Development of a Low-dose Percutaneous Delivery System of Lenalidomide for Hematologic Malignancies: The Journey from Ideation to Phase 2

Dr Jamie Oliver
Chief Medical Officer

STAR-LLD (lenalidomide) development strategy
Three unique continuous delivery technologies

Subcutaneous infusions
Ambulatory pump

Oral Controlled Release (OCR)
24 h blood levels with ± 20% deviation

Transdermal Patch Technologies
Adhesive matrix
Polymer dermal

Strong intellectual property protection

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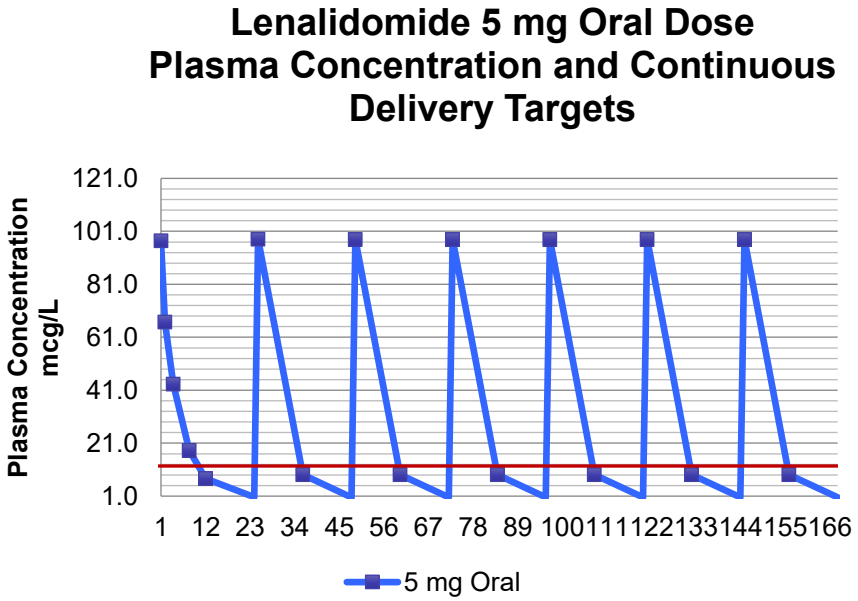
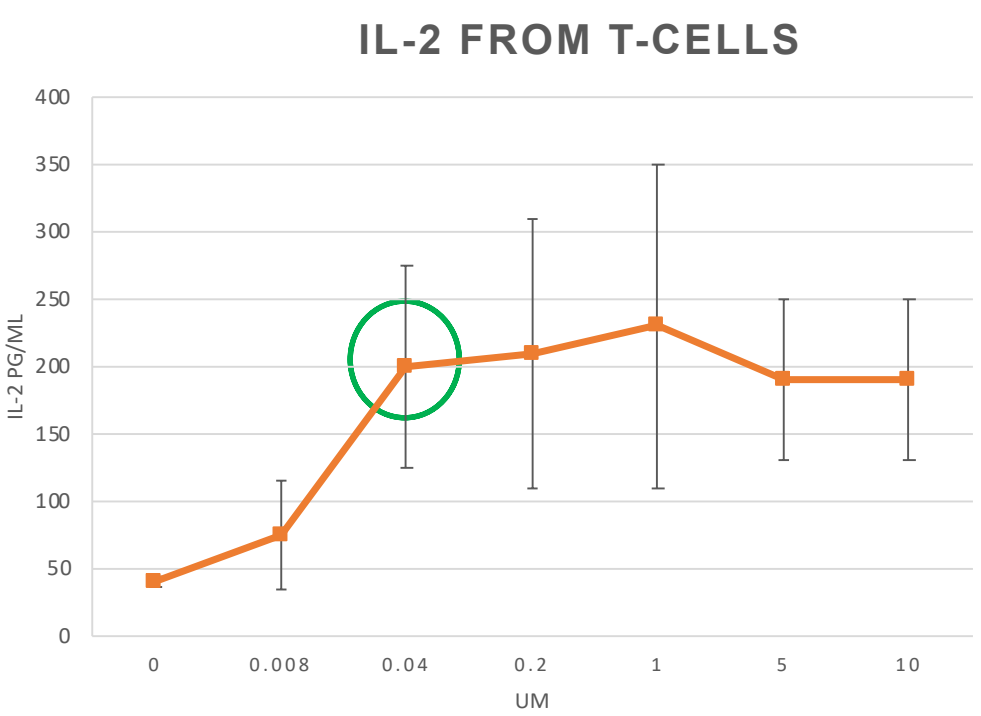
Lenalidomide (Revlimid)

- Flattening the blood concentration curve
- Used for a number of hematologic malignancies (MM/CLL)
- Has a very short half-life but administered 1x a day
- By 16 hours blood levels are subtherapeutic
- Toxicity is primarily related to AUC not Cmax
- Efficacy not associated with Cmax
- Continuous delivery is able to target effective blood levels without excess drug being administered
- We are targeting patients with MM who are experiencing toxicity with Revlimid
- Intend to follow with CLL maintenance with BTK inhibitor and/or venetoclax
- Other uses would be mantle cell, lymphomas, potentially prostate cancer
- Expand use to CAR-T cell progression and Bispecific antibody therapy

