ULN	Permanently discontinue	
Immune-mediated rash or dermatitis (including pemphigoid)	Grade 2 for > 1 week or Grade 3 or suspected SJS, TEN, or DRESS	Withhold dose[c]	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 4 or confirmed SJS, TEN, or DRESS	Permanently discontinue	
Immune-mediated myocarditis	Grade 2-4	Permanently discontinue	Initiate 2 to 4 mg/kg/day prednisone or equivalent followed by a taper[f]
Immune-mediated myositis/polymyositis	Grade 2 or 3	Withhold dose[c,g]	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 4	Permanently discontinue	
Infusion-related reactions	Grade 1 or 2	Interrupt or slow the rate of infusion	May consider pre-medications for prophylaxis of subsequent infusion reactions
	Grade 3 or 4	Permanently discontinue	Manage severe infusion-related reactions per clinical practice
Immune-mediated myasthenia gravis	Grade 2-4	Permanently discontinue	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper

Adverse Reactions	Severity[a]	Treatment Modification	Corticosteroid Treatment Unless Otherwise Specified[b]
Immune-mediated encephalitis	Grade 2-4	Permanently discontinue	Initiate 1 mg/kg/day to 2 mg/kg/day prednisone or equivalent followed by a taper
Immune-mediated transverse myelitis	All grades	Permanently discontinue	Initiate 1 mg/kg/day to 2 mg/kg/day prednisone or equivalent followed by a taper
@Other immune-mediated adverse reactions[h]	Grade 2 or 3	Withhold dose[c]	Initiate 1 mg/kg/day to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 4	Permanently discontinue	

[*] Since IMJUDO is given as a single dose in combination with durvalumab, dose modifications are applicable to durvalumab only.

[a] Common Terminology Criteria for Adverse Events, version 4.03. ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal.

[b] Upon improvement to ≤ Grade 1, corticosteroid taper should be initiated and continued over at least 1 month. Consider increasing dose of corticosteroids and/or using additional systemic immunosuppressants if there is worsening or no improvement.

[c] Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or an inability to reduce corticosteroid dose to 10 mg of prednisone or less per day (or equivalent) within 12 weeks of initiating corticosteroids.

[d] For patients with alternative cause follow the recommendations for AST or ALT increases without concurrent bilirubin elevations.

[e] If AST and ALT are less than or equal to ULN at baseline in patients with liver involvement, withhold or permanently discontinue durvalumab based on recommendations for hepatitis with no liver involvement.

[f] If no improvement within 2 to 3 days despite corticosteroids, promptly start additional immunosuppressive therapy. Upon resolution (Grade 0), corticosteroid taper should be initiated and continued over at least 1 month.

[g] Permanently discontinue IMJUDO and durvalumab if the adverse reaction does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory insufficiency.

[h] Includes immune thrombocytopenia and pancreatitis.

Special patient groups

Based on a population pharmacokinetic analysis, no dose adjustment of IMJUDO is recommended based on patient age, body weight, gender and race (see section “Pharmacokinetics”).

Children and adolescents

The safety and efficacy in children and adolescents have not been demonstrated.

Elderly patients

No dose adjustment is required for elderly patients (≥ 65 years of age) (see sections “Pharmacokinetics” and “Properties/Effects”). Data on patients aged 75 years of age or older are limited. Of the 462 patients with uHCC treated with IMJUDO in combination with durvalumab, 236 patients were 65 years or older and 63 patients were 75 years or older (see section “Warnings and precautions”). Increased mortality was observed in patients ≥ 75 years (see section "Warnings and precautions").

Patients with renal disorders

Based on a population pharmacokinetic analysis, no dose adjustment of IMJUDO is recommended in patients with renal impairment. IMJUDO has not been studied in patients with severe renal impairment (see section “Properties/Effects”).

Patients with hepatic disorders

Based on a population pharmacokinetic analysis, no dose adjustment of IMJUDO is recommended for patients with mild or moderate hepatic impairment. IMJUDO has not been studied in patients with severe hepatic impairment (see section “Properties/Effects”).

Mode of administration

IMJUDO is for intravenous use.
For uHCC, administer IMJUDO prior to durvalumab on the same day. IMJUDO and durvalumab are administered as separate intravenous infusions. Refer to the Prescribing Information for durvalumab administration information.
For instructions on dilution of the medicinal product before administration, see section “Other information”.

Contraindications

Hypersensitivity to the active substance or to any of the excipients according to composition.

Warnings and precautions

IMJUDO is a monoclonal antibody that blocks T-cell inhibitory signals induced by the CTLA-4 pathway, thereby removing inhibition of the immune response. In combination with durvalumab, a PD-L1 inhibitor, these drugs have the potential for induction of immune-mediated adverse reactions. Immune-mediated adverse reactions listed herein may not be inclusive of all possible severe and fatal immune-mediated reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. Immune-mediated adverse reactions can occur at any time after starting IMJUDO in combination with durvalumab. While immune-mediated adverse reactions usually manifest during treatment, immune-mediated adverse reactions can also manifest after discontinuation of IMJUDO and/or durvalumab.

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of IMJUDO in combination with durvalumab. Monitor for signs and symptoms that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate clinical chemistries including liver enzymes, creatinine, adrenocorticotropic hormone (ACTH) level, and thyroid function at baseline and before each dose. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue treatment depending on severity (see section “Dosage/Administration”). In general, if combination of IMJUDO and durvalumab requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy.

Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (e.g., endocrinopathies and dermatologic reactions) are discussed below.

Refer to section “Dosage/Administration”, Table 2 for recommended treatment modifications and management of immune-mediated adverse reactions.

Immune-Mediated Pneumonitis

Immune-mediated pneumonitis or interstitial lung disease, including such with fatal outcome, defined as requiring use of systemic corticosteroids and with no clear alternate etiology, occurred in patients receiving IMJUDO in combination with durvalumab (see section “Undesirable effects”). Patients should be monitored for signs and symptoms of pneumonitis. Suspected pneumonitis should be confirmed with radiographic imaging and other infectious and disease-related etiologies excluded, and managed as recommended in section “Dosage/Administration”.

Pneumonitis

Patients should be monitored for signs and symptoms of pneumonitis. Suspected pneumonitis should be confirmed with radiographic imaging and other infectious and disease-related aetiologies excluded, and managed as recommended in section “Dosage/Administration”.

Immune-mediated hepatitis

Immune-mediated hepatitis, including such with fatal outcome, defined as requiring use of systemic corticosteroids and with no clear alternate etiology, occurred in patients receiving IMJUDO in

combination with durvalumab (see section “Undesirable effects”). Patients should be monitored for abnormal liver tests prior to and periodically during treatment. Immune-mediated hepatitis should be managed as recommended in section “Dosage/Administration”.

Immune-mediated colitis

Immune-mediated colitis or diarrhoea, defined as requiring use of systemic corticosteroids and with no clear alternate etiology, occurred in patients receiving IMJUDO in combination with durvalumab (see section “Undesirable effects”). Intestinal perforation and large intestine perforation were reported in patients receiving IMJUDO in combination with durvalumab. Patients should be monitored for signs and symptoms of colitis/diarrhoea and intestinal perforation and managed as recommended in section “Dosage/Administration”.

Immune-mediated endocrinopathies

Immune-mediated hypothyroidism/hyperthyroidism/thyroiditis

IMJUDO in combination with durvalumab can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement therapy for hypothyroidism or institute medical management of hyperthyroidism as clinically indicated.
Immune-mediated hypothyroidism, hyperthyroidism or thyroiditis have occurred in patients receiving IMJUDO in combination with durvalumab (see section “Undesirable effects”). Patients should be monitored for abnormal thyroid function tests prior to and periodically during treatment and managed as recommended in section “Dosage/Administration”.

Immune-mediated adrenal insufficiency

Immune-mediated adrenal insufficiency occurred in patients receiving IMJUDO in combination with durvalumab (see section “Undesirable effects”). Patients should be monitored for clinical signs and symptoms of adrenal insufficiency and managed as recommended in section “Dosage/Administration”.

Immune-mediated type 1 diabetes mellitus

Immune-mediated type 1 diabetes mellitus, which can present with diabetic ketoacidosis, occurred in patients receiving IMJUDO in combination with durvalumab (see section “Undesirable effects”). Patients should be monitored for clinical signs and symptoms of type 1 diabetes mellitus and managed as recommended in section “Dosage/Administration”.

Immune-mediated hypophysitis/hypopituitarism

IMJUDO in combination with durvalumab can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or

visual field cuts. Hypophysitis can cause hypopituitarism. Initiate symptomatic treatment including hormone replacement as clinically indicated.
Immune-mediated hypophysitis or hypopituitarism occurred in patients receiving IMJUDO in combination with durvalumab (see section “Undesirable effects”). Patients should be monitored for clinical signs and symptoms of hypophysitis or hypopituitarism and managed as recommended in section “Dosage/Administration”.

Immune-mediated nephritis

Immune-mediated nephritis, defined as requiring use of systemic corticosteroids and with no clear alternate etiology, occurred in patients receiving IMJUDO in combination with durvalumab (see section “Undesirable effects”). Patients should be monitored for abnormal renal function tests prior to and periodically during treatment and managed as recommended in section “Dosage/Administration”.

Immune-mediated rash

IMJUDO in combination with durvalumab can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens Johnson Syndrome (SJS), drug rash with eosinophilia and systemic symptoms (DRESS), and toxic epidermal necrolysis (TEN), has occurred with CTLA-4 and PD-1/L-1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold or permanently discontinue treatment depending on severity (see section “Dosage/Administration).
Immune-mediated rash or dermatitis (including pemphigoid), defined as requiring use of systemic corticosteroids and with no clear alternate etiology, occurred in patients receiving IMJUDO in combination with durvalumab (see section “Undesirable effects”). Patients should be monitored for signs and symptoms of rash or dermatitis and managed as recommended in section “Dosage/Administration”.

Immune-mediated myocarditis

Immune-mediated myocarditis, which can be fatal, occurred in patients receiving IMJUDO in combination with durvalumab (see section “Undesirable effects”). Patients should be monitored for signs and symptoms of immune-mediated myocarditis and managed as recommended in section “Dosage/Administration”.

Immune-mediated haemophagocytic lymphohistiocytosis (HLH)

HLH has occurred in patients treated with IMJUDO in combination with durvalumab. HLH is a potentially life-threatening syndrome with pathological activation of the immune system. Without early recognition and treatment, HLH is commonly fatal. The condition is characterised by clinical signs and symptoms of severe systemic inflammation such as fever, skin rash, hepatosplenomegaly, cytopenia (in particular anaemia and thrombocytopenia), lymphadenopathy, neurological symptoms, high serum ferritin, hypertriglyceridemia, and impaired hepatic function and coagulation. Patients who experience

such signs and symptoms must be examined immediately and assessed for a possible diagnosis of HLH. Treatment should be withheld while no alternative etiology can be established.

