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# Treatment Cost in Patients with Relapsed Refractory Multiple Myeloma in Japan

Hitesh Bhandari,[1] Sandeep Tripathi,[1] Michael LoPresti,[2] Sandip Ranjan[1]

[1]SmartAnalyst India Pvt. Ltd, Gurugram, India, [2]INTAGE Healthcare Inc., Tokyo, Japan

## BACKGROUND

- Multiple myeloma (MM) is a malignant B-cell neoplasm accounting for 15% of all blood cancers and 0.8% of all new cancer cases in Japan.[1,2] Annual incidence and 5-year prevalence rates of MM were reported as 1.3 to 5.4 and 9.7 per 100,000 persons, respectively.[3]
- Approval of new treatment regimens over the past two decades have improved the overall survival from a median of 39 months in 1900-2000 to 61 months in 2001-2012.[4]
- While recent advancements in medical oncology have led to the development of multiple agents which has improved the survival outcomes, MM still remains an incurable disease and almost all MM patients experience periods of disease relapse despite treatment.[5]
- Treatment guidelines for patients with relapsed or refractory multiple myeloma (RRMM) offer many therapeutic options mostly as combination therapies of the various novel agents.[6] Given that most of the regimens recommended for RRMM are administered until progression, there is a concern that these may lead to an increase in cost of treatment especially the drug costs.
- The aim of this study was to compare drug treatment costs and drug cost per progression-free life year (PFLY) for the key regimens recommended for RRMM in Japan.

## METHODS

### List of regimens included in analysis

- The regimens included in the analysis were based on RRMM treatment guidelines in Japan. These included doublet and triplet regimens containing the following agents: bortezomib (Bort), lenalidomide (Len), ixazomib (Ixa), panobinostat (Pano), carfilzomib (Carf), pomalidomide (Pom), elotuzumab (Elo), daratumumab (Dara), cyclophosphamide (Cyclo) and dexamethasone (Dex).[6]
- The regimens included in the analysis were Bortezomib ± Dexamethasone (BortDex), Dexamethasone + Ixazomib + Lenalidomide (IxaLenDex), Elotuzumab + Lenalidomide + Dexamethasone (EloLenDex), Daratumumab + Lenalidomide + Dexamethasone (DaraLenDex), Bortezomib + Cyclophosphamide + Dexamethasone (BortCycloDex), Lenalidomide + Dexamethasone (LenDex), Panobinostat + Bortezomib + Dexamethasone (PanBortDex), Daratumumab + Bortezomib + Dexamethasone (DaraBortDex), Carfilzomib + Dexamethasone (CarfDex), Carfilzomib + Lenalidomide + Dexamethasone (CarfLenDex) and Pomalidomide + Dexamethasone (PomDex).

### Dosing, duration of treatment and progression-free survival

- For all regimens, the dosage and dosing schedule have been sourced from respective registrational trial or relevant treatment protocols. Body surface area and weight were assumed to be 1.7 $m^2$ and 60 kg, respectively.
- Duration of treatment (DOT) and progression-free survival(PFS) data were obtained from the respective studies of the regimens.

