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# Isatuximab, pomalidomide, and dexamethasone as salvage therapy for patients with multiple myeloma: the Italian, multicenter, retrospective clinical experience with 270 cases outside of controlled clinical trials

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**Authors Contributions**:

E.A.M, M.G., F.D.R., V.D.S., A.N., F.M., and P.M. designed the study; M.G. and F.M. performed statistical analysis; D.D., E.R., S.T., G.R., P.S., J.M., S.M., E.Z., M.O., A.F., G.B., F.L., C.L., A.L., R.D.P., G.B., E.B., C.C., C.D.M., L.D.P., V.B., A.M.C., A.M., P.B., C.Ce., C.B., E.A., N.S., S.A., G.M., G.Ba., S.P., O.A., R.B., M.A.F., G.M.C., A.R., R.F., F.F., E.V., A.B., K.M., D.N., S.M., E.R., C.Ca., A.A., D.R., A.L., A.C., G.U., R.Z., A.M., S.N., M.M., A.G., V.M., M.B., E.C., G.P.,

A.M.Q., V.A., N.D.R., M.C., M.Ga., M.T.P., analyzed and interpreted data. E.A.M., M.G., F.D.R., V.D.S., A.N., F.M., and P.M. wrote the manuscript; all authors gave final approval.

**Competing interests**: Nothing to disclose

**Availability of data and materials**

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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**Running title: An Italian real-world experience on IsaPd for RRMM**

**Keywords: Isatuximab, pomalidomide, dexamethasone, multiple myeloma, salvage therapy.**

This real-world multicenter study aimed to evaluate the efficacy and tolerability of isatuximab, pomalidomide, and dexamethasone (IsaPd) combination in relapsed/refractory multiple myeloma (RRMM). Our results confirm the safety and efficacy of IsaPd, aligning with findings from the pivotal clinical trial [1-2].

Isatuximab and daratumumab, both anti-CD38 antibodies, have demonstrated high response rates and improved survival in RRMM patients when used with agents like pomalidomide, lenalidomide, carfilzomib, and dexamethasone [3-8].

The pivotal ICARIA-MM trial, demonstrated a significant improvement in progression-free survival (PFS) of IsaPd, compared to Pd with a median PFS of 11.5 months vs 6.5 months in the control group [1]. Extended follow-up confirmed the outcome benefit, with a median overall survival (OS) of 24.6 months compared to 17.7 months in the control arm [2].

Our study analyzed 270 RRMM patients treated with IsaPd, across 51 Italian centers between January 2021 and June 2024. This study was approved by the ethics committee at all participating hospitals. It adhered to the Declaration of Helsinki and the Good Clinical Practice guidelines. All patients received prophylactic antibacterial, antiviral, and antithrombotic therapy. PFS, OS, and time-to-next treatment (TTNT) were evaluated as time-to-event endpoints. Safety and treatment responses were also assessed [9,10].

At baseline, 13.7% of patients were in stage III according to the International Staging System (ISS), and 26.7% had refractory disease (Table 1). About 29.3% of patients showed a creatinine clearance (CrCl)<60 mL/min. By cytogenetics evaluations, performed at IsaPd initiation, 104 out of 147 evaluable cases were classified as standard-risk and 43 as high-risk (Table 1). Furthermore, 23% of cases showed a gain/amplification of 1q21 (1q21+). About 64% had received two lines of therapy and most cases were refractory to lenalidomide; in addition, 51 patients had been exposed to daratumumab, with 98% refractory to this therapy. Twelve patients received IsaPd immediately after a daratumumab-containing regimen, while 39 patients received other schedules in between.

Median time between IsaPd and daratumumab-containing regimen was 10 months (range 0.5-41 months).

Compared to the ICARIA-MM trial [1], our cohort had a lower incidence of renal impairment (29.3% vs 39%), a higher proportion of high-risk cytogenetics (29.3% vs 16%), and daratumumab-refractory patients (20% in our study vs none in the trial), but similar distribution in ISS stage, and lenalidomide-refractory patients. Two other studies have been reported on IsaPd use in a real-world setting (Supplementary Table 1) [11,12]. Notably, our study represents the one with the longest median follow-up (23.5 months vs 12.1 and 14.2 of the British and French studies respectively). Our findings align with both the British and French studies, though they provide unique insights due to their scope and duration [11,12]. In comparison, the UK study reported a higher median number of prior therapies (three), but a lower rate of daratumumab-exposed patients (4.7%). The IMAGE study included more ISS stage III patients (36.4%) and daratumumab-exposed cases (26.5%). Finally, our cohort encompassed a greater number of high-risk cytogenetic patients (29.3%) (Supplementary Table 1).