Immune-mediated pancreatitis

IMJUDO in combination with durvalumab can cause immune-mediated pancreatitis.

Other immune-mediated adverse reactions

Given the mechanism of action of IMJUDO and durvalumab, other potential immune-mediated adverse reactions may occur in patients receiving the combination of IMJUDO with durvalumab. The following clinically significant, immune-mediated adverse reactions occurred at an incidence of less than 1% each in patients who received IMJUDO in combination with durvalumab or were reported with the use of other immune-checkpoint inhibitors.
Nervous system: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy. Patients should be monitored for signs and symptoms suggestive of myelitis.
Ocular: Uveitis, iritis, and other ocular inflammatory toxicities can occur. Some cases can be associated with retinal detachment. Various grades of visual impairment to include blindness can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Haradalike syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss.
The following immune-mediated adverse reactions have been observed: pericarditis, vasculitis, myositis, polymyositis and immune thrombocytopenia (see section “Undesirable effects”). Patients should be monitored for signs and symptoms and managed as recommended in section “Dosage/Administration”.

Infusion-related reactions

Severe or life-threatening infusion-related reactions have been observed under treatment with immune-checkpoint inhibitors. Patients should be monitored for signs and symptoms of infusion-related reactions and managed as recommended in section “Dosage/Administration”. See also section “Undesirable effects”.

Cerebrovascular accidents

Cerebrovascular accidents (CVA), including cerebrovascular hemorrhagic and ischemic events, including such with fatal outcome, were observed with tremelimumab treatment in combination with durvalumab. Patients treated with IMJUDO in combination with durvalumab must be monitored for signs and symptoms of cerebrovascular accidents.

Elderly patients

Data in patients >75 is limited in the IMJUDO + durvalumab pool (n=404/3781). Of the patients treated with IMJUDO in combination with durvalumab (n=3781), 45.1% (n=1703) of patients were 65 years or older and 10.7% (n=404) of patients were 75 years or older. The frequency of death in patients ≥ 75 years was 11.1%, in patients ≥ 65 and < 75 years 7.6%, and in patients < 65 years 5.7%.

Adverse reactions in transplant recipients

In patients treated with PD-1 / PD-L1 -inhibitors, solid organ transplant rejection has been observed in the postmarketing setting. In these patients, the benefit of treatment with PD-1/PD-L1 inhibitors, including durvalumab, should be weighed against the risk of possible organ rejection.

Patient populations not investigated in clinical trials

Patients with the following were excluded from the HIMALAYA study: Child-Pugh Score B or C, main portal vein thrombosis, liver transplant, uncontrolled hypertension, history of, or current brain metastases, spinal cord compression, co-infection of viral hepatitis B and hepatitis C, active or prior documented gastrointestinal (GI) bleeding within 12 months, ascites requiring non pharmacologic intervention within 6 months, hepatic encephalopathy within 12 months before the start of treatment, active or prior documented autoimmune or inflammatory disorders.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per film-vial i.e. it is almost «sodium free».

Interactions

Tremelimumab is an immunoglobulin and the primary elimination pathways of tremelimumab are protein catabolism via reticuloendothelial system or target-mediated disposition; therefore, no formal pharmacokinetic (PK) drug-drug interaction studies have been conducted with tremelimumab since no metabolic drug-drug interactions are expected. PK drug-drug interaction between tremelimumab in combination with durvalumab and platinum-based chemotherapy was assessed in the POSEIDON study, and no clinically meaningful PK drug-drug interaction was identified. PK drug-drug interaction between tremelimumab in combination with durvalumab was assessed in the HIMALAYA study and no clinically meaningful PK drug-drug interaction was identified.

Pregnancy, lactation

Pregnancy

There are no data on the use of tremelimumab in pregnant women. Reproduction studies in animals were not associated with maternal toxicity or any effects on pregnancy maintenance of embryofetal development (see section “Preclinical data”). Based on its mechanism of action, tremelimumab has

the potential to impact pregnancy maintenance and may cause foetal harm when administered to a pregnant woman. Human IgG2 is known to cross the placental barrier. Tremelimumab should not be used during pregnancy and in women of childbearing potential not using effective contraception during treatment and for at least 3 months after the last dose, unless treatment with tremelimumab is required due to the woman's clinical condition.'

Lactation

There is no information regarding the presence of tremelimumab in human milk, the absorption and effects on the breastfed infant, or the effects on milk production. Human IgG2 is excreted in human milk. Because of the potential for adverse reactions from tremelimumab in breastfed infants, lactating women are advised not to breastfeed during treatment and for at least 3 months after the last dose.

Fertility

There are no data on the potential effects of tremelimumab on fertility in humans.

Effects on ability to drive and use machines

Based on its pharmacodynamic properties, tremelimumab is unlikely to affect the ability to drive and use machines. However, if patients experience adverse reactions affecting their ability to concentrate and react, such as fatigue (see section “Undesirable effects”), they should be advised to use caution when driving or operating machinery.

Undesirable effects

Summary of the safety profile

The safety of IMJUDO in combination with durvalumab is based on data in 462 patients from the HIMALAYA study and Study 22 (uHCC, HCC pool) and 3319 patients treated with other experimental combinations using different dosages. The most frequent adverse reactions were diarrhoea (23.7%), rash (22.6%), pruritus (19.6%), cough/productive cough (15.5%), pyrexia (14.8%), abdominal pain (14.1%), hypothyroidism (12.6%) and aspartate aminotransferase increased/alanine aminotransferase increased (11.3%).