### Table 1: Dosing, duration of treatment and progression-free survival for regimens included in the analysis

| Regimen | Dosing | DOT (months) | PFS (months) | Trial/Source |
|---|---|---|---|---|
| BortDex | Bort: 1.3 mg/$m^2$ IV/SQ; Days 1, 4, 8, and 11 in cycles 1-8; Days 1 and 8 for cycle 9 onwards, Dex: 20 mg PO; Days 1, 2, 4, 5, 8, 9, 11 and 12 in cycle 1-8; Days 1, 2, 8, 9, 22, 23, 29 and 30 in cycle 9 onwards; 21-day cycle | 4.1 | 6.2 | APEX[7] |
| LenDex | Len: 25 mg PO on days 1-21, Dex: 40 mg PO on days 1-4, 9-12 and 17-20 for cycles 1-4 and on days 1-4 for cycle 5+; 28-day cycle | 10.3 | 11.0 | MM-009/010[8,9] |
| PomDex | Pom: 4mg PO on days 1-21, Dex: 40mg (<75years) or 20mg (>=75 yrs) PO on days 1,8,15,22; 28-day cycle | 3.6 | 4.0 | MM-003[10] |
| CarfDex | Carf: 20 mg/m2 IV on days 1-2 and 56 mg/$m^2$ IV on days 8, 9, 15, 16, 22 and 23 in cycle1; 56 mg/$m^2$ IV on days 1, 2, 8, 9, 15, 16, 22 and 23 in cycle 2 onwards; Dex: 20 mg on days 1, 2, 8, 9, 15, 16, 22 and 23; 28-day cycle. | 9.3 | 18.7 | ENDEAVOR[11] |
| BortCycloDex | Bort: 1.3mg/$m^2$ IV/SQ on days 1, 4, 8, 11, Cyclo: 150 mg/$m^2$ PO on days 1-4, Dex: 20 mg/$m^2$ PO on days 1, 4, 8, 11; 21 day cycle | 4.2 | 13.6 | Ahn J 2012[12] |
| PanBortDex | Pan: 20mg PO on days 1, 3, 5, 8, 10, 12 for 16 cycles; Bort: 1.3mg/$m^2$ IV/SQ on days 1,4,8,11 in cycles 1-8 and on days 1, 8 in cycles 9-16; Dex: 20mg PO on days, 1,2,4,5,8,9,11,12 in cycles 1-8 and on days 1,2,8,9 in cycles 9-16; 21 day cycle | 5.0 | 12.0 | PANORAMA-1[13] |
| IxaLenDex | Ixa: 4 mg PO on days 1, 8, and 15; Len: 25 mg PO on days 1-21; Dex: 40mg PO on days 1, 8, 15 and 22; 28 day cycle | 15.9 | 20.6 | TOURMALINE-MM1[14] |
| CarfLenDex | Len: 25 mg PO on days 1-21; Carf: 20 mg/m2 IV days 1-2 and 27 mg/$m^2$ IV on days 8, 9, 15, 16 in cycle1; 27 mg/$m^2$ IV on days 1, 2, 8, 9, 15, 16 in cycles 2-12; 27mg/$m^2$ IV on days 1,2,15,16 in cycles 13-18; Dex; 40mg PO on days 1, 8, 15 and 22; 28 day cycle | 20.5 | 26.3 | ASPIRE[15] |
| DaraBortDex | Dara: 16 mg/kg IV once a week for weeks 1-9; once every three weeks for weeks 10-24; once every four weeks for week 25+; Bort: 1.3mg/$m^2$ IV/SQ on days 1, 4, 8, 11 for 8 cycles of 21-day each; Dex: 20mg PO on days 1-2, 4-5, 8-9, 11-12 for 8 cycles of 21-day each | 13.4 | 16.7 | CASTOR[16] |
| EloLenDex | Elo: 10 mg/kg IV on days 1, 8, 15, and 22 in cycles 1-2 and on days 1, 15 in cycle 3+; Len: 25 mg PO on days 1-21; Dex: on days 1, 8, 15, 22 - 28mg PO + 8mg IV on days coinciding with elo dose and 40 mg PO on days without elo dose; 28 day cycle | 17.7 | 19.4 | ELOQUENT-2[17] |
| DaraLenDex | Dara: 16 mg/kg IV once a week for weeks 1-8; once every two weeks for weeks 9-24; once every four weeks for week 25+; Len: 25 mg PO on days 1-21; Dex: 20 or 40mg PO on days 1, 8, 15, and 22; 28 days cycle | 34.3 | 45.8 | POLLUX[18] |

IV, Intravenous; PO, oral; SQ, subcutaneous; yrs, years

### Unit Costs

- Drug acquisition costs were based on reimbursement costs per unit in FY2019 as obtained from INTAGE Healthcare internal database DI Track®.[19]
- Unit costs for drug administration have been obtained from the national reimbursement tariff list in FY2019 provided by Ministry of Health, Labor and Welfare.
  - For IV drugs, in addition to dispensing and administration fees, facility charges of ¥6,000 per administration were applied.
  - For oral agents, a dispensing and prescription fee was applied.