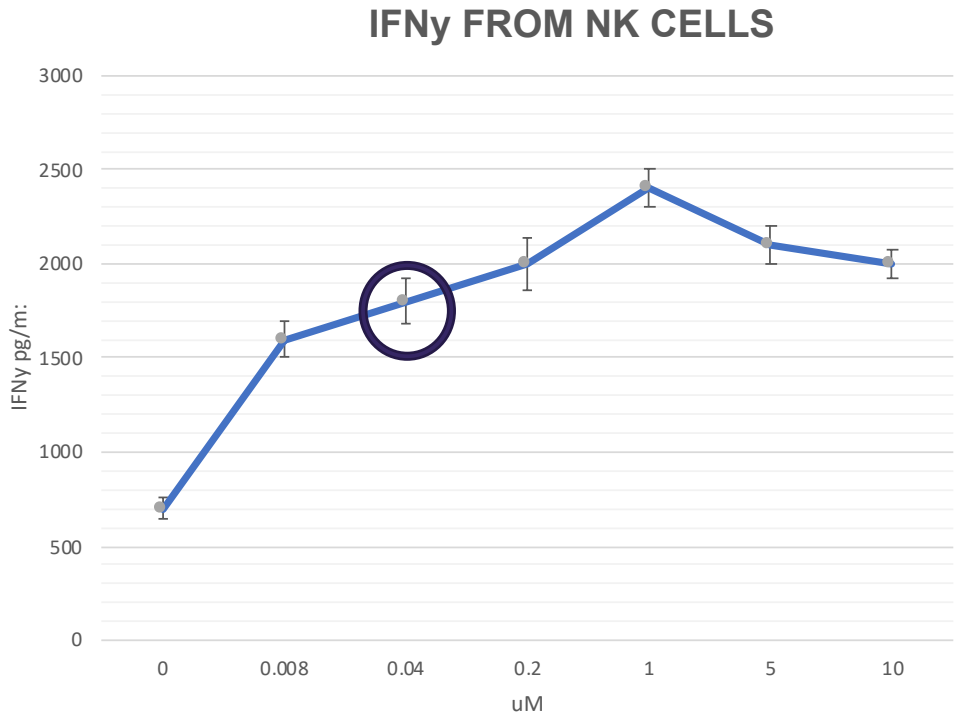


Defining targeted blood levels

Immune activation thresholds for lenalidomide in multiple myeloma



IL-2 release from T cells



IFN-y release from NK Cells

Minimum effective concentration is 0.04 µM/L = 10 ng/mL

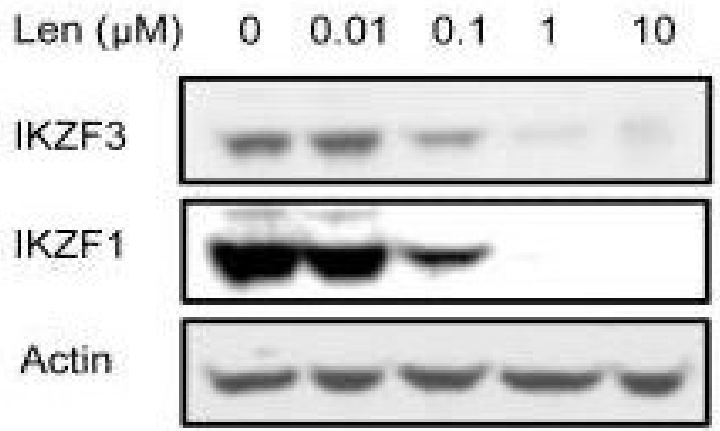
Constant exposure at the µM target produced these results

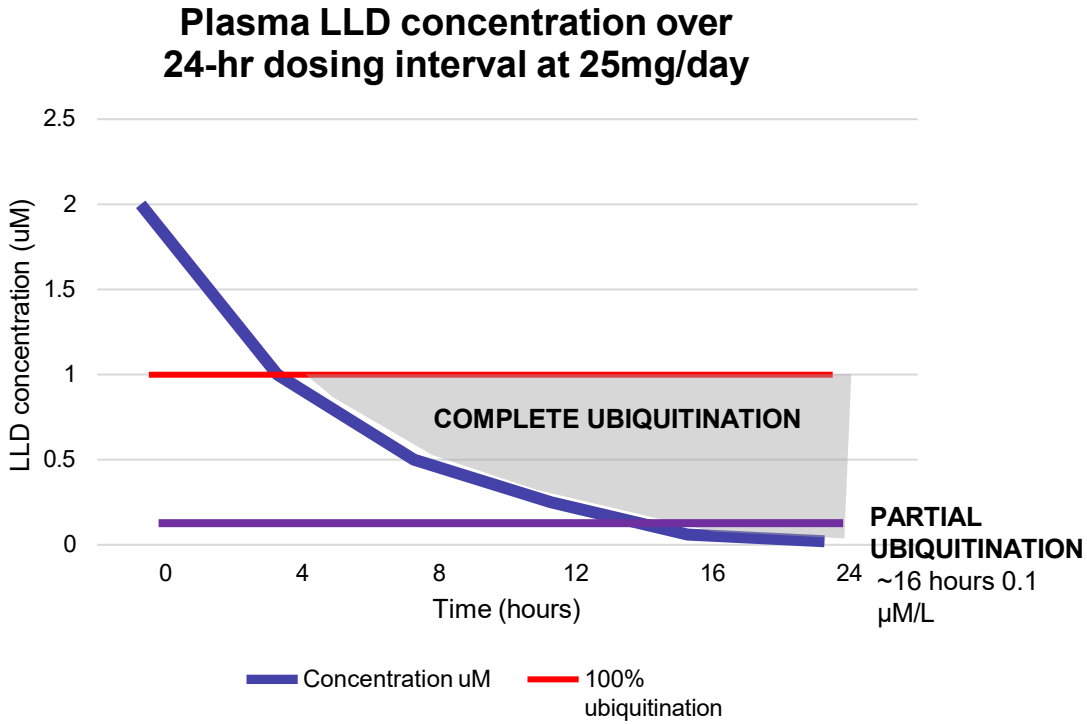
Gandhi et al Dexamethasone Synergizes with Lenalidomide to Inhibit Multiple Myeloma Tumor Growth, But Reduces Lenalidomide-Induced Immuno-modulation of T and NK Cell Function Current Cancer Drug Targets, 2010, 10, 155-167

STAR-LLD targets optimal dose-related cereblon activity

Continuous delivery concentration selected to induce ubiquitination of Ikaros/Aeolos proteins; IKZF1 and IKZF3

- Cereblon protein expressed in myeloma cell lines
- Cereblon expression an important biomarker of IMiD response
  (Stankova Klin Oncol 2014)
- Minimum LLD concentration to induce degradation of IKZF1/3 proteins 0.1 µM/L = 25 ng/mL *





Kronke et al. Science 2014: 343:301-305

https://www.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&retmode=ref&cmd=prlinks&id=24292625

* At maximum daily oral dose

Rodent Studies of PK, Safety, and Tolerability of LLD

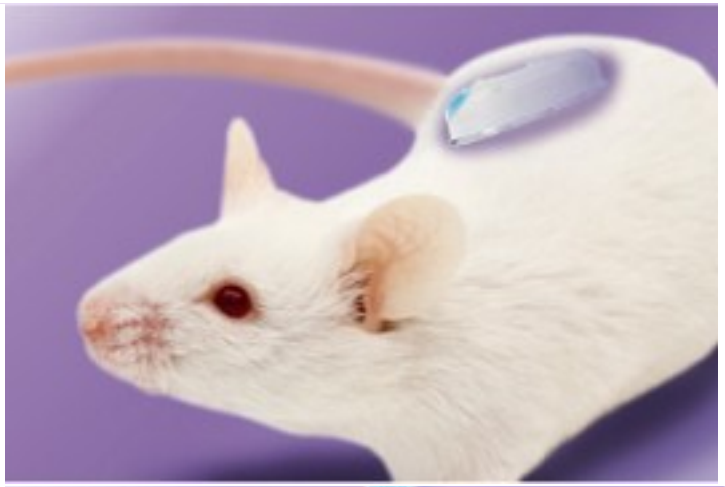
Lenalidomide (LLD) nonclinical rodent studies