Tabulated list of adverse reactions

Table 3 lists the incidence of adverse reactions (ADRs) in patients treated with IMJUDO in combination with durvalumab in the HCC pool and in other experimental combinations using different dosages. Adverse drug reactions are listed according to system organ class in MedDRA. Within each system organ class, the adverse drug reactions are presented in decreasing frequency. In addition, the corresponding frequency category for each ADR is based on the CIOMS III convention and is defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1’000 to < 1/100); rare (≥ 1/10’000 to < 1/1000); very rare (< 1/10’000); "not known" (frequency cannot be estimated from the available data).

Table 3. Adverse drug reactions in patients treated with IMJUDO in combination with durvalumab (HCC pool (n=462) and other experimental combinations using different dosages (n=3319)

Adverse drug reaction (Frequency of any grade) [Frequency of max. Grade 3-4]	
Blood and Lymphatic System Disorders	
Unknown	Immune thrombocytopenia[a]
Cardiac disorders	
Uncommon	Myocarditis[b,u] (0.1%) [<0.1%]
Endocrine disorders	
Very common	Hypothyroidism[c] (12.6%) [0.2%]
Common	Hyperthyroidism[d] (7.6%) [0.3%]
	Adrenal insufficiency (1.5%) [0.6%]
	Thyroiditis (1.1%)[e] [<0.1%]
Uncommon	Hypopituitarism/ Hypophysitis (0.9%) [0.4%]
	Type 1 diabetes mellitus[a] (0.2%) [<0.1%]
Rare	Diabetes insipidus[a] (<0.1%)
Gastrointestinal disorders	
Very common	Diarrhoea[u] (23.7%) [2.9%]
	Abdominal pain[f] (14.1%) [1.7%]
Common	Lipase increased (6.8%) [4.7%]
	Amylase increased (5.8%) [2.6%]
	Colitis[g] (3.7%) [1.9%]
Uncommon	Pancreatitis[h,u] (0.9%) [0.4%]
	Large intestine perforation[a,u] (0.1%) [<0.1%]
Rare	Intestinal perforation[a,u] (<0.1%) [<0.1%]
General disorders and administration site conditions	
Very common	Pyrexia (14.8%) [0.5%]
Common	Oedema peripheral[i] (9.4%) [0.3%]
Hepatobiliary disorders	
Very common	Aspartate aminotransferase increased/Alanine aminotransferase increased[j] (11.3%) [3.8%]
Common	Hepatitis[k,u] (2.4%) [1.4%]
Infections and infestations	
Common	Upper respiratory tract infections[l,u] (9.3%) [0.2%]
	Pneumonia[m,u] (8.6%) [4.2%]
	Oral candidiasis (1.9%) [<0.1%]
	Influenza (1.3%) [0.2%]
Uncommon	Dental and oral soft tissue infections[n] (0.9%) [<0.1%]

Injury, poisoning and procedural complications	
Common	Infusion-related reaction[o] (1.7%) [<0.1%]
Musculoskeletal and connective tissue disorders	
Common	Myalgia (3.8%) [0.1%]
Uncommon	Myositis (0.2%) [0.1%]
Rare	Polymyositis (<0.1%) [<0.1%]
	Traverse myelitis
Nervous system disorders	
Uncommon	Myasthenia gravis[u] (0.1%) [<0.1%]
Rare	Encephalitis[a,p] (<0.1%)
Renal and urinary disorders	
Common	Blood creatinine increased (3.7%) [0.2%]
	Dysuria (1.4%)
Uncommon	Nephritis[q] (0.4%) [0.1%]
Respiratory, thoracic and mediastinal disorders	
Very common	Cough/Productive cough (15.5%) [0.2%]
Common	Pneumonitis[r] (3.9%) [1.0%]
	Dysphonia (1.8%) [<0.1%]
Uncommon	Interstitial lung disease[u] (0.8%) [0.2%]
Skin and subcutaneous tissue disorders	
Very common	Rash[s] (22.6%) [1.2%]
	Pruritus (19.6%) [0.3%]
Common	Night sweats (1.3%)
Uncommon	Dermatitis[t] (0.8%) [<0.1%]
	Pemphigoid (0.3%) [<0.1%]

[a] Adverse reaction was not observed in the HCC pool, but was reported in patients treated with IMJUDO and durvalumab in other experimental combinations using different dosages.
[b] Includes autoimmune myocarditis.
[c] Includes blood thyroid stimulating hormone increased and hypothyroidism.
[d] Includes blood thyroid stimulating hormone decreased and hyperthyroidism.
[e] Includes autoimmune thyroiditis, immune-mediated thyroiditis, thyroiditis and thyroiditis subacute.
[f] Includes abdominal pain, abdominal pain lower, abdominal pain upper and flank pain.
[g] Includes colitis, enteritis and enterocolitis.
[h] Includes pancreatitis and pancreatitis acute.
[i] Includes oedema peripheral and peripheral swelling.
[j] Includes alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased and transaminases increased.
[k] Includes autoimmune hepatitis, hepatitis, hepatocellular injury, hepatotoxicity and immune-mediated hepatitis.
[l] Includes nasopharyngitis, pharyngitis, rhinitis, tracheobronchitis and upper respiratory tract infection.
[m] Includes pneumocystis jirovecii pneumonia and pneumonia.
[n] Includes periodontitis, pulpitis dental, tooth abscess and tooth infection.