At the last follow-up, the overall response rate (ORR) was achieved in 74.1% of patients, including 14.8% attaining a complete remission (CR), and 29.6% a very good partial response (VGPR). The response rate surpassed those of the ICARIA-MM trial (ORR=60%, CR=4.5%) [1-2]. The English real-world study similarly reported an ORR of 66.4%, whereas the French study observed that 46.3% of patients achieved $\geq$VGPR [11,12]. In our cohort the median time to response was 1.9 months.

A higher ORR has been observed in patients with CrCl$\geq$60 mL/min (74% vs 65.8%; P=0.047), with ISS stage I and II (78.6% vs 74.5% vs 56.8%; P=0.027), with normal LDH levels (78.4% vs 54.2%; P=0.001), and in those not exposed to daratumumab (78.1% vs 56.9%; P=0.002). Age, gender, prior therapy lines, previous ASCT, and disease status at IsaPd initiation did not significantly affect response rates. No differences in ORR were observed based on the time ($\leq$12 vs >12 months and $\leq$6

vs >6 months) or the sequencing (immediately after vs other schedules in between) of IsaPd after daratumumab-containing regimens.

After a median follow-up of 23.5 months, 57.8% of patients experienced disease progression or death, and 31.5% had died. The median PFS was 15.7 months, with a 2-year PFS probability of 38.8% (Figure 1A). This is higher than the 11.5 months in the pivotal study [1] and the 12.4 and 10.9 months observed in the IMAGE study and in the UK-wide dataset, respectively [11,12]. Differences may be attributed to the number of prior therapies in the ICARIA-MM trial and the higher proportion of advanced ISS stages in the latter studies.

In univariable analyses, CrCl<60 mL/min, ISS stage II and III, abnormal LDH value, and previous daratumumab exposure (Figure 1B) were significantly associated with lower PFS (Supplementary Table 2 Panel A).

However, no significant PFS differences were observed based on the time or the sequencing of IsaPd after daratumumab-containing regimens. In multivariable analysis, ISS stages II (HR=1.47; P=0.035) and III (HR=2.44; P=0.001), abnormal LDH value (HR=1.51; P=0.04), and previous daratumumab exposure (HR=1.87; P=0.002) were independent predictors of worse PFS (Supplementary Table 2 Panel A).

The lower PFS in patients previously treated with daratumumab aligns with real-world data. In the IMAGE study, daratumumab-refractory patients had a median PFS of 3 months, while daratumumab-exposed but not refractory patients experienced a median PFS of 8.4 months. Daratumumab-naïve patients had a median PFS of 16.6 months [11], highlighting the negative impact of prior daratumumab treatment in IsaPd-treated patients. There was no significant difference in PFS between age groups (≤70 vs >70 years), consistent with the ICARIA-MM trial, which demonstrated that IsaPd was effective regardless of age [13].

The median OS was not reached, with a 2-year OS probability of 64.2% (Figure 1C). In comparison, the ICARIA-MM trial reported a median OS of 24.6 months [9]. The IMAGE study also reported an OS not reached, whereas in the UK-wide real-world study was attested at 18.8

months [11,12]. Univariable analyses showed that CrCl<60 mL/min, ISS stages II and III, abnormal LDH, more than two previous lines of therapy, and previous daratumumab exposure (Figure 1D), were significantly associated with shorter OS (Supplementary Table 2 Panel B). In the multivariable analysis, ISS stages II (HR=1.77; P=0.029) and III (HR=2.23; P=0.02), and abnormal LDH value (HR=2; P=0.006) were independent predictors of shorter OS (Supplementary Table 2 Panel B). Since prior daratumumab exposure showed a trend toward significance (HR=1.52; P=0.088), a longer follow-up is desirable to confirm this data. Again, no differences in OS were observed based on the time or the sequencing of IsaPd after daratumumab-containing regimens.

After discontinuing the IsaPd regimen, 38.5% of patients received subsequent treatment, with a median TTNT of 17.7 months, and a 2-year retreatment probability of 39% (Figure 1E). A total of 21 different salvage therapy regimens were used after IsaPd discontinuation or failure (Supplementary Table 3).