- Multiphase project – Assess SC dosing and PK of Lenalidomide in mice
  - Step 1: Determine the mouse pharmacokinetics of LLD from literature and in vivo
  - Step 2: Create a parenteral formulation to achieve required solubility for optimal pump operation
  - Step 3: Model the once daily LLD i.p. control dose and s.c. test concentrations distributed above and below the dosing mid-point – Test with iPrecio pump for 10-days in CB17 healthy mice
  - Step 4: Assess PK and tolerability of 4 doses to translate to SCID mouse study
  - Step 5: Select 4 infusional doses plus once daily i.p. Len based on tolerability data
  - Step 6: Perform 29-day implantable pump treatment in CB17 NCI H929 xenograft SCID mice (100 mm^3 at start of treatment)
  - Step 7: Perform 26-day implantable pump treatment in CB17 RPMI IMiD resistant xenograft SCID (100 mm^3 at start of treatment)
  - Step 8: Perform a 28-day continuous infusion toxicology study in healthy CD20 mice

iPrecio wireless programable subcutaneous pump

The World's First, Smallest,
High precision,
Wirelessly controlled, Programmable
Implantable Micro Infusion Pump for Mice

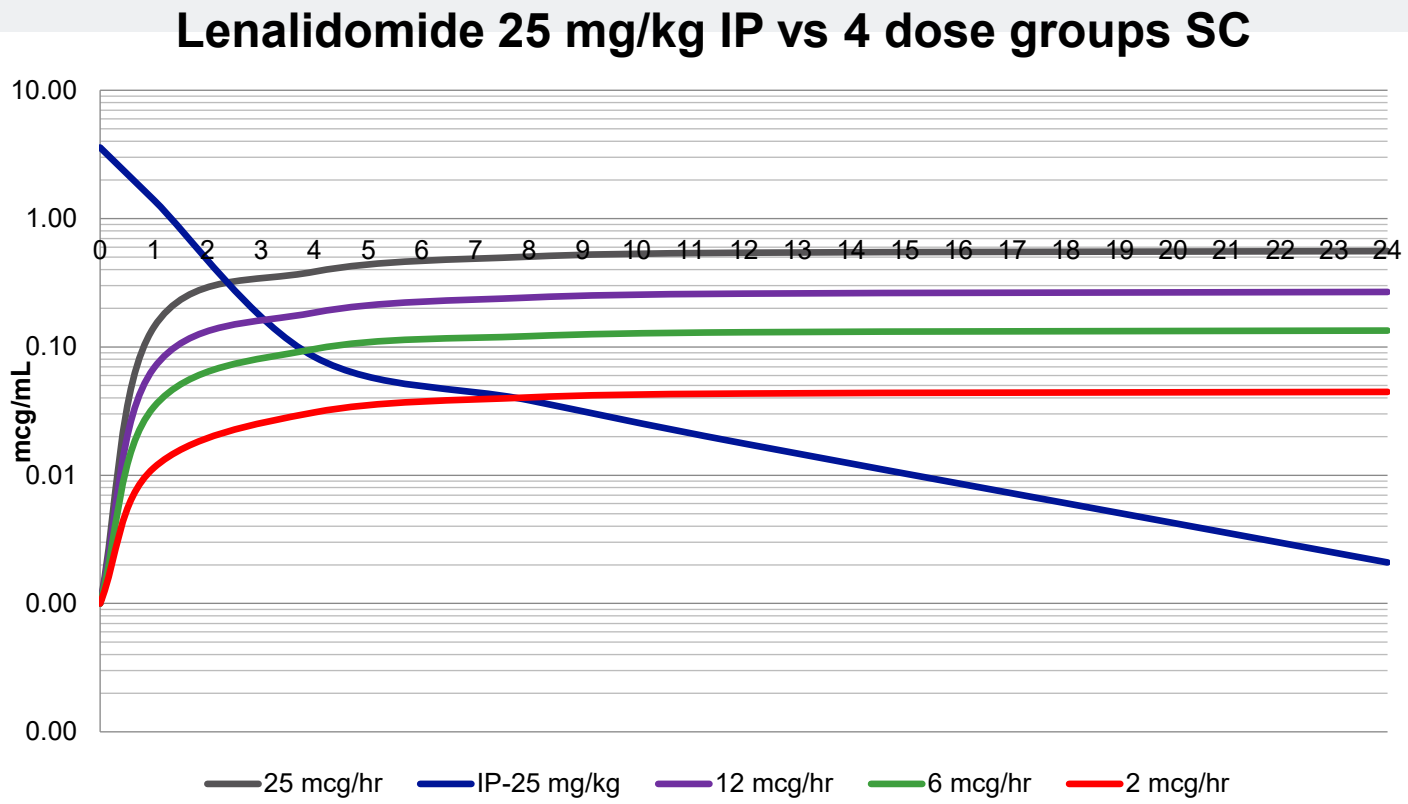
**Implantable,
Programmable
and Refillable**



NA-p354: preclinical rodent study 1 of 4: dose finding study in CB.17 mice

CB.17 mice
N=3 animals per group

Study evaluated tolerability of lenalidomide (LLD) intraperitoneal (IP) injection (standard of care in the MM model) vs. LLD continuous subcutaneous delivery in healthy mice



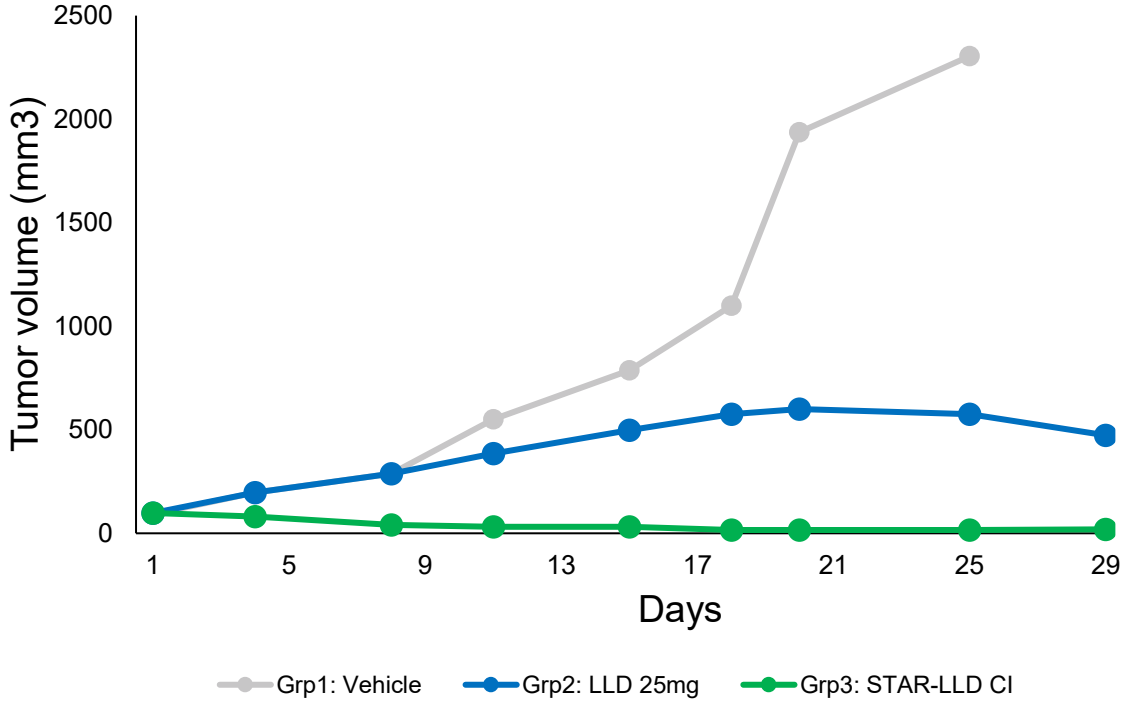
Agent	Active dose	Route	Schedule
vehicle	na	ip	qd x 10
lenalidomide	25 mg/kg (550 µg bolus)	ip	qd x 10
lenalidomide	600 µg/day	sc osm pump[1]	Continuous for 10 days
lenalidomide	288 µg/day	sc osm pump[1]	Continuous for 10 days
lenalidomide	144 µg/day	sc osm pump[1]	Continuous for 10 days
lenalidomide	48 µg/day	sc osm pump[1]	Continuous for 10 days