[o] Includes infusion-related reaction and urticaria.
[p] Includes encephalitis and encephalitis autoimmune.
[q] Includes autoimmune nephritis and immune-mediated nephritis.
[r] Includes immune-mediated pneumonitis and pneumonitis.
[s] Includes eczema, erythema, rash, rash macular, rash maculo-papular, rash papular and rash pruritic.
[t] Includes dermatitis and immune-mediated dermatitis.
[u] Includes fatal outcomes

Description of specific adverse reactions and additional information

The data below reflects information from adverse reactions for IMJUDO in combination with durvalumab (n = 3781) including in patients with HCC (HCC pool, n = 462) and patients who received other experimental combinations using different dosages (D+T Pan-tumor pool, n = 3319).The management guidelines for these adverse reactions are described in sections "Dosage/Administration" and "Warnings and precautions".

Immune-mediated pneumonitis

In patients receiving IMJUDO in combination with durvalumab, immune-mediated pneumonitis occurred in 131 (3.5%) patients, including Grade 3 in 39 (1.0%) patients, Grade 4 in 7 (0.2%) patients and Grade 5 in 11 (0.3%) patients. All patients received systemic corticosteroids, and 115 of the 131 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Eleven patients also received other immunosuppressants. Treatment was discontinued in 62 patients. Resolution occurred in 73 patients.

Immune-mediated hepatitis

In patients receiving IMJUDO in combination with durvalumab, immune-mediated hepatitis occurred in 164 (4.3%) patients, including Grade 3 in 99 (2.6%) patients, Grade 4 in 16 (0.4%) patients and Grade 5 in 5 (0.1%) patients. All patients received systemic corticosteroids, and 145 of the 164 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Twenty-six patients also received other immunosuppressants. Treatment was discontinued in 56 patients. Resolution occurred in 94 patients.

Immune-mediated colitis

In patients receiving IMJUDO in combination with durvalumab, immune-mediated colitis or diarrhoea occurred in 284 (7.5%) patients, including Grade 3 in 125 (3.3%) patients and Grade 4 in 3 (< 0.1%) patients. All patients received systemic corticosteroids, and 258 of the 284 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Thirty-three patients also received other immunosuppressants. Treatment was discontinued in 87 patients. Resolution occurred in 236 patients.
Intestinal perforation was observed in one patient receiving IMJUDO in combination with durvalumab.

Immune-mediated intestinal perforation

In patients receiving IMJUDO in combination with durvalumab, immune-mediated intestinal perforation occurred in 1 (<0.1%) patient (Grade 4). The patient received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Treatment was discontinued in this patient and the event resolved.

Immune-mediated endocrinopathies

Immune-mediated hypothyroidism

In patients receiving IMJUDO in combination with durvalumab, immune-mediated hypothyroidism occurred in 369 (9.8%) patients, including Grade 3 in 10 (0.3%) patients. Twenty patients received systemic corticosteroids, and 13 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Three-hundred-sixty-four patients required other therapy (endocrine therapy, thiamazole, carbimazole, propylthiouracil, perchlorate, calcium channel blocker, or beta-blocker). Resolution occurred in 82 patients. Immune-mediated hypothyroidism was preceded by immune-mediated hyperthyroidism in 287 patients.

Immune-mediated hyperthyroidism

In patients receiving IMJUDO in combination with durvalumab, immune-mediated hyperthyroidism occurred in 107 (2.8%) patients, including Grade 3 in 8 (0.2%) patients. Thirty-one patients received systemic corticosteroids, and 22 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Ninety-three patients required endocrine therapy (thiamazole, carbimazole, propylthiouracil, perchlorate, calcium channel blocker, or beta-blocker). Three patients discontinued treatment due to hyperthyroidism. Resolution occurred in 81patients.

Immune-mediated thyroiditis

In patients receiving IMJUDO in combination with durvalumab, immune-mediated thyroiditis occurred in 26 (0.7%) patients, including Grade 3 in 2 (<0.1%) patients. Ten patients received systemic corticosteroids, and 6 of the 10 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Twenty-four of the patients required endocrine therapy including hormone replacement therapy, thiamazole, carbimazole, propylthiouracil, perchlorate, calcium channel blocker, or beta-blocker. Treatment was discontinued in 1 patient. Resolution occurred in 8 patients.

Immune-mediated adrenal insufficiency

In patients receiving IMJUDO in combination with durvalumab, immune-mediated adrenal insufficiency occurred in 59 (1.6%) patients, including Grade 3 in 25 (0.7%) patients and Grade 4 in 2 (< 0.1%) patients. Fifty-eight patients received systemic corticosteroids, and 19 of the 58 patients

received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Treatment was discontinued in 2 patients. Resolution occurred in 18 patients.

Immune-mediated type 1 diabetes mellitus

In patients receiving IMJUDO in combination with durvalumab, immune-mediated type 1 diabetes mellitus was observed in 8 (0.2%) patients, including Grade 3 in 2 (<0.1%) patients and Grade 4 in 2 (<0.1%) patients. All patients required endocrine therapy. Treatment was discontinued in one patient. Resolution occurred in one patient.