At the last update, the median number of IsaPd courses was 11 with 61.9% of patients discontinuing treatment mainly due to disease progression (50%). Other discontinuation reasons included toxicity (19 infections, 3 severe neutropenia, and 2 acute myocardial infarctions), therapy-unrelated deaths (4 cases), second ASCT (2 cases), and patient decision (1 case). Infusion reactions occurred in 11.8% of patients, mostly mild, with only 1 patient discontinuing therapy. Major adverse events (AEs) included grade 3/4 neutropenia (56.3%), thrombocytopenia (15.9%), and anemia (13.7%) (Table 2). The incidence of grade 3-4 neutropenia and thrombocytopenia appears lower than that reported in the ICARIA-MM trial (Supplementary Table 1), possibly attributed to the more diverse population and under-reporting of AEs in real-world settings. All grade infection rate was 47.8% with 26.7% developing pneumonia. The lack of significant differences in AEs observed between patients based on age or renal function (data not shown) supports the feasibility of IsaPd in elderly and renally impaired patients, aligning our study with other real-world analyses [11,12].

Cytogenetic data were available for 54.4% of cases. The similarity in features between patients with and without available FISH data, apart from a higher rate of refractoriness to the last therapy in

those in whom FISH was not available, suggests that these findings are likely representative of the entire patient cohort. Indeed, our study's findings underscore the prognostic significance of cytogenetic risk stratification. The analysis revealed a significantly higher ORR in the standard-risk group compared to the high-risk group (82.7% vs 62.8%; P=0.009).

Furthermore, patients with high-risk cytogenetic exhibited significantly shorter PFS (HR 2.57, 95%CI 1.64-4.03; P<0.0001) (Figure 1F), with a 2-year PFS of 21.6% in the high-risk group compared to 50.4% in the standard-risk group. Additionally, OS was poorer in the high-risk group (Figure 1G), with a 2-year OS of 56% vs 70.4% in the standard-risk group (HR 1.86, 95%CI 1.01-3.46; P=0.049), underscoring the prognostic value of cytogenetic profiling. Moreover, in line with the ICARIA-MM trial [15], IsaPd appeared to overcome the negative impact of 1q21+, with similar outcomes (ORR 82.4% vs 75.2%; 2-year PFS 44.8% vs 41.4%, and 2-year OS 69% vs 65.2%) in patients with and without this abnormality.

In conclusion, IsaPd is effective and safe in a real-world setting for RRMM patients who received two prior lines of therapy. Alternative therapeutic strategies, i.e., bispecific antibodies and CAR-T are needed for the high-risk and daratumumab-exposed patients.

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**Table 1. Main characteristics of patients at the time of IsaPd initiation.**

| | **No. of patients (%)** |
|---|---|
| **Age, (years)** | |
| **Median (range)** | 69 (38-88) |
| <70 | 159 (58.9) |
| ≥70 | 111 (41.1) |
| **Sex** | |
| Male | 147 (54.4) |
| Female | 123 (45.6) |
| **Paraproteins (isotype)** | |
| Immunoglobulin G | 159 (58.9) |
| Immunoglobulin A | 57 (21.1) |
| Immunoglobulin D | 2 (0.7) |
| Immunoglobulin M | 1 (0.4) |
| Light chain only | 51 (18.9) |
| **Creatinine (mg/dL)** | |
| **Median (range)** | 0.92 (0.38-8.47) |
| **Creatinine Clearance (mL/min)** | |
| **Median (range)** | 70 (3-172) |
| ≥60 | 191 (70.7) |
| <60 | 79 (29.3) |
| **Stage ISS, (%)** | |
| I | 131 (48.5) |
| II | 102 (37.8) |
| III | 37 (13.7) |
| **LDH serum level** | |
| **Median (range)** | 197 (112-1125) |
| Normal | 222 (82.2) |
| Elevated° | 48 (17.8) |
| **Previous lines of therapy** | |
| **Median (range)** | 2 (2-7) |
| 2 | 172 (63.7) |
| 3 | 67 (24.8) |
| ≥4 | 31 (10.5) |
| **Previous ASCT** | |
| No | 107 (39.6) |
| Yes | 163 (60.4) |
| **Previous daratumumab** | |
| No | 219 (81.1) |
| Yes | 51 (18.9) |
| **Lenalidomide refractory** | |
| No | 4 (1.5) |
| Yes | 266 (98.5) |
| **Disease status** | |
| Biochemical relapse | 57 (21.1) |
| Symptomatic relapse | 141 (52.2) |
| Refractory to last treatment | 72 (26.7) |
| **Cytogenetic analysis available (n= 147)** | |
| Standard Risk | 104 (70.7) |
| High Risk* | 43 (29.3) |

°Elevated= higher-than-normal LDH levels; *High Risk= patients with the presence of either t(4;14), or t(14;16) or del(17p)

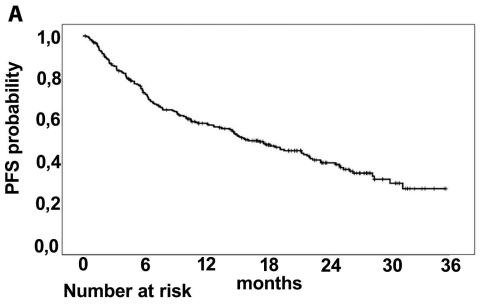
**Table 2. Incidence of adverse events**

