A multicenter, phase Ib study of subcutaneous administration of isatuximab in combination with pomalidomide and dexamethasone in patients with relapsed/refractory multiple myeloma

Authors

Hang Quach,[1] Gurdeep Parmar,[2] Enrique M. Ocio,[3] H. Miles Prince,[4] Albert Oriol,[5] Helen Crowther,[6] Nobuhiro Tsukada,[7] Pierre Bories,[8] Sumit Madan,[9] Nitya Nathwani,[10] Kazutaka Sunami,[11] Dorothee Semiond,[12] Disa Yu,[12] Paul Cordero,[13] Sandrine Macé,[14] Florence Suzan[14] and Philippe Moreau[15]

[1]Clinical Hematology Service, St Vincent's Hospital, University of Melbourne, Melbourne, Australia; [2]Illawarra Cancer Care Center, Wollongong, Australia; [3]Hospital Universitario Marqués de Valdecilla (IDIVAL), Universidad de Cantabria, Santander, Spain; [4]Molecular Oncology and Cancer Immunology, Epworth HealthCare and University of Melbourne, Melbourne, Australia; [5]Institut Català d'Oncologia and Institut Josep Carreras, Hospital Germans Trias i Pujol, Barcelona, Spain; [6]Department of Hematology, Blacktown and Mount Druitt Hospitals, Blacktown, Australia; [7]Department of Hematology, Japanese Red Cross Medical Center, Tokyo, Japan; [8]Early Phase Unit, Institut Claudius Regaud, Institut Universitaire du Cancer de Toulouse, Toulouse, France; [9]Banner MD Anderson Cancer Center, Gilbert, AZ, USA; [10]Department of Hematology, City of Hope National Medical Center, Duarte, CA, USA; [11]Department of Hematology, National Hospital Organization Okayama Medical Center, Okayama, Japan; [12]Research & Development, Sanofi, Cambridge, MA, USA; [13]Research & Development, Sanofi, Reading, UK; [14]Research & Development, Sanofi, Vitry-sur-Seine, France; [15]Department of Hematology, University Hospital of Nantes, Nantes, France.
Correspondence:
H. QUACH - Hang.Quach@svha.org.au

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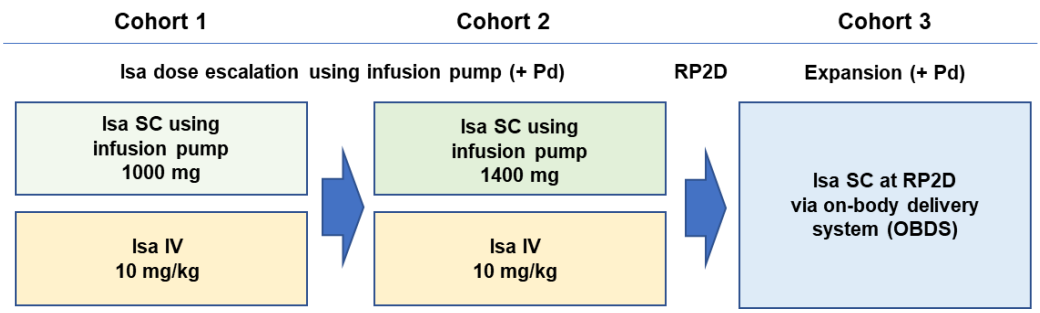
SUPPLEMENTARY INFORMATION

A multi-center, phase Ib study of subcutaneous administration of isatuximab in combination with pomalidomide and dexamethasone in patients with relapsed / refractory multiple myeloma

