# Activity and tolerability of lenalidomide (LLD) is enhanced following low-dose continuous percutaneous delivery compared to once daily dosing in an NCIH929 MM xenograft model in SCID mice.

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## ABSTRACT

**INTRODUCTION** The daily administration of lenalidomide (LLD) is well established in the treatment of MM. LLD has a short half-live, which leads to high peak to trough fluctuations leading to excessive or sub-therapeutic exposure with daily dosing while toxicity is associated with its high exposure (AUC). Continuous drug delivery is an ideal method to eliminate peak to trough variations and may improve tolerability and efficacy.

**METHODS**: The study employed an implantable osmotic pump (iPrecio) which can deliver a continuous s.c. infusion of LLD. An H929 MM xenograft was implanted in SCID mice and allowed to reach a tumor volume (TV) of > 100 $mm^3$ prior to any treatment. Six groups of N=10 animals were evaluated which included: Grp1 i.p. vehicle injected controls; Grp2 LLD 25 mg/kg i.p. once daily; Grp3 LLD 6 μg/hr sc; Grp4 LLD 2 μg/hr sc; Grp5 LLD 1 μg/hr sc; and, Grp6 LLD 0.5 μg/hr sc. Grps 3-6 received LLD by a continuous infusion while Grps 1-2 where dosed once a day Treatment was administered daily over 29-days. The maximum dose of 6 mcg/h as the MTD based on a separate tolerability study in healthy mice. TV was assessed by caliper measures and treatment failure was considered a TV of > 2000 $mm^3$. LLD pharmacokinetics were measured using a sparse technique. CBCs were also obtained in a sparse fashion. A separate toxicology study was performed in healthy male and female mice treated with continuous LLD at 6 μg/h and 2 μg/h compared to control vehicle over 29 days.

**RESULTS:** Changes in body weight were acceptable in all treatment groups. Animals in Grp 3 had a PR (60%) or CR (40%) while no animals in Grp 2 achieved a decrease in tumor volume. No animals in any other group had a PR or better. The time to 100% treatment failure was 53 days in Grp 2, 71 days in Grp 4, and >100 days in Grp3. In Grp 3, 2 animals remained tumor free at 100 days and were euthanized. The daily exposure (AUC) and dose (μg/day) in Grp3 was ~29% of that observed with a standard i.p. dose. Results from the toxicology study demonstrated no treatment-related histopathologic changes. There was no significant difference in any hematology parameters (e.g., WBC, ANC, platelets) compared to the vehicle controls at day 29.

**CONCLUSION:** To our knowledge, these data represent the first demonstration that dosing of LLD can be altered to improve the efficacy and tolerability of treatment. A percutaneous delivery of just 29% of the standard i.p. LLD dose was superior in disease control and can produced objective responses in this model. Tolerability in terms of body weight, histopathology, and hematology suggest no aberrant effects from continuous delivery. These data suggest percutaneous administration of continuous low-doses of LLD may improve the tolerability and efficacy compared to once daily dosing.

## METHODS

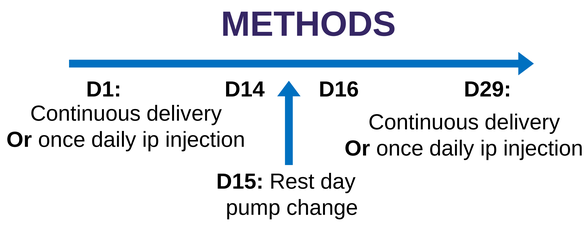
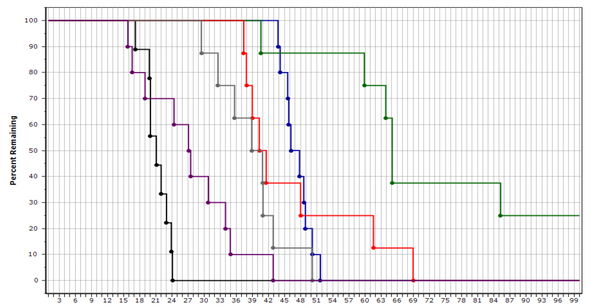



**Fig 1.** iPrecio Implantable pump

**Fig 2.** Implanted pump Refilled daily

## EFFICACY

**Fig 3.** Kaplan-Meier plot for all groups to 100% treatment failure




Group 1: vehicle (ip, qd x 14 / 1 day off / qd x 14)
Group 2: lenalidomide (25mg/kg, ip, qd x 14 / 1 day off / qd x 14)
Group 3: lenalidomide (144 μg/day, sc osm pump)
Group 4: lenalidomide (48 μg/day, sc osm pump)
Group 5: lenalidomide (24 μg/day, sc osm pump)
Group 6: lenalidomide (12 μg/day, sc osm pump)
} (continuous for 14 days / 1 day off / continuous for 14 days)

