Potent pre-clinical and early phase clinical activity of EP300/CBP bromodomain inhibitor CCS1477 in multiple myeloma

Luciano Nicosia, Nigel Brooks, Fabio MR Amaral, Oliver Sinclair, Neil Pegg, Will West, Tomasz Knurowski, Kris Frese, Karen Clegg, James Cavet, Emma Searle and ***Tim CP Somervaille***

Session Date: Saturday, December 10, 2022

Presentation Time: 4:00 PM

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Tim Somervaille Disclosures

CellCentric	research funding
AbbVie	consulting fees
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Imago Biosciences	research funding
Novartis	consulting fees

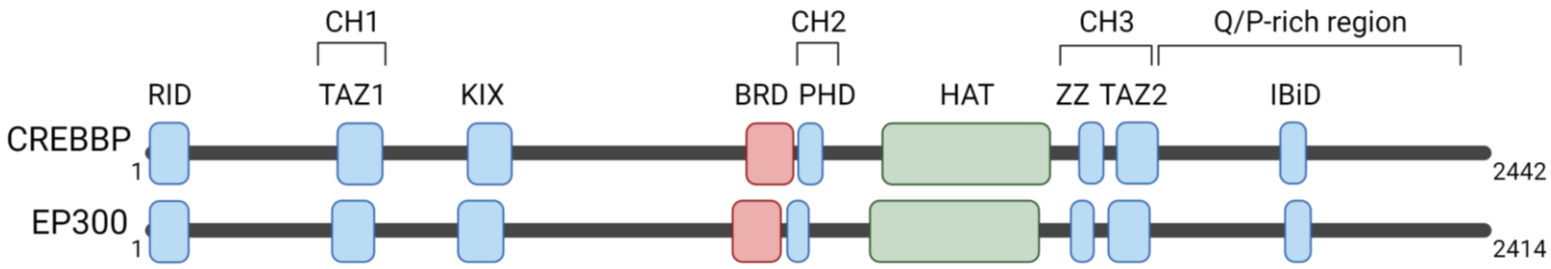
EP300, CREBBP and CCS1477 (inobrodib)

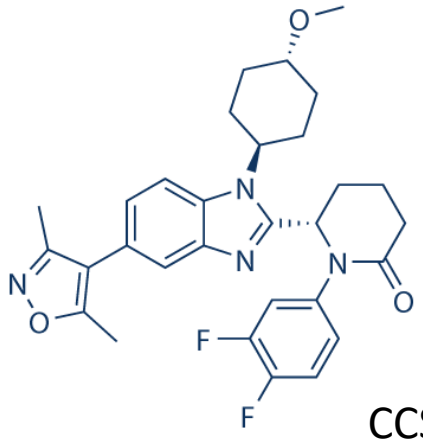
CCS1477 (inobrodib) is a first-in-class clinical grade inhibitor of the bromodomains of histone acetyltransferases EP300 & CREBBP

EP300 and CREBBP are homologous, essential histone acetyltransferases which acetylate targets such as histones and transcription factors

Longstanding interest as a therapeutic target in cancer, in view of recurrent mutations, over-expression and oncogenic dependencies

Act as transcriptional co-activators of cancer associated proteins incl. MYC, MYB, IRF4, AR





CCS1477

Potent (Kd 1nM) & highly selective (>200-5000 fold) for EP300/CBP versus bromodomains in other proteins e.g. BRD2/3/4