1- iPrecio subcutaneous(sc) pump

Study 2 of 4: Continuous LLD dosing in NCI H929 MM xenograft SCID mice

Gr.	N	Agent	Formulation dose	Active dose	Route	Schedule	Vehicle	Dosing volume scale ml/kg
1#	10	vehicle		na	ip	qd x 14 / 1 day off / qd x 14	-	10
2	10	lenalidomide	25 mg/kg	550 µg x1	ip	qd x 14 / 1 day off / qd x 14	-	10
3	10	lenalidomide	144 µg/day	144 µg/day	sc osm pump[1]	continuous for 14 days / 1 day off / continuous for 14 days	-	10
4	10	lenalidomide	48 µg/day	48 µg/day	sc osm pump[1]	continuous for 14 days / 1 day off / continuous for 14 days	-	10
5	10	lenalidomide	24 µg/day	24 µg/day	sc osm pump[1]	continuous for 14 days / 1 day off / continuous for 14 days	-	10
6	10	lenalidomide	12 µg/day	12 µg/day	sc osm pump[1]	continuous for 14 days / 1 day off / continuous for 14 days	-	10

H929-p216: lenalidomide continuous infusion displayed superior efficacy over standard of care at the end of active treatment



Group	Tumor volume change from BL (day 29)
GRP 1 (vehicle)	+ 2518%*
GRP 2 (lenalidomide IP 25mg/kg)	+ 483%
GRP 3 (144 µg/day continuous infusion)	- 81%