**Fig 4.** Tumor volume over the 29-day treatment cycle, Grp 1 - 3

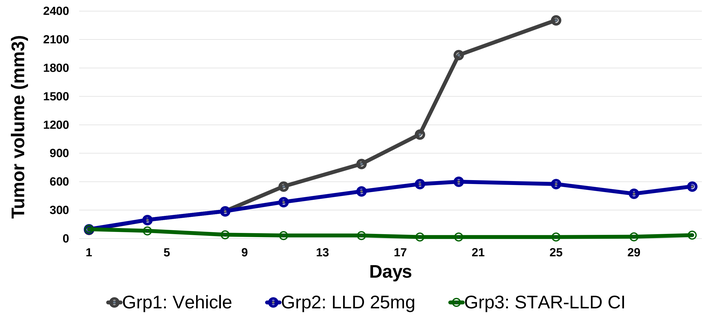



**Table 1.** Summary of Responses / Median Time to Endpoint / Days to 100% Treatment Failure / Nadir of Body Weight

| Group | n | Treatment Regimen 1 | | | | Median TTE | Days to TTF | PR | CR | TFS | BW Nadir |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Agent | Mcg/d | Route | Schedule | | | | | | |
| 1[#] | 10 | vehicle | - | ip | qd x 14 / 1 day off / qd x 14 | 21 | 25 | 0 | 0 | 0 | -0.1% |
| 2 | 10 | lenalidomide | 500 | ip | qd x 14 / 1 day off / qd x 14 | 47 | 53 | 0 | 0 | 0 | -1.2% |
| 3 | 10 | lenalidomide | 144* | sc osm pump[1] | continuous for 14 days / 1 day off / 14 days | 65 | >100 * | 6 | 4 | 2 | -4.9% |
| 4 | 10 | lenalidomide | 48* | sc osm pump[1] | continuous for 14 days / 1 day off / for 14 days | 41 | 71 | 0 | 0 | 0 | -8.0% |
| 5 | 10 | lenalidomide | 24* | sc osm pump[1] | continuous for 14 days / 1 day off / for 14 days | 40 | 53 | 0 | 0 | 0 | -3.3% |
| 6 | 10 | lenalidomide | 12* | sc osm pump[1] | continuous for 14 days / 1 day off / for 14 days | 27 | 43 | 0 | 0 | 0 | -1.9% |

TTE = time to endpoint
TTF = time to 100% treatment failure
TFS = tumor free survival
* P < 0.05 mean days to 100% TTF compared to ip lenalidomide

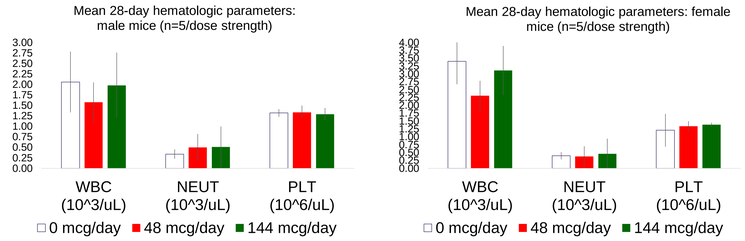
## SAFETY & PK

**Fig 5.** Semi-log plot of blood levels over each 24 hours


**Table 2.** Comparative daily dose and AUC, active treatments

| Group | Prescribed Dose | Daily Dose (mcg/day) | Median Actual Plasma Level (ng/mL) | AUC 0-24 (mcg/mL/hr) | % Exposure to Grp 2 by AUC | % Exposure to Grp 2 by Daily Dose |
|---|---|---|---|---|---|---|
| 2 | 25 mg/kg/d | 500 | 3075/1.99 | 10.9 | 100% | 100% |
| 3 | 6 mcg/hr | 144 | 125 | 2.6 | 23.4% | 28.8% |
| 4 | 2 mcg/hr | 48 | 41 | 0.9 | 7.8% | 9.6% |
| 5 | 1 mcg/hr | 24 | 27 | 0.6 | 5.2% | 4.8% |
| 6 | 0.5 mcg/hr | 12 | 12 | 0.3 | 2.3% | 2.4% |

**Fig 6.** Key blood counts in HEALTHY CB.17 mice following 29 days of continuous treatment from toxicology study




## CONCLUSIONS

- Low-dose continuous LLD delivery produces significant improvements in ORR
- Low-dose continuous LLD delivery produces significant improvements in TTF
- The most effective dose was >70% lower than the ip standard of care in this model
- Hematology parameters were no different in LLD-treated animals than vehicle control
- Changes in body weight during treatment were acceptable but slightly higher with continuous delivery
- Continuous delivery of LLD is superior to once daily dosing and is currently being evaluated in humans