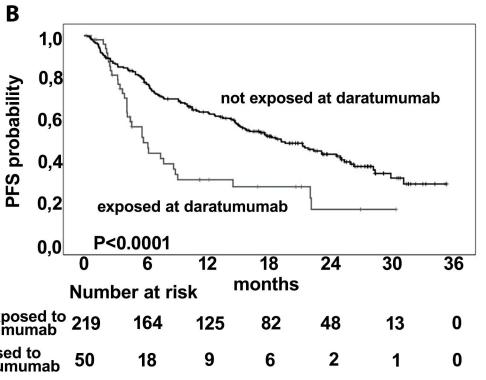
| | IsaPd (N=270) | |
|---|---|---|
| | **All grades (%)** | **Grade 3-4 (%)** |
| **Hematological toxicities** | | |
| Anemia | 230 (85.2) | 37 (13.7) |
| Thrombocytopenia | 205 (75.9) | 43 (15.9) |
| Neutropenia | 265 (98.1) | 152 (56.3) |
| **Non-hematological toxicities** | | |
| Infections | 175 (64.8) | 129 (47.8)* |
| Pneumonia | 84 (31.1) | 72 (26.7) |
| Fatigue | 78 (28.9) | 44 (16.3) |
| Gastrointestinal toxicity | 92 (34.1) | 17 (6.3) |

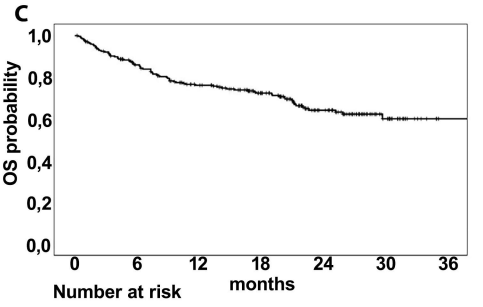
*Grade 3-4 infections; pneumonia=72 cases; genito-urinary tract infection=22 cases; bronchitis=17 cases; upper respiratory tract infection=15 cases; sepsis=2 cases.

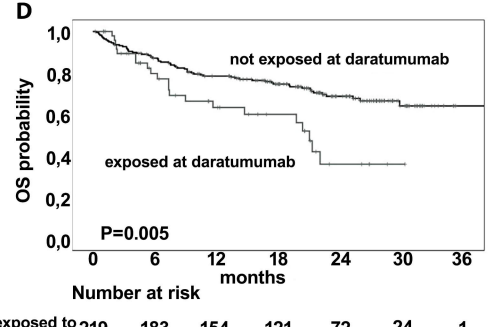
**Figures legend**

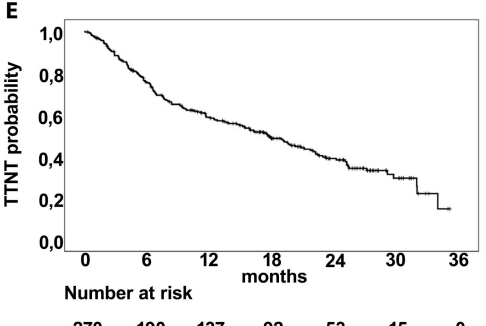
**Figure 1.** Kaplan Meier curves for all 270 RRMM patients treated with IsaPd. **Panel A**. Kaplan Meier curve of PFS; **Panel B**. Kaplan Meier curves of PFS according to daratumumab exposure; **Panel C**. Kaplan Meier curve of OS. **Panel D**. Kaplan Meier curves of OS according to daratumumab exposure; **Panel E.** Kaplan Meier curve of TTNT; **Panel F**. Kaplan Meier curves of PFS according to cytogenetic risk; **Panel G**. Kaplan Meier curves according to cytogenetic risk.