Immune-mediated hypophysitis/hypopituitarism

In patients receiving IMJUDO in combination with durvalumab, immune-mediated hypophysitis/hypopituitarism occurred in 37 (1.0%) patients, including Grade 3 in 15 (0.4%) patients. Thirty-five patients received systemic corticosteroids, and 17 of the 35 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Eleven patients also required endocrine therapy. Treatment was discontinued in 6 patients. Resolution occurred in 14 patients.

Immune-mediated nephritis

In patients receiving IMJUDO in combination with durvalumab, immune-mediated nephritis occurred in 23 (0.6%) patients, including Grade 3 in 4 (0.1%) patients. All patients received systemic corticosteroids, and 17 of the 23 received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Treatment was discontinued in 8 patients. Resolution occurred in 15 patients.

Immune-mediated rash

In patients receiving IMJUDO in combination with durvalumab, immune-mediated rash or dermatitis (including pemphigoid) occurred in 182 (4.8%) patients, including Grade 3 in 38 (1.0%) patients and Grade 4 in 1 (<0.1%) patient. All patients received systemic corticosteroids and 93 of the 182 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). One patient received other immunosuppressants. Treatment was discontinued in 14 patients. Resolution occurred in 114 patients.

Infusion-related reactions

In patients receiving IMJUDO in combination with durvalumab, infusion-related reactions occurred in 64 (1.7%) patients.

Immune-mediated pancreatitis

In patients receiving IMJUDO in combination with durvalumab, immune-mediated pancreatitis occurred in 67 (1.8%) patients, including Grade 3 in 31 (0.8%) patients and Grade 4 in 18 (0.5%) patient. All patients received systemic corticosteroids, and 54 patients received high-dose

corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Treatment was discontinued in 10 patients. Resolution occurred in 54 patients.

Immune-mediated myocarditis

In patients receiving IMJUDO in combination with durvalumab, immune-mediated *myocarditis* occurred in 3 (<0.1%) patients, including Grade 4 in 1 (<0.1%) patient and Grade 5 in 1 (<0.1%) patient. All 3 patients received systemic corticosteroids, and all 3 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). One patient received other immunosuppressants. Two patients discontinued treatment. Resolution occurred in 1 patient.

Immune-mediated myasthenia gravis

In patients receiving IMJUDO in combination with durvalumab, immune-mediated myasthenia gravis occurred in 4 (0.1%) patients, including Grade 3 in 1 (<0.1%) patient and Grade 5 in 1 (<0.1%) patient. All patients received systemic corticosteroids, and 3 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Treatment was discontinued in 1 patient. Resolution occurred in 1 patient.

Immune-mediated Guillain-Barre syndrome

In patients receiving IMJUDO in combination with durvalumab, immune-mediated Guillain-Barre syndrome occurred in 1 (<0.1%) patient. The patient received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). The patient discontinued the treatment and resolution occurred.

Immune-mediated myositis

In patients receiving IMJUDO in combination with durvalumab, immune-mediated myositis occurred in 10 (0.3%) patients, including Grade 3 in 9 (0.2%) patients. All patients received systemic corticosteroids, and 9 of the 10 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). One patient received other immunosuppressants. Five patients discontinued treatment. Resolution occurred in 5 patients.

Other Immune Mediated Adverse Reactions

In patients receiving IMJUDO in combination with durvalumab, immune-mediated *Adverse Reactions* occurred in 41 (1.1%) patients including Grade 3 in 11 (0.3%) patients. All patients received systemic corticosteroids, and 19 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). One patient received other immunosuppressants. Treatment was discontinued in 3 patients. Resolution occurred in 24 patients.
Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

There is no specific treatment in the event of tremelimumab overdose, and symptoms of overdose are not established. In the event of an overdose, physicians should follow general supportive measures and should treat symptomatically.

Properties/Effects

ATC code

L01FX20

Mechanism of action / Pharmacodynamics

CTLA-4 is primarily expressed on the surface of T lymphocytes. Interaction of CTLA-4 with its ligands, CD80 and CD86, limits effector T-cell activation, through a number of potential mechanisms, but primarily by limiting co-stimulatory signalling through CD28.
Tremelimumab is a selective, fully human IgG2 antibody that blocks CTLA-4 interaction with CD80 and CD86, thus enhancing T-cell activation and proliferation, resulting in increased T-cell diversity and enhanced antitumour immune activity.
The combination of durvalumab, a PD-L1 inhibitor, and tremelimumab functions to enhance anti-tumour T-cell activation and function at multiple stages of the immune response, maximizing anti-tumour immunity.
The effect of IMJUDO in combination with durvalumab on the quantities of proliferative cytotoxic CD8+ T cells was evaluated in Study 22 in patients with uHCC using a CD8+Ki67+ assay. At Day 15 a marked increase of proliferating CD8+ T cell populations was observed in the IMJUDO in combination with durvalumab arm compared to the durvalumab monotherapy arm. Patients receiving IMJUDO in combination with durvalumab also experienced a higher Objective Response Rate (ORR) compared to other treatment arms and responders across all arms exhibited higher median proliferative cytotoxic CD8+ T cell when compared to non-responding patients.