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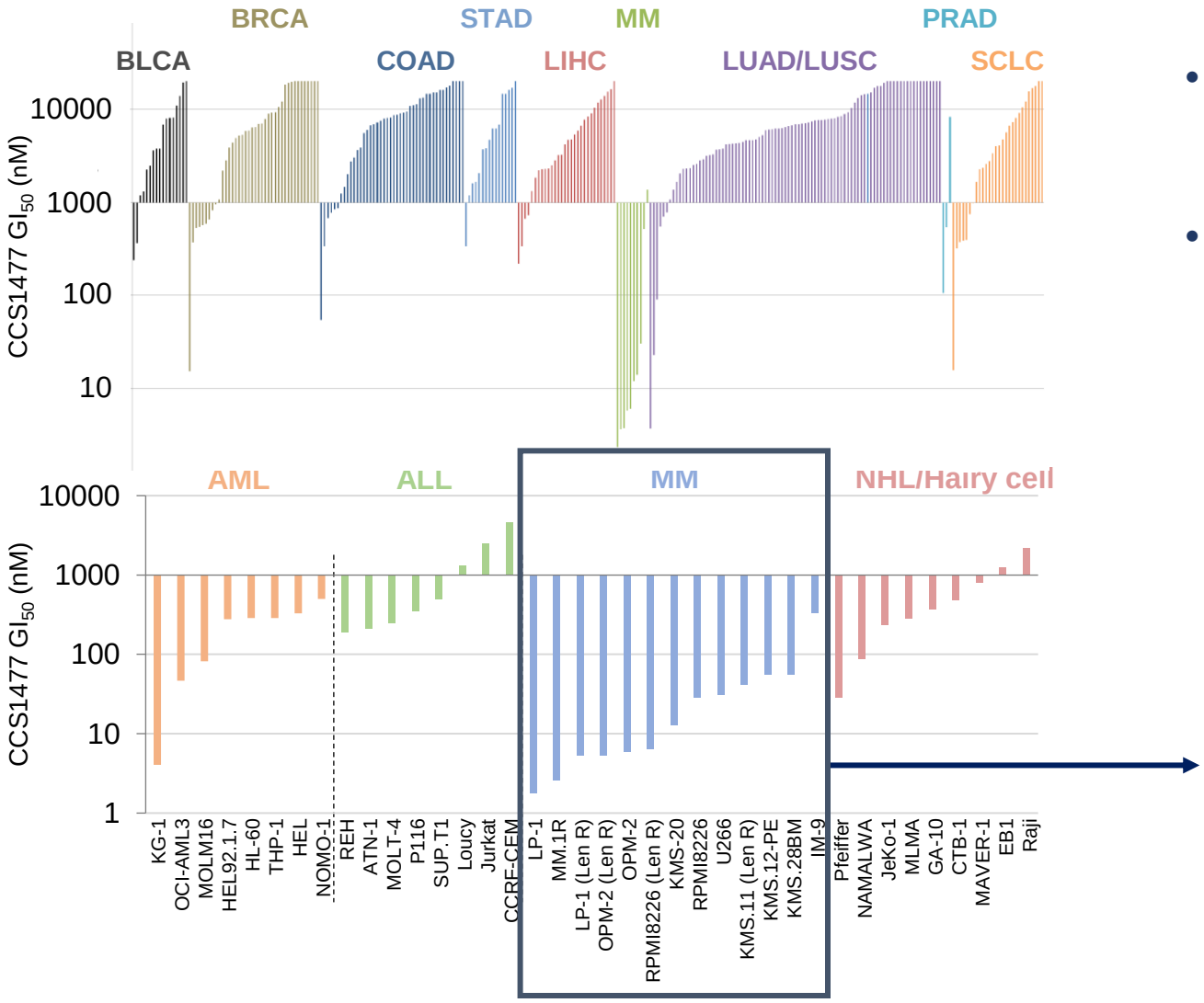