** = at failure < 25 days*

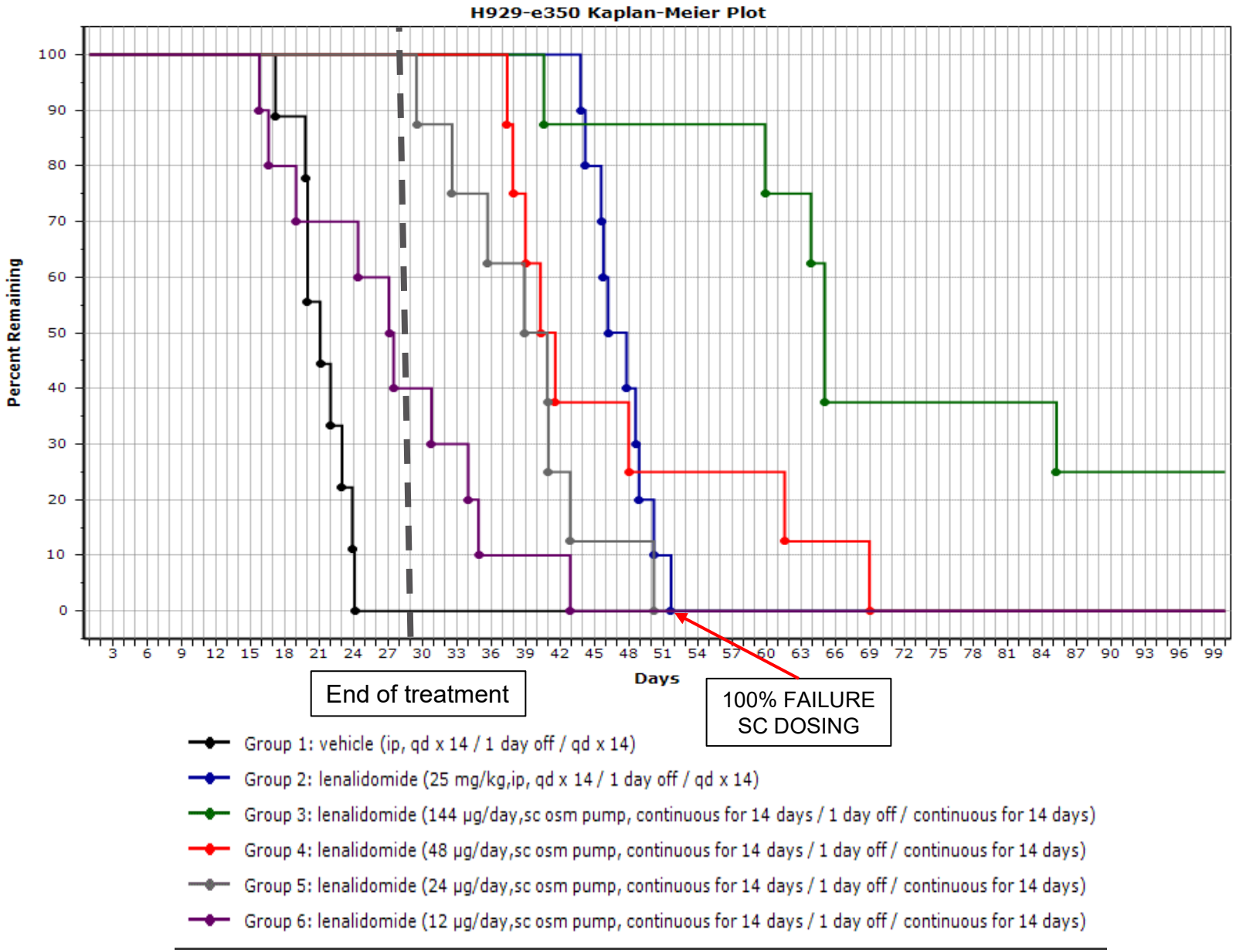
Data on file for 48ug/day strength

Baseline tumor volume 100mm3

SCID: severe combined immunodeficient

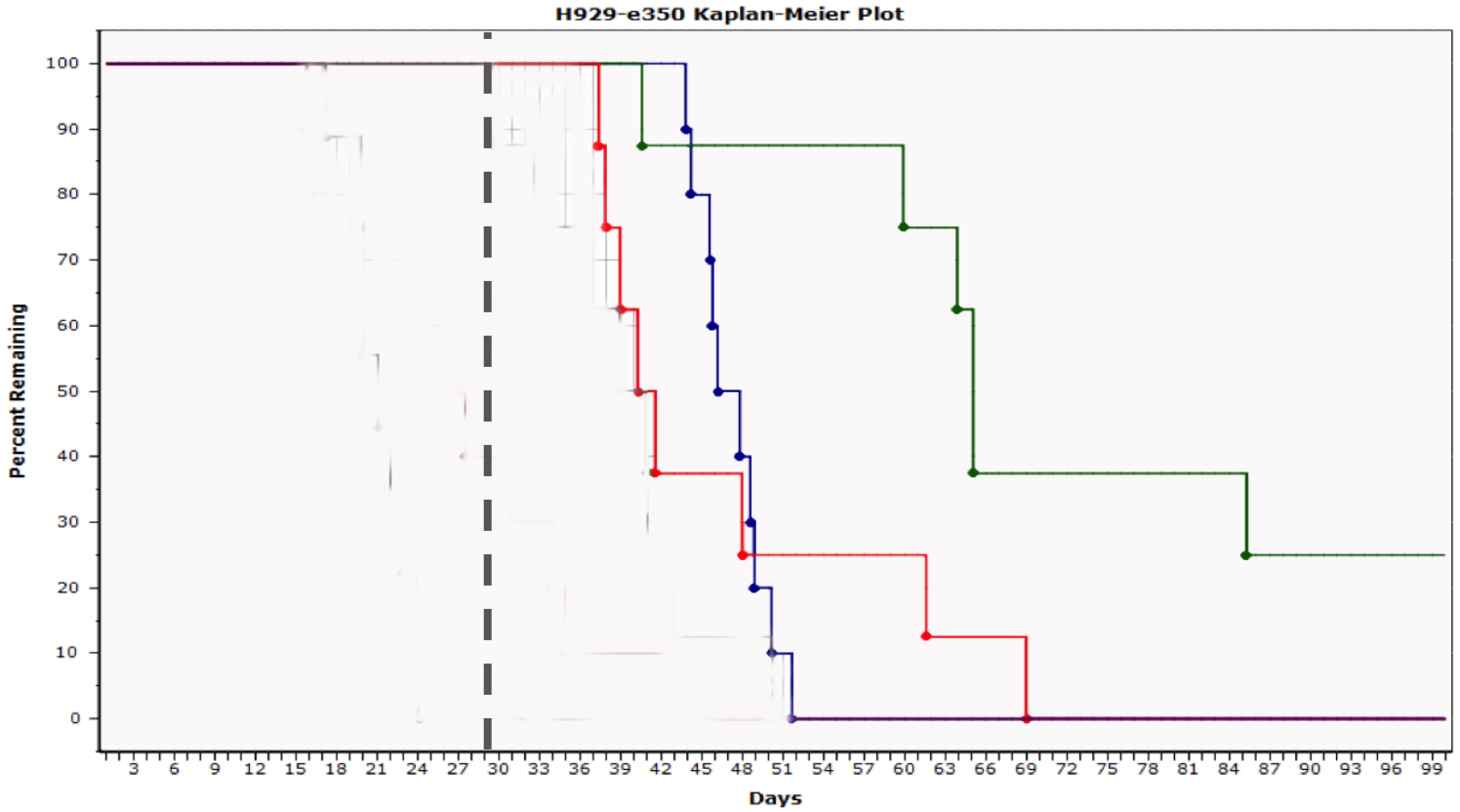
TTE = MEDIAN TIME TO TREATMENT ENDPOINT **TTF = TIME TO TOTAL GROUP TREATMENT FAILURE**

Lenalidomide rodent studies – results – efficacy – time to treatment failure



2 animals with Tumor Free Survival

H929-p216: RESULTS – EFFICACY – Time to Treatment Failure (TTF)



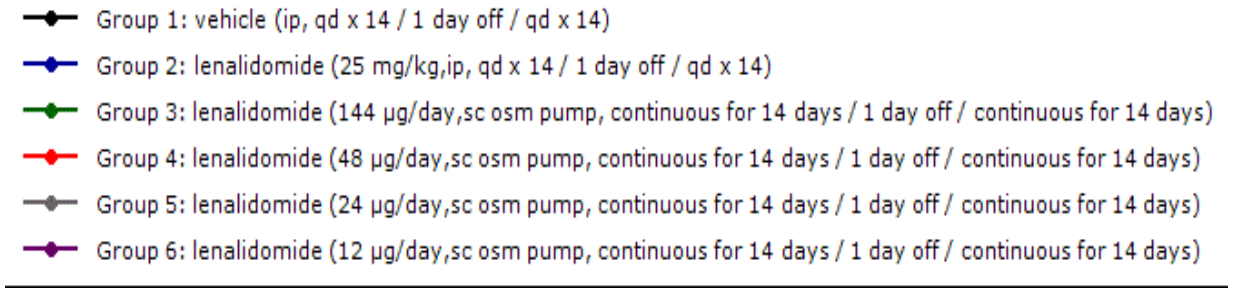
Route	Active dose
IP	25 mg/kg
sc osm pump	144 µg/day
sc osm pump	48 µg/day

2 SC animals with Tumor Free Survival

Route	Active dose	Median TTE (days)	TTF (days)	Partial Response (PR)	Complete Response (PR)	Tumor Free Survival (TFS)
IP	25 mg/kg	47	53	0	0	0
sc osm pump	144 µg/day	65	>100	6	4	2
sc osm pump	48 µg/day	41	71	1	0	0

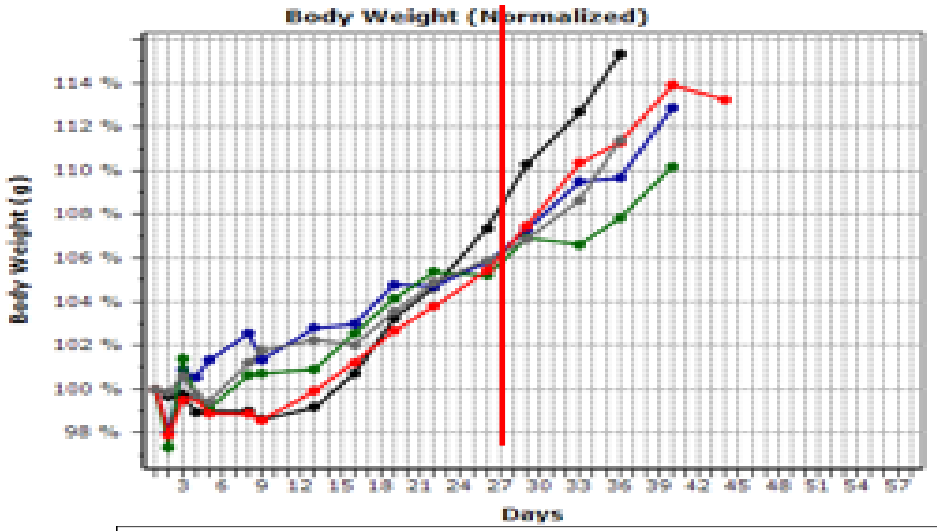
PK and administered doses in each treatment group