### Cost analysis

- Using the dosing information and unit costs, cost per dose were obtained for each agent. Month-on-month costs were estimated for each regimen based on the dosing schedule and cost per dose.
- Costs were cumulated over DOT to estimate per-patient total drug treatment cost which was then divided by PFS duration to estimate drug cost per PFLY for each regimen.

### Table 2: Unit costs for drugs

| Generic name | Brand name | Formulation | Reimbursement level per unit (JPY) |
|---|---|---|---|
| Bortezomib | Velcade | Injection | 3mg: ¥139,827.0 |
| Carfilzomib | Kyprolis | IV infusion | 10mg: ¥24,426.0; 40mg: ¥87,852.0 |
| Cyclophosphamide | Endoxan | Tablet | 50mg: ¥30.3 |
| | Endoxan | Powder | 100mg: ¥160.3 |
| Daratumumab | Darzalex | IV infusion | 100mg: ¥52,262.0; 400mg: ¥187,970.0 |
| Dexamethasone | LenaDex | Tablet | 4mg: ¥172.5 |
| | Dexart | Injection | 1.65mg: ¥57.0; 3.3mg: ¥88.0; 6.6mg: ¥158.0 |
| Elotuzumab | Empliciti | IV infusion | 300mg: ¥163,672; 400mg: ¥213,468.0 |
| Ixazomib | Ninlaro | Capsule | 4mg: ¥163,865.4 |
| Lenalidomide | Revlimid | Capsule | 5mg: ¥9,512.1 |
| Panobinostat | Farydak | Capsule | 10mg: ¥37,261.4 |
| Pomalidomide | Pomalyst | Capsule | 4mg: ¥61,669.3 |