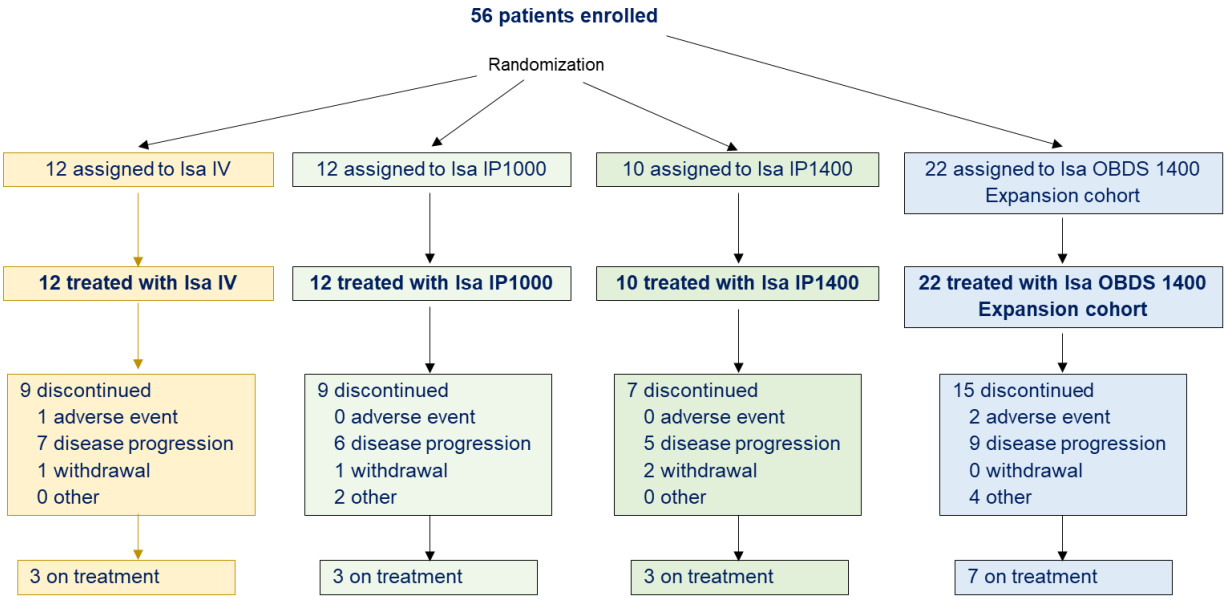
Supplementary Figure S1. Study design, on-body delivery system (OBDS), and patient flow diagram

A



B

C



Footnote

(A) Study design. Patients were randomized 2:1 to SC IP 1000 mg or IV Isa 10 mg/kg in cohort 1 and then to SC IP 1400 mg or IV Isa 10 mg/kg in cohort 2, plus Pd, by a centralized randomization procedure using an interactive response system. Subsequently, patients were

recruited in an expansion cohort for treatment with Isa SC via OBDS at the RP2D of 1400 mg (cohort 3). After determination of the RP2D for SC Isa, 4 patients still on treatment in the IV cohort were allowed by protocol amendment to switch to SC Isa 1400 mg given by infusion pump. Three of these 4 patients switched to SC Isa administration via OBDS at 1400 mg after the final OBDS results became available and a further protocol amendment was implemented to offer more convenience to patients. Both Isa IP1000 mg and IP1400 mg were delivered through an infusion pump (IP) at a 0.8 mL/min flow rate. (B) OBDS applied to the patient's abdomen*. *CAUTION - Investigational device. Limited by Federal (or United States) law to investigational use. (C) Patient flow diagram. IP: infusion pump; Isa: isatuximab; Pd: pomalidomide-dexamethasone; RP2D: recommended phase 2 dose; SC: subcutaneous; IV: intravenous; OBDS: on-body delivery system.