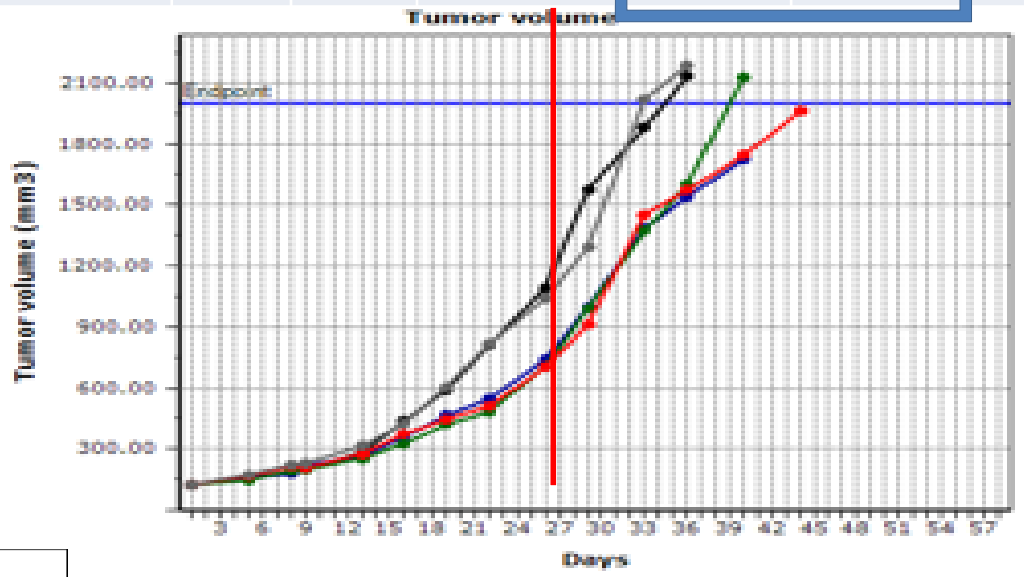
Group	Prescribed Dose	Daily Dose (µg/day)	Cmax µg/mL	AUC 0-24 (µg/mL/hr)	% Exposure to Grp 2 by AUC	% Exposure to Grp 2 by Daily Dose
2	25 mg/kg/d	500 mcg	3.2	10.9	100%	100%
3	6 mcg/hr	144 mcg	0.15	2.6	23.8%	28.8%
4	2 mcg/hr	48 mcg	0.05	0.9	8.3%	9.6%
5	1 mcg/hr	24 mcg	0.025	0.5	4.6%	4.8%
6	0.5 mcg/hr	12 mcg	0.0125	0.3	2.3%	2.4%



Study 3 of 4: STAR-LLD in RPMI-IMiD resistant cell line: study results

Group	n	Treatment Regimen 1				100% TTF (days)	Mean TTE (days)	TTF Stats (not adjusted for multiple tests)	MTV (mm3), Day 27	Day 27 Stats (not adjusted for multiple tests)	PR	CR	TFS	BW Nadir
		Agent	mcg/day	Route	Schedule									
1[#]	10	vehicle	-	sc osm pump[1]	13/ 1 day off /13 pump refill	51	36	1 vs 5 = 0.81	1116 ± 215	1 vs 5 = 0.99	0	0	0	-1.4% (9)
2	10	lenalidomide-CHMC	144[*]	sc osm pump[1]	13/ 1 day off /13 pump refill	51	41	2 vs 5 = 0.14	740 ± 130	2 vs 5 = 0.03	0	0	0	-2.0% (2)
3	10	lenalidomide-CHMC	216[*]	sc osm pump[1]	13/ 1 day off /13 pump refill	58	42	3 vs 5 = 0.07	707 ± 77	3 vs 5 = 0.003	0	0	0	-2.6% (2)
4	10	lenalidomide-CHMC	288[*]	sc osm pump[1]	13/ 1 day off /13 pump refill	58	43	4 vs 5 = 0.049	702 ± 128	4 vs 5 = 0.018	0	0	0	-2.1% (2)
5	10	lenalidomide	550	ip	13/1/13	51	36		1116 ± 108		0	0	0	-0.6% (5)





Group 1: vehicle (sc osm pump, 13/ 1 day off /13 pump refill)
Group 2: lenalidomide-CHMC (144 µg/day,sc osm pump, 13/ 1 day off /13 pump refill)
Group 3: lenalidomide-CHMC (216 µg/day,sc osm pump, 13/ 1 day off /13 pump refill)
Group 4: lenalidomide-CHMC (288 µg/day,sc osm pump, 13/ 1 day off /13 pump refill)
Group 5: lenalidomide (25 mg/kg,ip, 13/1/13)

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Study 4 of 4: LLD-SC-GLPM-052021: toxicology/safety study

HEALTHY CD20 mice
N=20 animals per group

Study evaluated effect of chronic subcutaneous (SC) administration of continuous lenalidomide on tolerability, histopathology, and key hematologic parameters

Route	Active dose	Population	Stratification
Vehicle control	--	N=20 (10 male + 10 fem)	1:1 8 days or 28 days
sc tethered pump	144 µg/day	N=20 (10 male + 10 fem)	1:1 8 days or 28 days
sc tethered pump	48 µg/day	N=20 (10 male + 10 fem)	1:1 8 days or 28 days

Key endpoints:

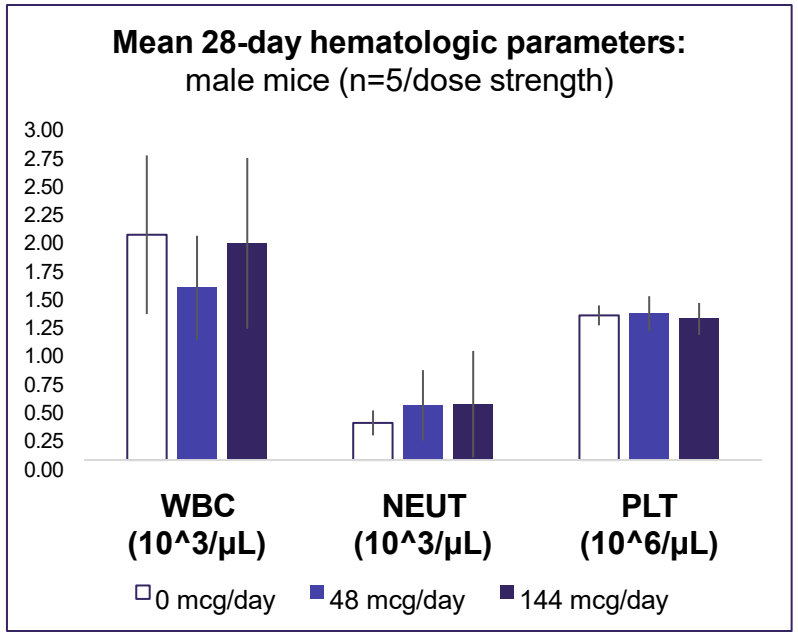
I. Local tolerability
- Survival
- Body weight
- Infusion site tolerability