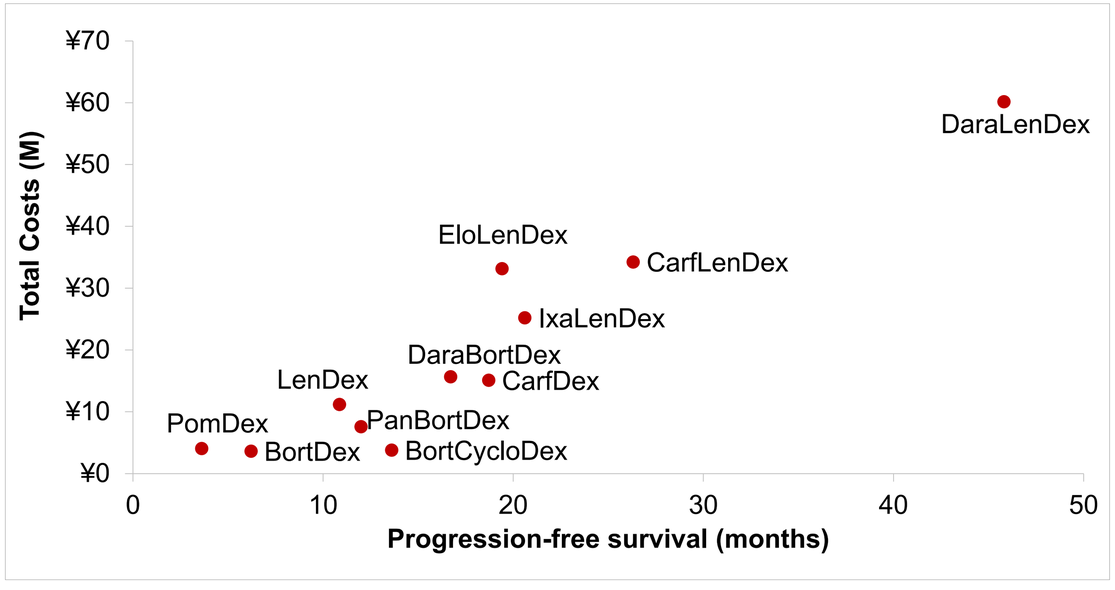
## RESULTS

- PFS varied from 4 months for PomDex to 46 months for DaraLenDex **(Table 1).**
- Total drug cost, including drug acquisition costs and administration costs, for one line of treatment with the various regimens showed a wide variation. It ranged from ¥3.6M for BortDex to ¥60.2M for DaraLenDex **(Table 3, Figure 1)**. Total drug costs were
  - below ¥10M for BortDex, PomDex, BortCycloDex, and PanBortDex.
  - between ¥10M - ¥20M for CarfDex, LenDex and DaraBortDex.
  - greater than ¥20M for IxaLenDex, CarfLenDex, EloLenDex and DaraLenDex.
- Drug cost per PFLY ranged from ¥3.3M for BortCycloDex to ¥20.5M for EloLenDex **(Figure 2).**

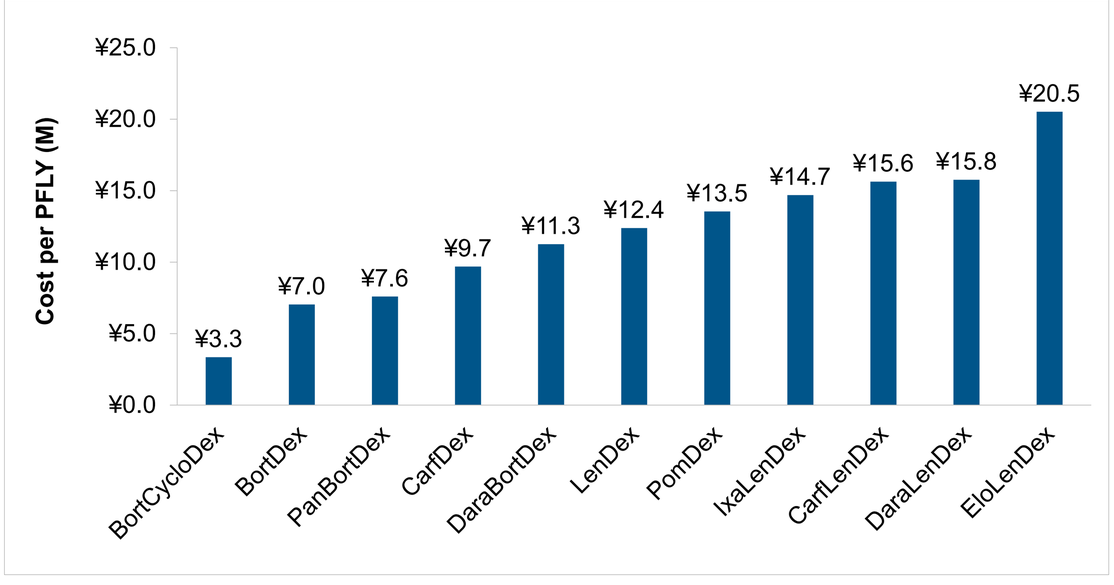
### Table 3: Total drug costs for various RRMM regimens

| | Bort Dex | Len Dex | Pom Dex | Carf Dex | BortCyclo Dex | PanBort Dex | IxaLen Dex | CarfLen Dex | DaraBort Dex | EloLen Dex | DaraLen Dex |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Total costs, JPY (M) | ¥3.6 | ¥11.2 | ¥4.1 | ¥15.1 | ¥3.8 | ¥7.6 | ¥25.2 | ¥34.3 | ¥15.7 | ¥33.2 | ¥60.2 |

### Figure 1: Total treatment costs and PFS for various RRMM regimens




### Figure 2: Total treatment costs per PFLY for various RRMM regimens




- Drug costs for triplet regimens were substantially higher than the doublet regimens.
  - Triplet regimens with LenDex as the backbone treatment had higher costs compared to those with BortDex as the backbone therapy owing to fact that lenalidomide is administered till disease progression whereas bortezomib is administered only for a fixed duration.

## CONCLUSION

- RRMM drug treatment cost in Japan varies significantly depending upon the regimen being prescribed.
- While the newer treatment options have improved PFS for RRMM patients, they have also resulted in substantial increase in drug costs.
- Further analysis should be conducted to explore the overall costs of treatment by including other medical costs such as monitoring, diagnostic tests, adverse event management costs etc, in the analysis.

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