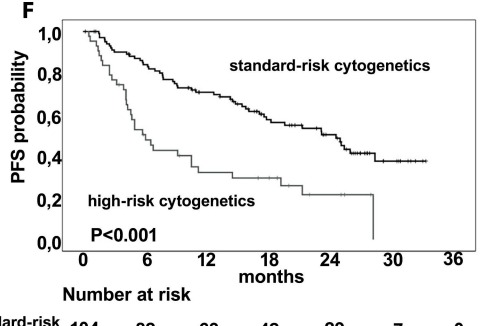

A
PFS probability
1,0
0,8
0,6
0,4
0,2
0,0
0 6 12 18 24 30 36
months
Number at risk
270 183 165 89 51 14

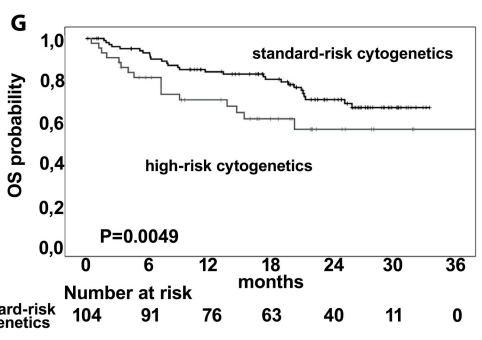

B
PFS probability
not exposed at daratumumab
exposed at daratumumab
P<0.0001
0 6 12 18 24 30 36
months
Number at risk
Not exposed to daratumumab 219 164 125 82 48 13 0
Exposed to daratumumab 50 18 9 6 2 1 0


C
OS probability
1,0
0,8
0,6
0,4
0,2
0,0
0 6 12 18 24 30 36
months
Number at risk
270 214 175 136 77 25 1


D
OS probability
not exposed at daratumumab
exposed at daratumumab
P=0.005
0 6 12 18 24 30 36
months
Number at risk
Not exposed to daratumumab 219 183 154 121 72 24 1
Exposed to daratumumab 51 30 20 14 4 1 0


E
TTNT probability
0 6 12 18 24 30 36
months
Number at risk
270 190 137 92 53 15 0


F
PFS probability
standard-risk cytogenetics
high-risk cytogenetics
P<0.001
0 6 12 18 24 30 36
months
Number at risk
Standard-risk cytogenetics 104 82 63 42 29 7 0
High-risk cytogenetics 43 19 11 9 3 0 0


G
OS probability
standard-risk cytogenetics
high-risk cytogenetics
P=0.0049
0 6 12 18 24 30 36
months
Number at risk
Standard-risk cytogenetics 104 91 76 63 40 11 0
High-risk cytogenetics 43 30 23 15 6 2 1

**SUPPLEMENTARY APPENDIX CONTENTS**

# Isatuximab, pomalidomide, and dexamethasone as salvage therapy for patients with multiple myeloma: the Italian multicenter, retrospective clinical experience with 270 cases outside of controlled clinical trials.

**Enrica Antonia Martino[1], Daniele Derudas[2], Elena Rossi[3], Sofia Terlizzi[4], Giovanni Reddiconto[5], Paola Stefanoni[6], Jacopo Micozzi[7], Silvia Mangiacavalli[8], Elena Zamagni[9,10], Massimo Offidani[11], Anna Furlan[12], Gabriele Buda[13], Flavia Lotti[14], Carmine Liberatore[15,16], Antonio Lazzaro[17], Roberta Della Pepa[18], Giuseppe Bertuglia[19], Emiliano Barbieri[20], Concetta Conticello[21], Claudio De Magistris[22], Lorenzo De Paoli[23], Velia Bongarzoni[24], Anna Maria Cafro[25], Anna Mele[26], Pietro Benvenuti[27], Claudio Cerchione[28], Cirino Botta[29], Elisabetta Antonioli[30], Nicola Sgherza[31], Sara Aquino[32], Giuseppe Mele[33], Gregorio Barilà[34], Salvatore Palmieri[35], Ombretta Annibali[36], Rosario Bianco[37], Massimiliano Arangio Febbo[38], Gloria Margiotta Casaluci[39], Angela Rago[40], Raffaele Fontana[41], Francesca Farina[42], Ernesto Vigna[1], Antonella Bruzzese[1], Katia Mancuso[9,10], Davide Nappi[27], Sonia Morè[11], Elena Rivolti[20], Catello Califano[43], Angela Amendola[44], Daniela Roccotelli[45], Alessandra Lombardo[46], Annalisa Citro[47], Giuseppina Uccello[48], Renato Zambello[49], Alessandro Maggi[50], Santo Neri[51], Michele Monachesi[14], Alessandro Gozzetti[52], Vittorio Montefusco[53], Marino Brunori[54], Emilia Cotzia[55], Giuseppe Pietrantuono[56], Angela Maria Quinto[57], Valeria Amico[58], Nicola Di Renzo[5], Marta Coscia[26], Monica Galli[6], Valerio De Stefano[3], Maria Teresa Petrucci[7], Antonino Neri[59], Francesco Di Raimondo[20], Fortunato Morabito[60], Pellegrino Musto[30,61], Massimo Gentile[1, 62].**