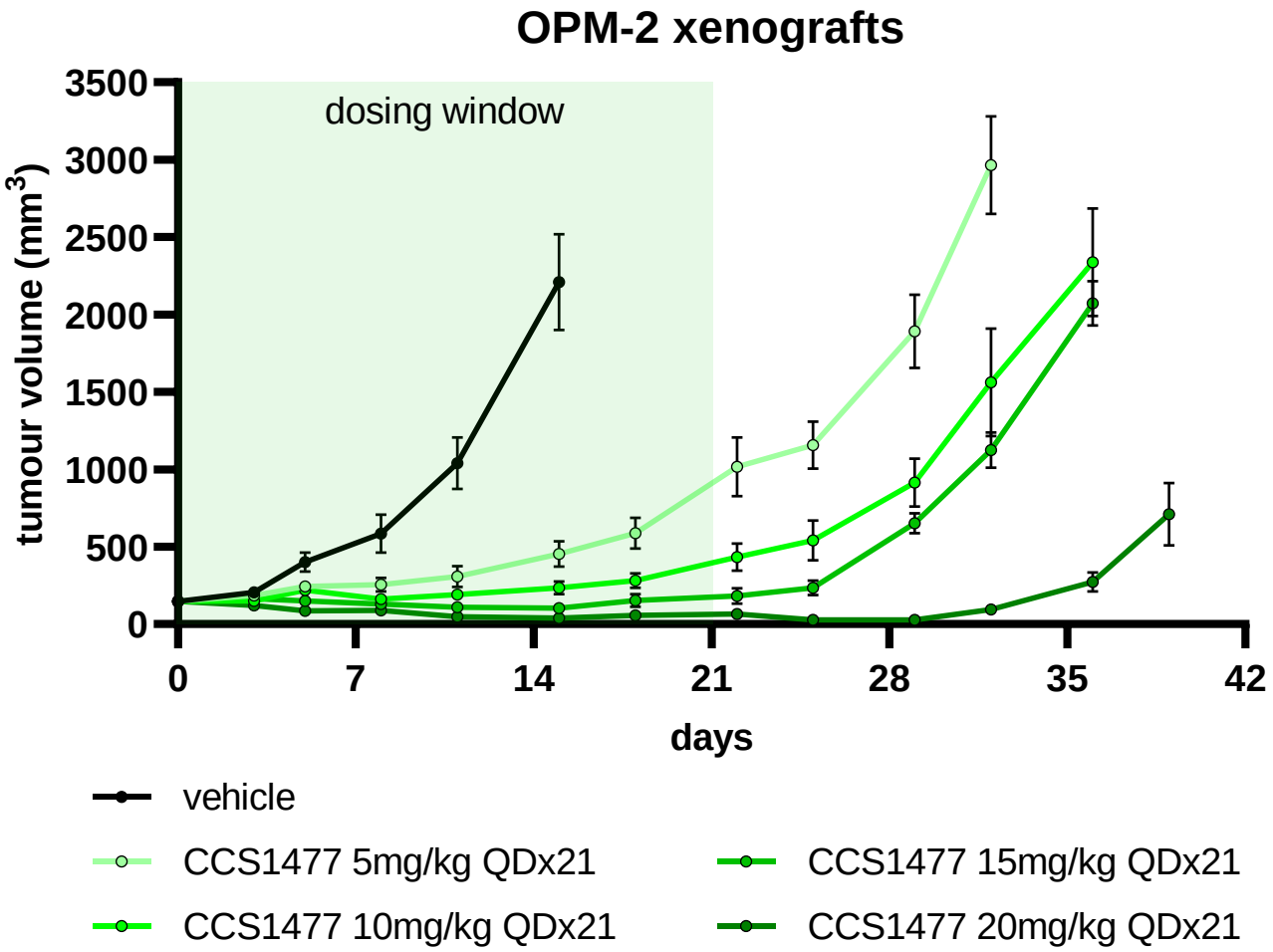
Low nanomolar sensitivity of myeloma cell lines to CCS1477