Supplementary Table S1. Any-grade, non-hematologic, treatment-emergent adverse events in ≥25% of patients in any treatment group, by primary system organ class (including selected preferred terms)[a]

	Isa IV 10 mg/kg + Pd (n=12)		Isa IP1000 + Pd (n=12)		Isa IP1400 (RP2D) + Pd (n=10)		Isa OBDS (RP2D) + Pd (n=22)		Isa OBDS and IP1400 (RP2D) + Pd (n=32)	
n (%)	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
COVID-19	0	0	1 (8.3)	1 (8.3)	4 (40.0)	0	6 (27.3)	3 (13.6)	10 (31.3)	3 (9.4)
Respiratory tract infection	0	0	2 (16.7)	0	2 (20.0)	0	1 (4.5)	0	3 (9.4)	0
Upper respiratory tract infection	3 (25.0)	1 (8.3)	1 (8.3)	0	1 (10.0)	0	4 (18.2)	0	5 (15.6)	0
Insomnia	2 (16.7)	2 (16.7)	4 (33.3)	2 (16.7)	2 (20.0)	2 (20.0)	5 (22.7)	2 (9.1)	7 (21.9)	4 (12.5)
Mood altered	1 (8.3)	1 (8.3)	0	0	3 (30.0)	1 (10.0)	2 (9.1)	2 (9.1)	5 (15.6)	3 (9.4)
Confusional state	0	0	3 (25.0)	0	0	0	0	0	0	0
Dizziness	1 (8.3)	0	3 (25.0)	0	1 (10.0)	0	1 (4.5)	0	2 (6.3)	0
Hypotension	1 (8.3)	0	3 (25.0)	0	1 (10.0)	0	2 (9.1)	0	3 (9.4)	0
Dyspnea	3 (25.0)	0	1 (8.3)	0	2 (20.0)	0	2 (9.1)	1 (4.5)	4 (12.5)	1 (3.1)
Cough	3 (25.0)	0	1 (8.3)	0	1 (10.0)	0	2 (9.1)	0	3 (9.4)	0
Diarrhea	4 (33.3)	0	5 (41.7)	0	6 (60.0)	0	6 (27.3)	0	12 (37.5)	0
Constipation	2 (16.7)	0	7 (58.3)	0	1 (10.0)	0	6 (27.3)	0	7 (21.9)	0
Nausea	4 (33.3)	1 (8.3)	5 (41.7)	0	2 (20.0)	0	3 (13.6)	0	5 (15.6)	0
Vomiting	2 (16.7)	1 (8.3)	5 (41.7)	0	0	0	1 (4.5)	0	1 (3.1)	0
Back pain	5 (41.7)	0	4 (33.3)	1 (8.3)	4 (40.0)	0	6 (27.3)	0	10 (31.3)	0
Muscle spasms	1 (8.3)	0	3 (25.0)	0	2 (20.0)	0	6 (27.3)	0	8 (25.0)	0
Fatigue	5 (41.7)	0	4 (33.3)	0	4 (40.0)	1 (10.0)	6 (27.3)	2 (9.1)	10 (31.3)	3 (9.4)

Injection site erythema	0	0	2 (16.7)	0	5 (50.0)	0	4 (18.2)	0	9 (28.1)	0
Peripheral edema	2 (16.7)	0	4 (33.3)	0	3 (30.0)	0	2 (9.1)	0	5 (15.6)	0
Injection site bruising	0	0	2 (16.7)	0	3 (30.0)	0	0	0	3 (9.4)	0
Pyrexia	4 (33.3)	1 (8.3)	1 (8.3)	0	1 (10.0)	0	2 (9.1)	0	3 (9.4)	0
Basal cell carcinoma	3 (25.0)	0	0	0	0	0	1 (4.5)	0	1 (3.1)	0
Fall	2 (16.7)	1 (8.3)	4 (33.3)	1 (8.3)	2 (20.0)	0	3 (13.6)	1 (4.5)	5 (15.6)	1 (3.1)
Contusion	3 (25.0)	0	1 (8.3)	0	0	0	1 (4.5)	0	1 (3.1)	0
Infusion reaction	1 (8.3)	0	1 (8.3)	0	1 (10.0)	0	0	0	1 (3.1	0

[a]Adverse events were summarized by primary system organ class and preferred terms using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v.5.0. Isa: isatuximab; IP: infusion pump; IV: intravenous; OBDS: on-body delivery system; Pd: pomalidomide-dexamethasone; RP2D: recommended phase 2 dose.