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**[27]Department of Medicine and Surgery, University of Insubria and Department of Oncology, ASST Sette Laghi, Ospedale di Circolo, Varese, Italy; [28]Department of Hematology, IRCCS Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST), Meldola, Forlì-Cesena, Italy; [29]Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties, University of Palermo, Palermo, Italy; [30]Haematology Unit Careggi University Hospital, Florence, Italy; [31]Unit of Hematology and Stem Cell Transplantation, AOUC Policlinico, Bari, Italy; [32]Hematology and Hematopoietic Stem Cell Transplantation Unit, IRCCS Ospedale Policlinico San Martino, Genoa, Italy; [33]Department of Hematology, Hospital Perrino, Brindisi, Italy; [34]Hematology Unit, Ospedale San Bortolo, Vicenza, Italy; [35]Hematology Unit, Ospedale Cardarelli, Napoli, Italy; [36]Hematology, stem cell transplantation, Fondazione Policlinico Universitario Campus Bio medico di Roma, Rome, Italy; [37]Hematology, Hospital "Sant'Anna e San Sebastiano", Caserta, Italy; [38]Onco Hematology Unit, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy; [39]Division of Hematology, Department of Translational Medicine, University of Eastern Piedmont, Novara, Italy; [40]UOSD Ematologia ASL Roma 1, Rome, Italy; [41]Hematology and Transplant Center, University Hospital "San Giovanni di Dio e Ruggi d'Aragona", Salerno, Italy; [42]Hematology and BMT unit, IRCCS Ospedale San Raffaele, Milan, Italy; [43]Onco-Hematology Unit, "A. Tortora" Hospital, Pagani, Italy; [44]Hematology Unit, Azienda Ospedaliera Regionale "San Carlo", Potenza, Italy; [45]Department of Hematology and Bone Marrow Transplant, IRCSS Casa Sollievo Della Sofferenza, San Giovanni Rotondo, Italy; [46]Onco-hematology Unit Azienda Ospedaliera Santa Maria of Terni, Terni, Italy; [47]Hematology Unit, Legnano General Hospital, Legnano (Milan), Italy; [48]Hematology Unit, Azienda Ospedaliera di Rilievo Nazionale e di Alta Specializzazione (ARNAS) Garibaldi, Catania, Italy; [49]Department of Medicine (DIMED), Hematology and Clinical Immunology, Padua University School of Medicine, Padova, Italy; [50]Haematology, Ospedale G. Moscati, Taranto, Italy; [51]Hematology Unit, Azienda Ospedaliera Papardo, Messina, Italy; [52]Department of Medicine, Surgery and Neurosciences, University of Siena Policlinico S Maria alle Scotte, Siena, Italy; [53]Division of Hematology, Azienda Socio Sanitaria Territoriale (ASST) Santi Paolo e Carlo, Milan, Italy; [54]Internal Medicine, Ospedale Santa Croce, Fano, Italy; [55]Section of Hematology- Ospedale E. Muscatello-Augusta, Siracusa, Italy; [56]IRCCS CROB, Referral Cancer Center of Basilicata, Rionero In Vulture, Italy; [57]Haematology and Transplant Unit, IRCCS - Istituto Tumori "Giovanni Paolo II", Bari, Italy; [58]UOSD Ematologia, AORN San Pio, Benevento, Italy.[59]Scientific Directorate, Azienda USL-IRCCS di Reggio Emilia, Italy; [60]Gruppo Amici Dell'Ematologia Foundation-GrADE, Reggio Emilia, Italy; [61]Department of Precision and Regenerative Medicine and Ionian Area, "Aldo Moro" University School of Medicine, Bari, Italy; [62]Department of Pharmacy, Health and Nutritional Science, University of Calabria, Rende, Italy.**

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**CONFLICT OF INTERESTS:** No conflict

**Supplementary Tables**

**Supplementary Table 1. Comparison of characteristics at baseline between the cohorts of patients treated with IsaPd in a real-world setting and those enrolled in the ICARIA-MM clinical trial.**