- Across a large panel of solid tumour lines, most are not sensitive to CCS1477
- Marked sensitivity across myeloma cell lines including
  - ***multiple genetic subtypes***
  - ***lenalidomide-resistant***

Cell line	Canonical translocation
LP-1	t(4;14)
MM.1R	t(14;16) + t(8;14)
LP-1 (Len R)	t(4;14)
OPM-2 (Len R)	t(4;14)
OPM-2	t(4;14)
RPMI8226 (Len R)	t(16;22) + t(8;22)
KMS-20	-
RPMI8226	t(16;22) + t(8;22)
U266	t(11;14)
KMS.11 (Len R)	t(4;14) + t(8;14) + t(14;16)
KMS.12-PE	t(11;14)
KMS.28BM	t(4;14)
IM-9	-

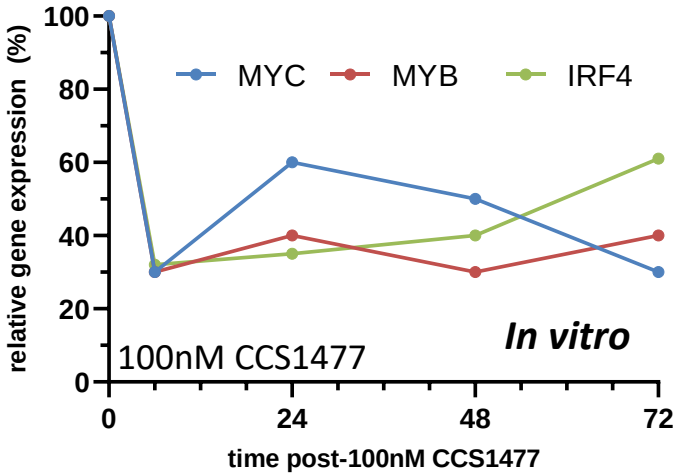
Dose dependent activity of CCS1477 in OPM-2 myeloma cell xenografts



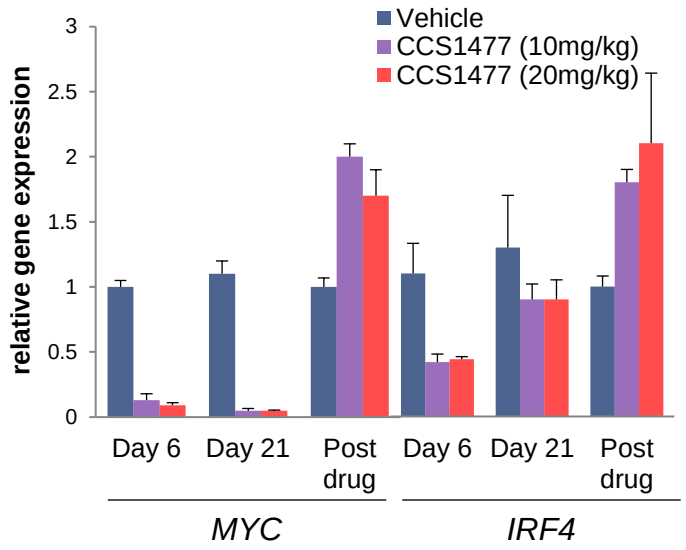
- Robust dose-dependent tumour growth inhibition
- Extended efficacy (20mg/kg) well beyond treatment window & clearance of drug from blood and tissues
- Suggestive of durable epigenetic re-wiring
- Provides rationale for intermittent clinical dosing

Rapid, extensive transcriptional changes in CCS1477-treated OPM-2 cells *in vitro* and *in vivo*