Supplementary Table S2. Isa pharmacokinetic parameters after first intravenous (IV) or subcutaneous (SC) administration at cycle 1 and mean C_{trough} (± SD) after multiple dosing of Isa administered IV or SC, in combination with pomalidomide-dexamethasone[a].

	Isa IV 10 mg/kg + Pd (n=12)	**Isa IP1000 + Pd (n=12)**	**Isa IP1400 + Pd (n=10)**	**Isa OBDS (RP2D) + Pd (n=22)**	**Isa OBDS and IP1400 (RP2D) + Pd (n=32)**
PK parameters at cycle 1					
n	12	12	10	22	32
C_{max}, µg/mL, mean (SD)	234 (66.7)	120 (56.1)	104 (34.8)	145 (71.4)	132 (64.6)
n	11	11	10	21	31
AUC_{last}, µg•h/ml, mean (SD)	18700 (5460)	15200 (7760)	13100 (5080)	18500 (8470)	16700 (7880)
n	12	12	10	22	32
t_{max}, h, median (range)	3.63 (3.33-11.3)	83.2 (44.4-168)	92.6 (68.4-168)	95.1 (46.9-192)	94.7 (46.9-192)
C_{trough} (µg/mL)[b]					
Cycle 2 (day 1)					
n	9	7	6	15	21
Mean (SD)	235 (93.2)	326 (86.2)	338 (120)	343 (158)	341 (145)
Cycle 2 (day 15)					
n	12	10	7	16	23
Mean (SD)	196 (117)	332 (122)	338 (151)	397 (202)	379 (186)
Cycle 3 (day 1)					
n	8	5	7	16	23
Mean (SD)	202 (131)	288 (187)	357 (136)	363 (173)	361 (160)
Cycle 3 (day 15)					
n	10	9	9	18	27
Mean (SD)	210 (111)	329 (93.2)	377 (175)	397 (226)	390 (208)
Cycle 4 (day 1)					
n	9	9	9	13	22
Mean (SD)	244 (139)	361 (154)	385 (149)	353 (118)	366 (129)
Cycle 4 (day 15)					
n	9	9	9	18	27
Mean (SD)	229 (144)	379 (108)	408 (155)	357 (147)	374 (149)
Cycle 6 (day 1)					

n	6	11	8	14	22
Mean (SD)	287 (183)	364 (173)	457 (165)	461 (196)	459 (181)

[a]Isa levels were assessed in plasma by a validated immunoassay using the Gyrolab platform. This quantitative, sandwich immunoassay consisted of biotinylated anti-Isa antibodies bound by streptavidin beads, within the Gyrolab Bioaffy™ CD microstructure (Gyros Protein Technologies, Uppsala, Sweden), for capture and Alexa Fluor® 647-conjugated CD38 antibody for detection, resulting in measurement of functional Isa plasma levels (Isa with ≥1 site available for target binding), with a lower limit of quantitation of 5.0 µg/ml and an upper limit of quantitation of 500 µg/ml. PK parameters were calculated from Isa plasma concentrations by non-compartmental analysis methods using Phoenix WinNonlin® v8.2 (Pharsight, Cary, NC) and summarized with descriptive statistics. [b]From cycle 2, the geometric mean ratios of C_{trough} between each SC cohort and the IV cohort remained constant and above 1, suggesting that a comparable or higher Isa exposure was maintained with SC compared with IV administration over the dosing interval, at the dose range evaluated in the study. AUC_{last}: area under the concentration-time curve from time zero to t_{last}; C_{max}: maximum concentration observed; C_{trough}: trough concentration; h: hours; IP: infusion pump; Isa: isatuximab; IV: intravenous; OBDS: on-body delivery system; Pd: pomalidomide-dexamethasone; PK: pharmacokinetics; RP2D: recommended phase 2 dose; SC: subcutaneous; SD: standard deviation; t_{max}: time to reach C_{max}.