| | ICARIA-MM trial | Italian Real-World study | UK-Wide Real-World study | IMAGE Real-World study |
|---|---|---|---|---|
| **Time of accrual** | Jan 2017/ Feb 2018 | Jan 2021/ Jun 2024 | Jan 2020/ May 2021 | Jul 2019/ Sep 2020 |
| **No of cases** | 154 | 270 | 107 | 299 |
| **Median follow-up (months)** | 52.4 | 23.5 | 12.1 | 14.2 |
| **Median age (years)** | 68 | 69 | 69 | 70.2 |
| range | (60-74) | (39-88) | (61-77) | (39.9-89.8) |
| ≥75 (%) | 21 | 24.1 | NR | 28.2 |
| **Creatinine Clearance (mL/min) (%)** | | | | |
| <60 | 39 | 29.3 | 43 | 36.6 |
| <30 | -- | 3.7 | 7.5 | 10.8 |
| **Stage ISS, (%)** | | | | |
| III | 22 | 13.7 | 32.9 | 36.4 |
| **Previous lines of therapy, median (range)** | 3 (2-4) | 2 (2-7) | 3 (3-3) | 2 (1-9) |
| **Prior daratumumab exposure (%)** | -- | 18.9 | 4.7 | 26.5 |
| **Lenalidomide refractory (%)** | 94 | 98.5 | 100* | 73.1 |
| **FISH analysis (%)** | | | | |
| High Risk° | 33.1 | 29.3 | 14 | 13.6 |
| **ORR (%)** | 63 | 74.1 | 66.4 | 46.3 |
| **median PFS (months)** | 11.1 | 15.7 | 10.9 | 12.4 |
| **median OS (months)** | 24.6 | NR | 18.8 | NR |
| **median TTNT (months)** | 15.5 | 17.7 | NA | 15.1 |
| **Grade 3-4 adverse events (%)** | | | | |
| Anemia | 35 | 13.7 | 8.4 | NA |
| Neutropenia | 51 | 56.3 | 45.8 | NA |
| Thrombocytopenia | 13 | 15.9 | 14 | NA |
| Infections | 53 | 47.8 | 18.7 | NA |
| Pneumonia | 23 | 26.7 | NA | NA |
| Fatigue | 4 | 16.3 | 0.9 | NA |
| Gastrointestinal toxicity | 9 | 6.3 | NA | NA |

*Lenalidomide exposed; *High Risk= patients with the presence of either t(4;14), or t(14;16) or del(17p); NR= not reached; NA= not available

**Supplementary Table 2. Univariable and multivariable analyses for PFS (Panel 1) and OS (Panel 2).**

**PANEL 1**

| | | Univariable analysis | | | Multivariable analysis | |
|---|---|---|---|---|---|---|
| | N | PFS @ 24 months | HR (%95 CI) | P-value | HR (%95 CI) | P-value |
| **Age, (years)** | | | | | | |
| ≤70 | 159 | 44.1 | | | | |
| >70 | 111 | 31.3 | 1.35 (0.98-1.85) | 0.064 | | |
| **Gender** | | | | | | |
| Male | 147 | 39 | | | | |
| Female | 123 | 39.1 | 1.16 (0.84-1.59) | 0.37 | | |
| **Creatinine Clearance mL/min** | | | | | | |
| ≥60 | 191 | 43 | | | | |
| <60 | 79 | 28.7 | 1.49 (1.07-2.09) | **0.019** | 1.15 (0.79-1.68) | 0.44 |
| **ISS** | | | | | | |
| I | 131 | 48.6 | | | | |
| II | 102 | 35.6 | 1.57 (1.1-2.22) | **0.011** | 1.47 (1.03-2.12) | **0.035** |
| III | 37 | 14.1 | 3.14 (1.99-4.96) | **<0.0001** | 2.44 (1.45-4.1) | **0.001** |
| **LDH serum level** | | | | | | |
| Normal | 222 | 42.5 | | | | |
| Elevated | 48 | 21.7 | 1.84 (1.26-2.69) | **0.001** | 1.51 (1.02-2.25) | **0.04** |
| **Previous lines of therapy** | | | | | | |
| 2 | 172 | 40.4 | | | | |
| >2 | 98 | 36.1 | 1.23 (0.90-1.7) | 0.19 | | |
| **Previous ASCT** | | | | | | |
| No | 107 | 36.7 | | | | |
| Yes | 163 | 40.5 | 1.08 (0.78-1.48) | 0.63 | | |
| **Previous daratumumab** | | | | | | |
| No | 219 | 42.9 | | | | |
| Yes | 51 | 16.3 | 2.12 (1.43-3.13) | **<0.0001** | 1.87 (1.26-2.79) | **0.002** |
| **Disease status** | | | | | | |
| Biochemical relapse | 57 | 44.6 | | | | |
| Symptomatic relapse | 141 | 38.7 | 1.21 (0.78-1.85) | 0.39 | | |
| Refractory to last treatment | 72 | 33.8 | 1.59 (0.98-2.54) | 0.06 | | |