Clinical efficacy

HCC - HIMALAYA Study

The efficacy of IMJUDO in combination with durvalumab was evaluated in the HIMALAYA study, a randomised, open-label, multicenter study in patients with confirmed uHCC who did not receive prior systemic treatment for HCC. The study included patients with BCLC Stage C or B (not eligible for locoregional therapy) and Child-Pugh Score Class A.
The study excluded patients with co-infection of viral hepatitis B and hepatitis C; active or prior documented GI bleeding within 12 months; ascites requiring non-pharmacologic intervention within 6

months; hepatic encephalopathy within 12 months before the start of treatment; active or prior documented autoimmune or inflammatory disorders. Patients with esophageal varices were included except those with active or prior documented GI bleeding within 12 months prior to study entry. Randomisation was stratified by macrovascular invasion (MVI) (yes vs. no), etiology of liver disease (confirmed hepatitis B virus vs. confirmed hepatitis C virus vs. others) and ECOG performance status (0 vs. 1).

The HIMALAYA study randomized 1171 patients 1:1:1 to receive:

- D: durvalumab 1500 mg every 4 weeks
- IMJUDO in combination with durvalumab: IMJUDO 300 mg as a single priming dose + durvalumab 1500 mg; followed by durvalumab 1500 mg every 4 weeks
- S: Sorafenib 400 mg twice daily

Treatment continued until progression or unacceptable toxicity. Patients in all arms could continue to receive treatment after evidence of disease progression if, in the Investigator's opinion, they were benefiting from study drug and met all inclusion and exclusion criteria for treatment beyond progression. In addition, patients in the IMJUDO in combination with durvalumab arm who continued treatment beyond progression were allowed to be rechallenged once with an additional single dose of IMJUDO 300 mg after cycle five of durvalumab.

Tumour assessments were conducted every 8 weeks for the first 12 months and then every 12 weeks thereafter. Survival assessments were conducted every month for the first 3 months following treatment discontinuation and then every 2 months.

The primary endpoint was OS. Key secondary endpoints were PFS, Investigator assessed ORR and DoR according to RECIST v1.1.

The demographics and baseline disease characteristics were generally representative for patients with uHCC. The baseline demographics of the overall study population were as follows: male (83.7%), age <65 years (50.4%) (median age at study entry was 64.0 years [range: 18 to 88 years]), white (44.6%), Asian (50.7%), black or African American (1.7%), other (2.3%), ECOG PS 0 (62.6%); Child-Pugh Class score A (99.5%), macrovascular invasion (25.2%), extrahepatic spread (53.4%), viral etiology; hepatitis B (30.6%), hepatitis C (27.2%), uninfected (42.2%).

The study demonstrated a statistically significant and clinically meaningful improvement in OS with IMJUDO in Kombination mit Durvalumabvs. Sorafenib [HR=0.78 [95% CI 0.66, 0.92]; p=0.0035].

See Table 5.

Table 5. Efficacy Results for the HIMALAYA Study for IMJUDO in combination with durvalumab vs. Sorafenib

	IMJUDO in combination with durvalumab **(n=393)**	**Sorafenib (n=389)**
Follow up duration		
Median follow up	33.2	32.2
Range	(31.7-34.5)	(30.4-33.7)
OS		
Number of deaths (%)	262 (66.7)	293 (75.3)
Median OS (months) (95% CI)	16.4 (14.2-19.6)	13.8 (12.3-16.1)
HR (95% CI)	0.78 (0.66, 0.92)	
p-value[a]	0.0035	
PFS		
Number of events (%)	335 (85.2)	327 (84.1)
Median PFS (months) (95% CI)	3.78 (3.68-5.32)	4.07 (3.75-5.49)
HR (95% CI)	0.90 (0.77 - 1.05)	
ORR		
ORR n (%)[b]	79 (20.1)	20 (5.1)
Complete Response n (%)	12 (3.1)	0

[a] Based on a Lan-DeMets alpha spending function with O'Brien Fleming type boundary and the actual number of events observed, the boundary for declaring statistical significance for IMJUDO in combination with durvalumab vs. S was 0.0398 (Lan◦and◦DeMets 1983).

[b] Confirmed complete response.

NR=Not Reached, CI=Confidence Interval

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Immunogenicity of tremelimumab is based on pooled data in 2075 patients who were treated with IMJUDO 75 mg or 1 mg/kg and evaluable for the presence of anti-drug antibodies (ADAs). Two-hundred fifty-two patients (12.1%) tested positive for treatment-emergent ADAs. Neutralizing antibodies against tremelimumab were detected in 10.0% (208/2075) patients. The presence of ADAs did not impact tremelimumab pharmacokinetics, and there was no apparent effect on efficacy and safety.'

In the HIMALAYA study, of the 182 patients who were treated with IMJUDO in combination with durvalumab and evaluable for the presence of ADAs against tremelimumab, 20 (11.0%) patients tested positive for treatment-emergent ADAs. Neutralizing antibodies against tremelimumab were

detected in 4.4% (8/182) patients. The presence of ADAs did not have an apparent effect on pharmacokinetics or safety.
Immunogenicity assay results are highly dependent on several factors, including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications and underlying disease.
For these reasons, comparison of incidence of antibodies to tremelimumab with the incidence of antibodies to other products may be misleading.

