# Key Paper Summary

Winstone J, Chadda S, Ralston S, Sajosi P. Review and comparison of clinical evidence submitted to support European Medicines Agency market authorization of orphan-designated oncological treatments. *Orphanet J Rare Dis* 2015;10:139

Open access publication available from: http://www.ojrd.com/content/10/1/139

**In a review of clinical trials of orphan drug treatments approved by the European Medicines Agency (EMA), Mepact® (mifamurtide) had the largest number of patient-years of follow-up (4068 patient-years) despite the low prevalence of the disease (0.5/10,000 persons)**

## Background

Clinical data submitted to support applications for EMA marketing authorization for orphan conditions may be less robust than non-orphan conditions as trials are often limited by low patient numbers, inadequate follow-up, lack of randomisation and the use of surrogate endpoints.

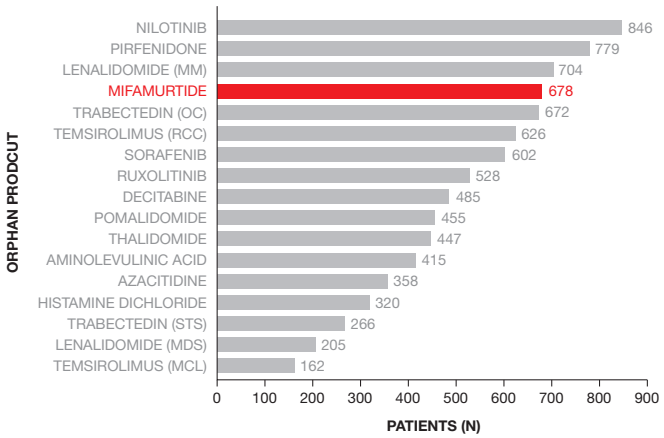
## Aims & Methods

- This study evaluated the pivotal clinical evidence packages presented to the EMA for orphan-designated treatments, comparing:
  - The number of patients included in pivotal trials
  - Cumulative duration of follow-up in pivotal trials (patient years)
  - Prevalence of the orphan condition
- All treatments reviewed were in ATC category L (antineoplastic and immuno-modulating agents) that includes nearly 50% of all EMA approved orphan-designated treatments
- All treatments were approved between 31 December 2006 - 1 February 2014
- All treatments had ≥1 survival based clinical endpoint (no short-term surrogate endpoints)

## Results & Conclusions

- A total of 14 products (17 studies) met all the study inclusion criteria. The overall quality of these trials was moderate as measured by the Jadad scoring system.

**Figure A.**
**Number of patients included in pivotal trials**




**Range 162-846 (median 485)**

MM, multiple myeloma; OC, ovarian cancer; RCC, renal cell carcinoma; STS, soft tissue sarcoma; MDS, myelodysplastic syndrome; MCL, mantle cell lymphoma

*Redrawn from Winstone J et al. Orphanet J Rare Dis 2015:10:139*

Mepact® mifamurtide



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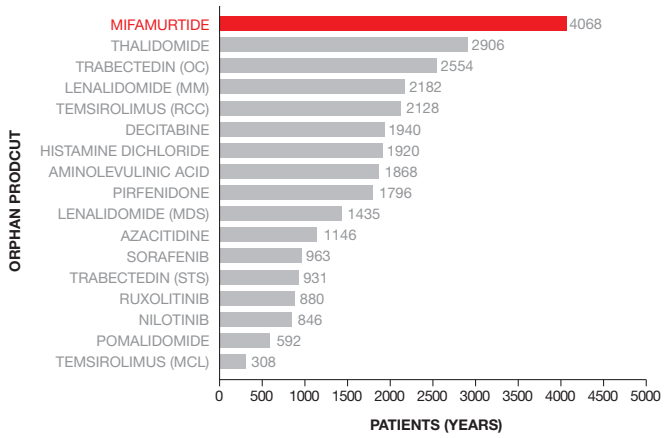
# Key Paper Summary *(cont.)*

**Figure B.**
**Cumulative duration of follow-up (patient years)**

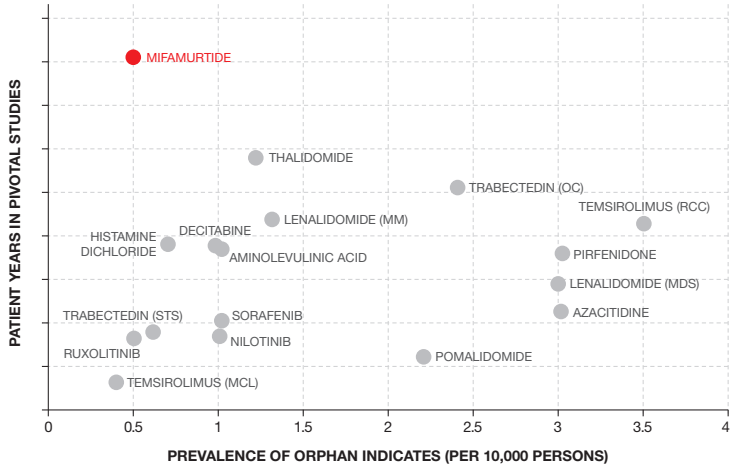



**Excluding mifamurtide: Range 308-2906 (median 1615*)**

MM, multiple myeloma; OC, ovarian cancer; RCC, renal cell carcinoma; STS, soft tissue sarcoma; MDS, myelodysplastic syndrome; MCL, mantle cell lymphoma

*Redrawn from Winstone J et al. Orphanet J Rare Dis 2015:10:139*

**Figure C.**
**Trial follow-up compared with disease prevalence**




MM, multiple myeloma; OC, ovarian cancer; RCC, renal cell carcinoma; STS, soft tissue sarcoma; MDS, myelodysplastic syndrome; MCL, mantle cell lymphoma

*Redrawn from Winstone J et al. Orphanet J Rare Dis 2015:10:139*

- The study of Mepact in osteosarcoma had the largest number of patient-years of follow-up (4068 patient-years) despite the low prevalence of the disease (0.5/10,000 persons) which provided the second smallest eligible patient population (after mantle cell lymphoma)
- This study shows that it is possible to conduct studies with an adequate patient size and duration of follow-up, and a comparative design with clinical, survival-based endpoints
- Pooling of expertise through establishment of rare disease reference networks and patient registries may improve the quality of clinical trial design included in EMA dossiers

* Please note: the calculation of median follow-up excluding mifamurtide of 1796 stated in the paper is incorrect.
The correct figures are:
Including mifamurtide: range 308-4068 (median 1796)
Excluding mifamurtide: range 308-2906 (median 1615)

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