Rapid decrease in key transcription factor genes



in vivo



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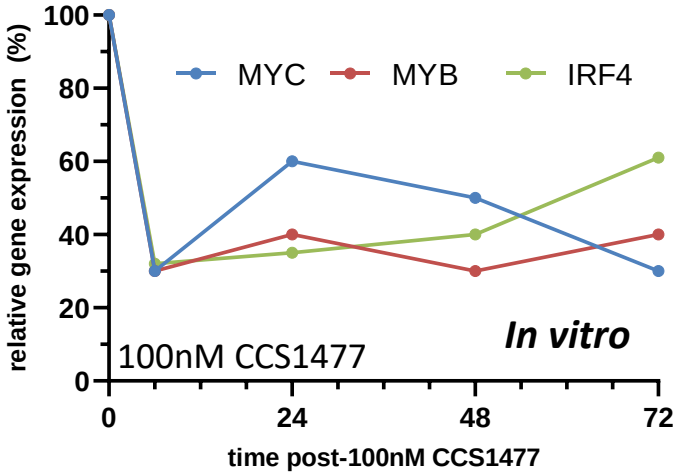
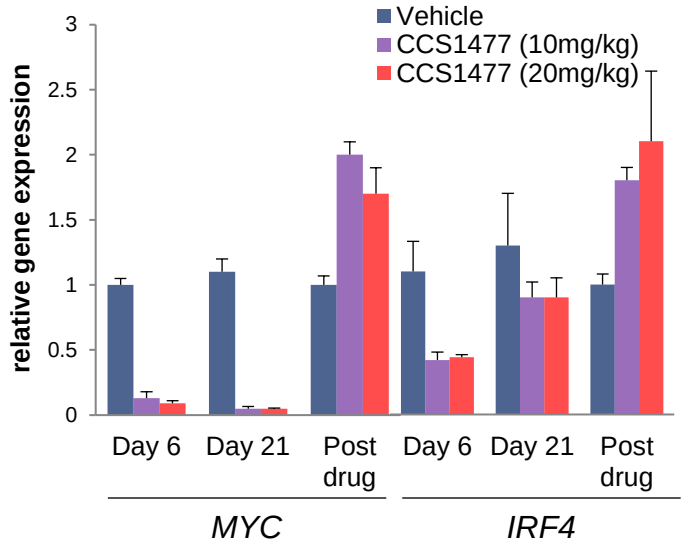
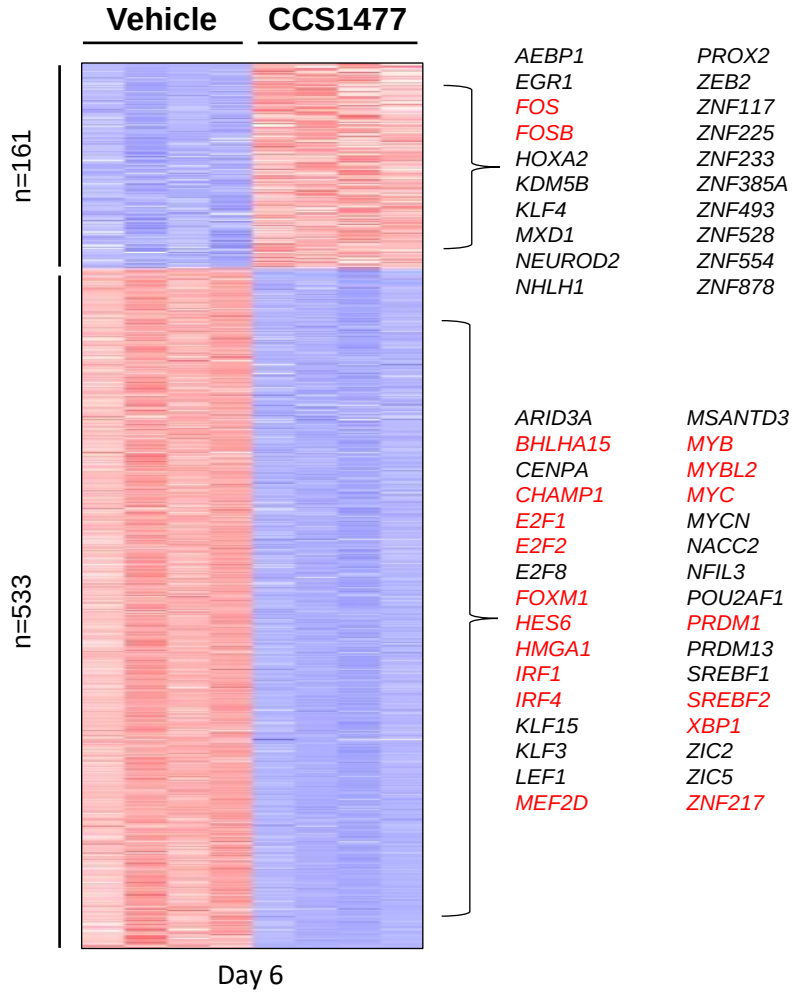


in vivo



Transcriptional rewiring *in vivo*



AEBP1
EGR1
FOS
FOSB
HOXA2
KDM5B
KLF4
MXD1
NEUROD2
NHLH1
PROX2
ZEB2
ZNF117
ZNF225
ZNF233
ZNF385A
ZNF493
ZNF528
ZNF554
ZNF878