**PANEL 2**

| | | Univariable analysis | | | Multivariable analysis | |
|---|---|---|---|---|---|---|
| | N | OS @ 24 months | HR (%95 CI) | P-value | HR (%95 CI) | P-value |
| **Age, (years)** | | | | | | |
| ≤70 | 159 | 66.9 | | | | |
| >70 | 111 | 60.2 | 1.42 (0.93-2.17) | 0.11 | - | |
| **Gender** | | | | | | |
| Male | 147 | 62.2 | | | | |
| Female | 123 | 66.9 | 0.95 (0.62-1.46) | 0.82 | - | |
| **Creatinine Clearance mL/min** | | | | | | |
| ≥60 | 191 | 70.1 | | | | |
| <60 | 79 | 49.5 | 2.05 (1.33-3.16) | **0.001** | 1.52 (0.94-2.46) | 0.088 |
| **ISS** | | | | | | |
| I | 131 | 75.1 | | | | |
| II | 102 | 60.8 | 2.03 (1.24-3.33) | **0.005** | 1.77 (1.06-2.95) | **0.029** |
| III | 37 | 31.1 | 3.63 (2.0-6.59) | **<0.0001** | 2.23 (1.13-4.4) | **0.02** |
| **LDH serum level** | | | | | | |
| Normal | 222 | 68.9 | | | | |
| Elevated | 48 | 42.9 | 2.44 (1.53-3.89) | **<0.0001** | 2 (1.22-3.28) | **0.006** |
| **Previous lines of therapy** | | | | | | |
| 2 | 172 | 68.1 | | | | |
| >2 | 98 | 57.5 | 1.59 (1.04-2.44) | **0.032** | 1.26 (0.8-1.98) | 0.31 |
| **Previous ASCT** | | | | | | |
| No | 107 | 66.2 | | | | |
| Yes | 163 | 62.7 | 1.07 (0.69-1.65) | 0.77 | - | |
| **Previous daratumumab** | | | | | | |
| No | 219 | 68.8 | | | | |
| Yes | 51 | 36.0 | 2.05 (1.25-3.38) | **0.005** | 1.6 (0.95-2.71) | 0.079 |
| **Disease status** | | | | | | |
| Biochemical relapse | 57 | 73.8 | | | | |
| Symptomatic relapse | 141 | 62.1 | 1.48 (0.8-2.7) | 0.21 | - | |
| Refractory to last treatment | 72 | 61 | 1.9 (0.98-3.72) | 0.06 | - | |

**Supplementary Table 3. Salvage therapy regimens after IsaPd.**

| Salvage therapy regimen | No of cases (%) |
|---|---|
| **Ab drug-conjugates** | **38 (33.9)** |
| Belantamab | 38 (33.9) |
| **PI containing regimens** | **27 (24.1)** |
| Kd | 9 (8) |
| KRd | 1 (0.9) |
| V-Ctx-d | 4 (3.6) |
| V-Benda-d | 1 (0.9) |
| VMP | 1 (0.9) |
| V-Caelyx-d | 2 (1.8) |
| Ixa-Rd | 8 (7.1) |
| Ixa-Ctx-d | 1 (0.9) |
| **XPO-1 inhibitor-containing regimens** | **9 (8)** |
| Selinexor | 1 (0.9) |
| SVd | 8 (7.1) |
| **BsAbs** | **8 (7.1)** |
| Teclistamab | 6 (5.4) |
| Talquetamab | 1 (0.9) |
| RO7425781 | 1 (0.9) |
| **Anti-SLAMF-7 containing regimens** | **1 (0.9)** |
| EloPd | 1 (0.9) |
| **CAR T-cell therapy** | **1 (0.9)** |
| Ciltacabtagene autoleucel | 1 (0.9) |
| **Other therapies** | **28 (25)** |
| Bendamustine | 1 (0.9) |
| Ctx | 20 (17.9) |
| CHOP | 2 (1.8) |
| Melphalan | 1 (0.9) |
| Melflufen | 2 (1.8) |
| D-PACE | 2 (1.8) |

**Legend**: Ab=antibody; PI=proteasome inhibitor; Kd=carfilzomib, dexamethasone; KRd=carfilzomib, lenalidomide, dexamethasone; V-Ctx-d=bortezomib, cyclophosphamide, dexamethasone; V-benda-d=bortezomib, bendamustine, dexamethasone; VMP=bortezomib, melphalan, prednisone; V-Caelyx-d=bortezomib, caelyx, dexamethasone; IxaRd=ixazomib, lenalidomide, dexamethasone; Ixa-Ctx-d=ixazomib, cyclophosphamide, dexamethasone; XPO-1=exportin-1; SVd=selinexor, bortezomib, dexamethasone; EloPd=elotuzumab, pomalidomide, dexamethasone; Ctx=cyclophosphamide; CHOP=cyclophosphamide, doxorubicin, vincristine, prednisone; D-PACE=dexamethasone, cisplatin, doxorubicin, cyclophosphamide, etoposide.