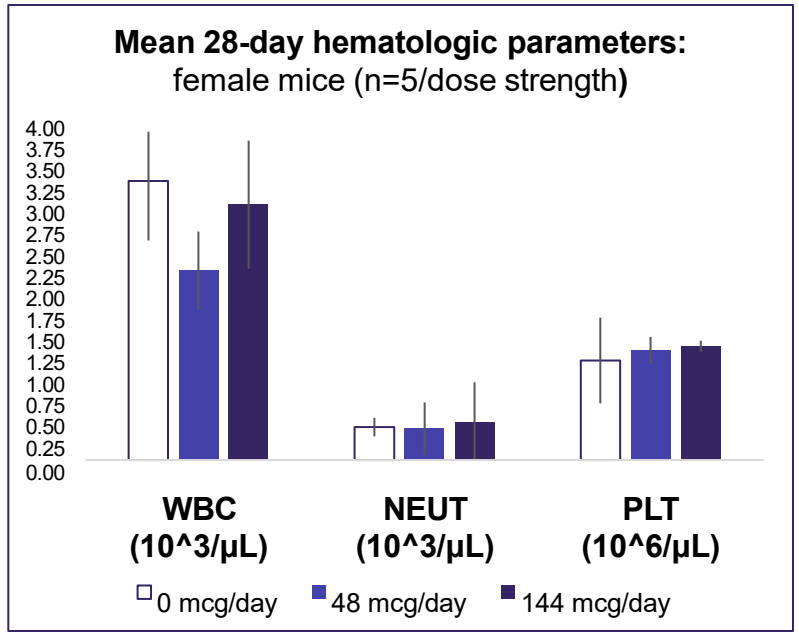
II. Hematology
- White blood cell (WBC)
- Neutrophil (ANC)
- Lymphocyte (ALC)
- Platelets

III. Histopathology
- Necrosis at infusion site
- Cellular damage

Preclinical rodent study 4: toxicology and hematologic tolerability

STAR-LLD showed no hematologic toxicity in chronic treatment





No significant differences compared to sham

- ✓ **No neutropenia**
- ✓ **No thrombocytopenia**
- ✓ **No local infusion site toxicity**
- ✓ **No test article related toxicity**

Healthy CD20 mice
3 treatment groups
N=20 animals per group
Terminal Sacrifice at 8 and 28 days

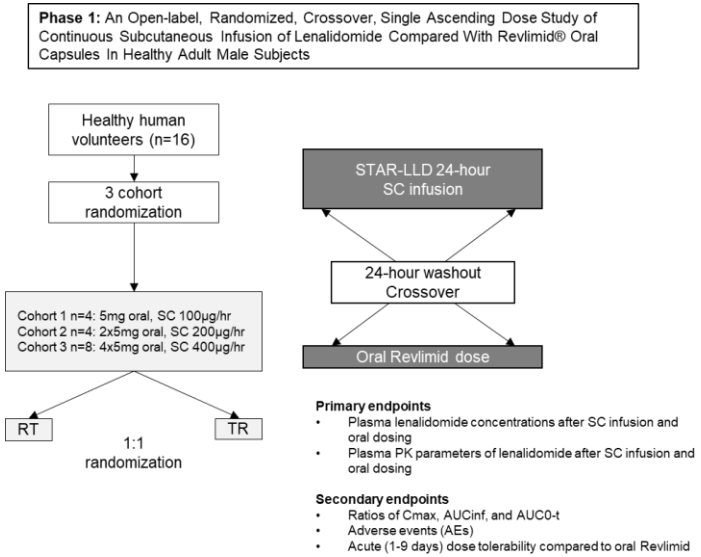
Study evaluated effect of chronic subcutaneous (SC) administration of continuous lenalidomide on tolerability, histopathology, and key hematologic parameters

NOAEL = in mice was 272 µg/hr/kg HED NOAEL = 1540 µg/hr

HED: Human equivalent dose; NEUT: neutrophils, NOAEL: No observed adverse event level, PLT: platelet, WBC: white blood cell

Into the clinic – Translational Program

STAR-LLD Phase 1a cross-over bioavailability study



STUDY RESULTS:

- **STAR-LLD well tolerated with no meaningful drug-related toxicity**
  - **7/17 subjects (41%) had TEAE**
  - **1 TRAE (headache @ 9.6mg/d)**
- **STAR LLD achieved >92% bioavailability across all doses**
- **Plasma levels where >90% lower Cmax, a ~57% lower AUC, and sustained Cmin at targeted dose levels**
- **Study validated compatibility and utility of subcutaneous delivery system**
- **Starting RP1D is** 400 µg/h (based on animal and human data)

	Dose	Subject	Revlimid AUC h*mcg/L	Revlimid Cmax mcg/L	LLD AUC h*mcg/L	Css sc mcg/L
100 µg/h Vs 5 mg qd	5/100	1	202	86.7	90.5	4.31
	5/101	2	270	67.9	112.9	5.16
	5/102	3	201	70.5	96.5	4.44
	5/103	4	174	75.3	73	3.59
		mean	211.75	75.1	93.23	4.38
		SD	40.9	8.3	16.5	0.64
200 µg/h Vs 10 mg qd	10/200	5	550	170.0	234	10.32
	10/201	6	427	143.7	190	8.36
	10/202	7	548	225.0	226	10.4
	10/203	8	524	170.5	220	10.03
		mean	512.25	177.3	217.50	9.78
		SD	58.0	34.1	19.2	0.96
400 µg/h Vs 20 mg qd	20/400	9	1057	312.8	493	21.54
	20/401	10	991	300.9	484	19.8
	20/402	11	1008	230.3	407	18.71
	20/403	12	941	271.3	398	17.69
	20/404	13	1091	236.8	475	20.89
	20/405	14	1028	332.6	440	20.85
	20/406	15	1208	309.3	496	21.72
	20/407	16	1104	429.2	452	20.7
		mean	1053.50	302.9	455.63	20.24
		SD	82.0	62.8	38.1	1.41

AUC: area under the curve,
TEAE: treatment emergent adverse event,
TRAE: treatment related adverse event

Phase 1b in patients with relapsed/refractory multiple myeloma

A Protocol to Assess the Safety, Efficacy, and Pharmacokinetics of Continuous Subcutaneous Administration of Low-dose Lenalidomide (STAR-LLD) for the Treatment of Multiple Myeloma (MM)