ARID3A
BHLHA15
CENPA
CHAMP1
E2F1
E2F2
E2F8
FOXM1
HES6
HMGA1
IRF1
IRF4
KLF15
KLF3
LEF1
MEF2D
MSANTD3
MYB
MYBL2
MYC
MYCN
NACC2
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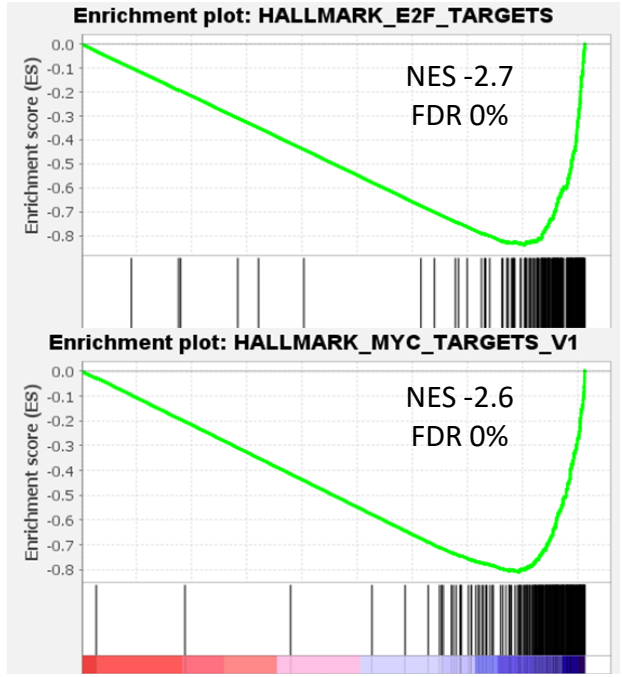
PRDM1
PRDM13
SREBF1
SREBF2
XBP1
ZIC2
ZIC5
ZNF217