Pharmacokinetics

The pharmacokinetics (PK) of tremelimumab was assessed tremelimumab in combination with durvalumab and platinum-based chemotherapy and for tremelimumab in combination with durvalumab.
The pharmacokinetics of tremelimumab was studied in patients with solid tumours with doses ranging from 75 mg to 750 mg or 10 mg/kg administered intravenously once every 4 or 12 weeks as monotherapy, or at a single priming dose of 300 mg. PK exposure increased dose-proportionally (linear PK) at doses ≥ 75 mg. Steady state was achieved at approximately 12 weeks (after three Q4W doses of 1 to 10 mg/kg tremelimumab). Based on population PK analysis that included patients who received tremelimumab monotherapy or in combination with durvalumab with or without chemotherapy in the dose range of ≥ 75 mg (or 1 mg/kg) every 3 or 4 weeks, the geometric mean steady state volume of distribution (V_{ss}) was 5.97 L. Tremelimumab clearance (CL) decreased over time in combination with durvalumab and chemotherapy resulting in a geometric mean steady state clearance (CL_{ss}) of 0.202 L/day at Day 365; the decrease in CL_{ss} was not considered clinically relevant. The geometric mean (CV%) terminal half-life was approximately 20.4 (34.7) days. There was no clinically meaningful difference between the PK of tremelimumab as monotherapy or in combination with durvalumab or in combination with durvalumab and chemotherapy.

Kinetics in specific patient groups

Age (18–87 years), body weight (34-149 kg), gender, positive anti-drug antibody (ADA) status, albumin levels, LDH levels, tumour type, race, mild renal impairment (creatinine clearance (CRCL) 60 to 89 mL/min), moderate renal impairment (creatinine clearance (CRCL) 30 to 59 mL/min), mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin > 1.0 to 1.5 × ULN and any AST), moderate hepatic impairment (bilirubin > 1.5 to 3 x ULN and any AST) or ECOG/WHO status had no clinically significant effect on the PK of tremelimumab.
The effect of severe renal impairment (CRCL 15 to 29 mL/min) or severe hepatic impairment (bilirubin > 3.0 x ULN and any AST) on the PK of tremelimumab is unknown.

Preclinical data

Animal toxicology and/or pharmacology

In the chronic six-month toxicity study in cynomolgus monkeys, weekly intravenous administration of tremelimumab was associated with dose-related incidence in skin rash, scabs and open sores, which were dose-limiting. These clinical signs were also associated with decreased appetite and body weight and swollen peripheral lymph nodes. At a dose of 50 mg/kg, 7 out of 12 animals were prematurely terminated due to treatment related findings. Histopathological findings correlating with the observed clinical signs included reversible inflammation in the cecum and colon, and mononuclear cell infiltration in a wide variety of tissues including the skin and lymphoid tissues, with dose-related incidence and severity.

Mutagenicity and carcinogenicity

The genotoxic and carcinogenic potential of tremelimumab has not been evaluated.

Reproductive toxicity

Animal fertility studies have not been conducted with tremelimumab. In reproduction studies, IV administration of tremelimumab to pregnant cynomolgus monkeys at dose levels of 5, 15, 30 mg/kg/week during organogenesis (from Gestation Day 20 to 50) was not associated with maternal toxicity or effects pregnancy losses, foetal weights, or external, visceral, skeletal abnormalities or weights of selected foetal organs. Exposure levels at the 30 mg/kg dose were approximately 1.2-3.7 times higher than those observed at a recommended clinical dose range of 75 mg to 300 mg based on area under the curve (AUC).‴

Other information

Incompatibilities

No incompatibilities between IMJUDO and 9 g/L (0.9%) sodium chloride or 50 g/L (5%) dextrose in polyvinylchloride or polyolefin IV bags have been observed.
This drug product must not be mixed with other drug products except those mentioned in subsection ”Instructions for handling”.
Do not co-administer other drugs through the same intravenous line.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Diluted solution

IMJUDO does not contain a preservative. Administer infusion solution immediately once prepared. If infusion solution is not administered immediately and it needs to be stored, follow the below recommendations:

Chemical and physical in-use stability has been demonstrated for up to 28 days at 2°C to 8°C and for up to 48 hours at room temperature (up to 30°C) from the time of preparation.

From a microbiological point of view, the prepared solution for infusion should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2°C to 8°C or 12 hours at room temperature (≤ 25°C), unless the dilution was carried out under controlled and validated aseptic conditions.

Special precautions for storage

Unopened vial

Store vials under refrigeration at 2°C to 8°C in original carton to protect from light.

Do not freeze.

Do not shake.

Keep out of reach of children.

Diluted Solution

For storage conditions after preparation of the infusion, see section “Diluted solution”.

Instructions for handling

Preparation of solution

IMJUDO is supplied as a single-dose vial and does not contain any preservatives, aseptic technique must be observed.

- Visually inspect drug product for particulate matter and discolouration. IMJUDO is clear to slightly opalescent, colourless to slightly yellow solution. Discard the vial if the solution is cloudy, discoloured or visible particles are observed. Do not shake the vial.
- Withdraw the required volume from the vial(s) of IMJUDO and transfer into an intravenous (IV) bag containing 0.9% Sodium Chloride Injection, or 5% Dextrose Injection. Mix diluted solution by gentle inversion. The final concentration of the diluted solution should be between 0.1 mg/mL and 10 mg/mL. Do not freeze or shake the solution.
- Care must be taken to ensure the sterility of prepared solutions.
- Do not re-enter the vial after withdrawal of drug.
- Discard any unused portion left in the vial.

Administration

- Administer infusion solution intravenously over 1 hour through an intravenous line containing a sterile, low-protein binding 0.2 or 0.22 micron filter.
- Do not co-administer other drugs through the same infusion line.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Authorisation number

68706 (Swissmedic)

Packs

1 vial containing 25 mg/1.25 ml [A]
1 vial containing 300 mg/15 ml [A]

Marketing authorisation holder

AstraZeneca AG, 6340 Baar

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