Six patients

- Two U.S. sites
  - Gabrail Cancer Center Canton, OH
  - Regional Cancer Center Wilson, NC
- 2nd line or greater transplant ineligible RR multiple myeloma
- Planned treatment with RVd
- Prior treatment with V is allowed if the patient was sensitive to V (6mo PFS after stopping V)
- Substitutes STAR-LLD for Revlimid at a 60% lower dose than Revlimid
- STAR-LLD given continuously on 28-day cycles
- STAR-LLD administered subcutaneously with a Smith Medical 510 K cleared ambulatory pump
- DLTs will be evaluated in cycle 1
- Safety will be assessed on TEAEs, TRAEs, and AESIs
- Efficacy will be assessed by ORR, PFS
- Biomarkers will be obtained for T and NK cell function/activation to provide a correlate to PK/PD

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Introduction

- Lenalidomide is a mainstay of treatment for MM
- The half-life of lenalidomide is very short necessitating high daily doses to maintain effective concentrations leading to toxicity
- In RRMM[3] Lenalidomide + dexamethasone produced Grade 3-4 hematologic toxicity of >59% and led to 19.8% discontinuation
- Predicted effective blood levels of Len are:
  - > 0.04 µM (10 µg/L) for immunologic activity[1], and
  - > 0.1 µM (25 µg/L) for cytotoxic effects[2]

1. Gandhi AK, Kang J, Capone L, et al. Dexamethasone synergizes with lenalidomide to inhibit multiple myeloma tumor growth, but reduces lenalidomide-induced immunomodulation of T and NK cell function. Curr Cancer Drug Targets. 2010 Mar;10(2):155–67.

2. Krönke J, Udeshi ND, Narla A, et al. Lenalidomide causes selective degradation of IKZF1 and IKZF3 in multiple myeloma cells. Science. 2014 Jan 17;343(6168): 301–5.

3, DM Weber et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. NEJM 2007; 357: 2133-2142.

Methods and Materials

- Patients were 2nd line or greater RRMM
- Regimen: Bortezomib 1.3 mg/m^2 and dexamethasone 20-40 mg weekly dosing on 28-day cycle. Lenalidomide continuous SC infusion at 400 µg/h (9.6 mg a day) with 28-day cycle
- Len delivered SC 24/7 continuously by Smith Medical Solis VIP ambulatory device
- Patient trained to administer Len infusion at home or could come to clinic 3 times a week

RRMM = relapsed/refractory multiple myeloma

Endpoints

Primary Endpoints

- The grade, frequency, and relationship of treatment-emergent adverse events (TEAE/TRAEs) including adverse events of special interest (AESIs): (gastrointestinal [GI] toxicity, fatigue, hematologic toxicity, rash (non-infusion site).
- The observation of dose-limiting toxicities (DLTs) of STAR-LLD during Cycle 1.

Secondary Endpoints

- Immune profiles, functional assays for NK cell activation and antigen specific T-cell activity.
- Blood concentrations of lenalidomide at on Day 1 and at steady state.
- Changes in biomarkers during treatment.
- Rate of complete response, very good partial response (VGPR), partial response (PR), stable disease (SD), and progressive disease.
- Determination of ORR, PFS, and DOR

Results – Baseline Findings

- Between Oct 2023 and April 2024 – 6 patients enrolled and treated
- Median age = 73
- 4 patients relapsed; 2 patients refractory
- Males to female ratio 1:1
- 100% Caucasian
- Median lines of prior therapy = 2 (range 1-7)
- 4 patients with previous lenalidomide exposure
- All patients with previous bortezomib exposure
- Serum protein electrophoresis monoclonal protein (SPEP) at baseline ranged from 0.2 – 2.1 g/dL
- Free-light chain (FLC) ratio ranged from 0.01 – 387.9
- Urinary protein electrophoresis (UPEP) 24 hr ranged from 17-1812 mg/d

Hematologic Toxicity Associated With STAR-LLD

	Hemoglobin		White Blood Cells		Absolute Neutrophils		Platelets	
	g/dL	Grade	$\times 10^9$/L	Grade	$\times 10^9$/L	Grade	$\times 10^9$/L	Grade
CTCAE Grade	<LLN – 10.0	1	<LLN – 3.0	1	<LLN – 1.5	1	<LLN - 75	1
	<10.0 -8.0	2	<3.0 – 2.0	2	<1.5 – 1.0	2	<75 – 50	2
	<8.0	3	<2.0 – 1.0	3	<1.0 – 0.5	3	<50 - 25	3
Patient number								
101-01	12.8	0	5.3	0	2.5	0	147	0
101-02	6.1[a]	3	2.4	2	1.1	2	117	1
101-03	8.5	2	3.7	1	2.1	1	151	0
101-04	12.5	0	5.3	0	3.6	0	74	2
102-01	11.4	1	4.8	0	2.4	1	108	1
102-02	9.4	2	4.9	0	2.5	0	234	0

[a] Event classified by Investigator as not related. Patient had hemoglobin of 8.3 g/dL at baseline (medical history of anaemia and had active GI bleed).

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Pharmacokinetics and Response Data by Patient

Patient	Prior # of lines	Steady State Concentration ± SD (µg/L)	Best Response On-study	PFS
101-01	3	28.0 + 3.2	PR	18*
101-02	2	62.2 + 16.3	PR	17*
101-03	1	43.3 + 2.7	PR	13*
101-04	7	36.8 + 1.3	PR	6
102-01	1	41.8 + 4.1	CR	11*
102-02	4	35.0 + 1.8	PR	9

CR: complete response; PR: partial response; SD: standard deviation * - ongoing – at last sampling

Discussion

- The number of patients treated was small and caution should be used evaluating the data
- The rationale for the selection of the Len dose is based on in vitro activity of Len on IL-2 and IFN-γ production and Icarus/Aeolus ubiquitination
- The Len target blood levels of > 25 µg/L were achieved, and we observed excellent ORR and tolerability with a continuous dose of 400 µg/h
- Data suggests low-dose continuous lenalidomide improves the therapeutic index vs. oral Len and avoids the grade 3-4 hematologic toxicity of >59% observed in a literature-based report in 2nd line RRMM[1]

1-DM Weber et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. NEJM 2007; 357: 2133-2142.

Conclusions

- The PK/PD data minimized Cmax and lowered AUC while achieving biologically active doses and reducing toxicity
- Continuous Len for ≥ 6+ cycles didn't result in any drug-related Grade 3-4 hematologic toxicity
- Non-hematologic toxicities didn't exceed Grade 2
- All patients achieved an objective response (1 CR and 5 PR)
- Continuous treatment with Len does not appear to significantly increase immune checkpoints associated with T cell exhaustion
- Based on these data, new delivery formulations are under development and include an on-body injector, transdermal patches, and controlled release oral tablets

Next Steps – Phase 2 Dose Finding

- Phase 2 amendment was made to phase 1b protocol
    - FDA requested additional dosing finding per Project Optimus
- Phase 2 study initiated in May 2025
- Up 24 patients in dose-finding and 45 patient in expansion cohort (if needed)
- Additional randomized groups are:
    - 300 µg/hr cohort
    - 500 µg/hr cohort
    - 600 µg/hr cohort
    - Revlimid 25 mg a day for 21 of 28 days
- All interventions are the same except no biomarker data is being obtained