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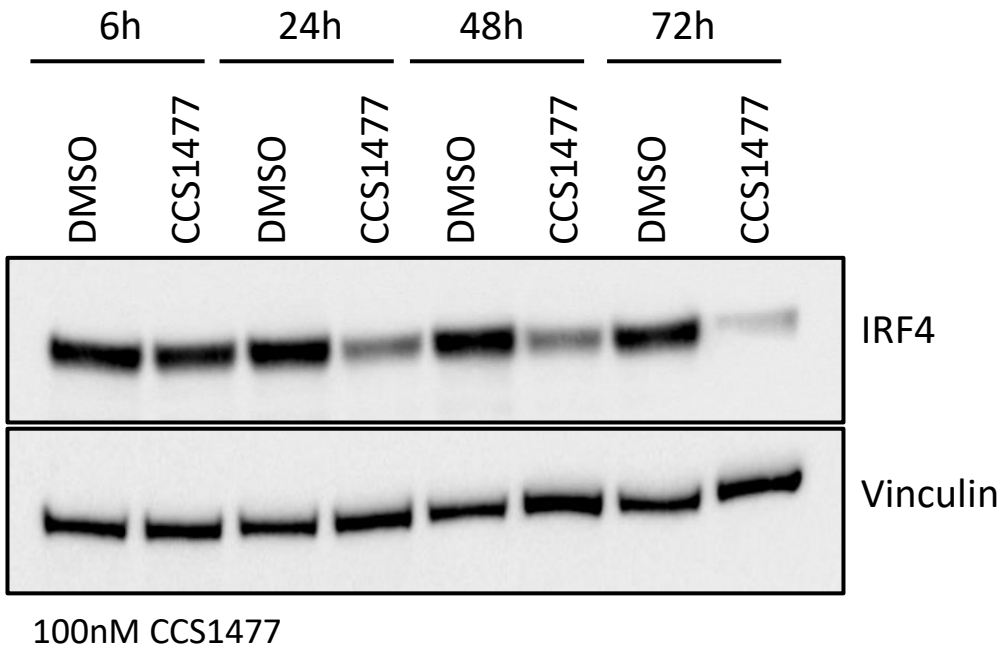
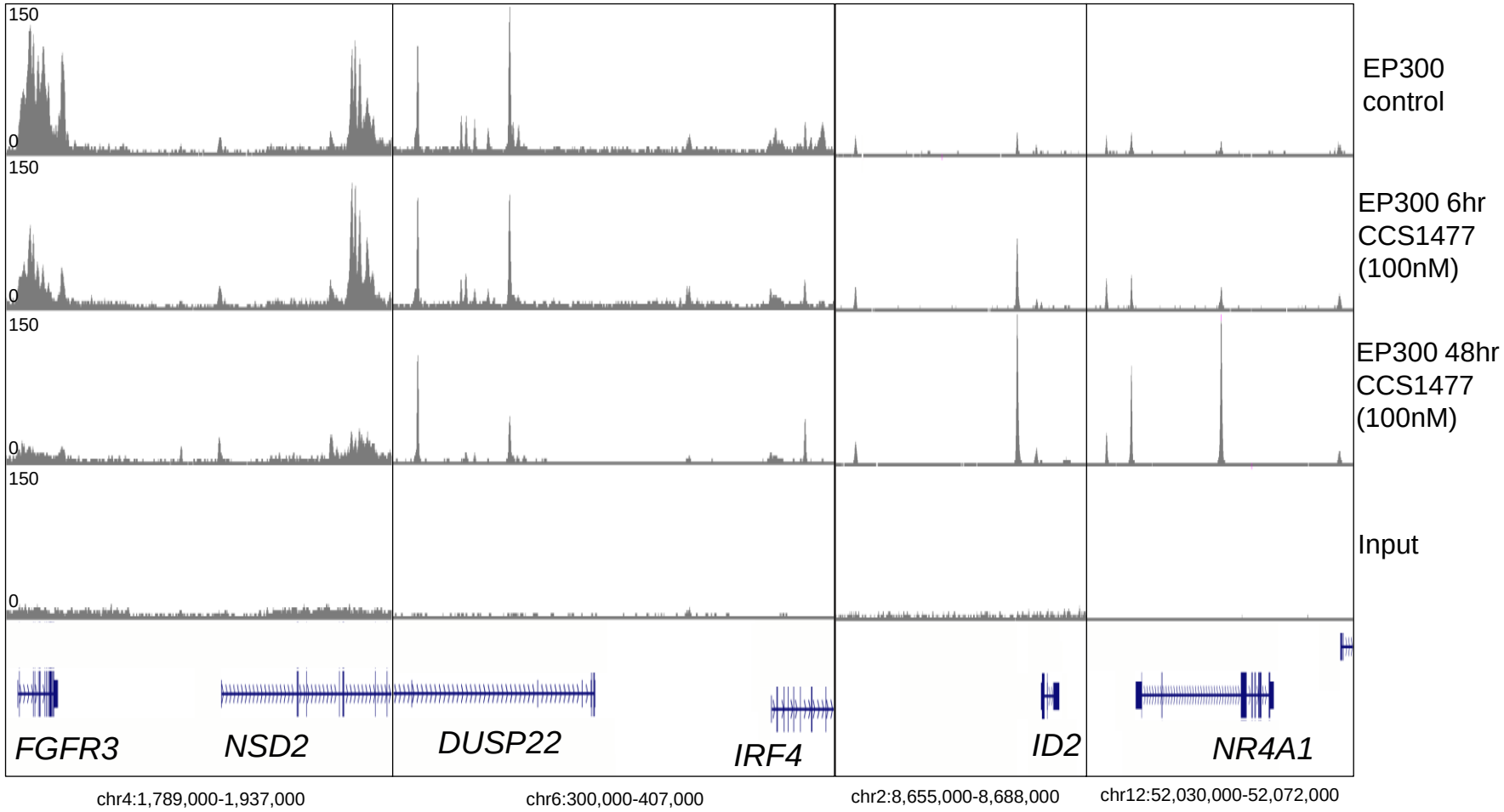
Progressive loss of IRF4 protein in CCS1477-treated OPM-2 cells *in vitro*



CCS1477 (100nM) triggers early loss of EP300 from *FGFR3*/*MMSET* and then genome wide loss of EP300 from IRF4 binding sites in OPM2 cells

EP300 ChIP sequencing tracks



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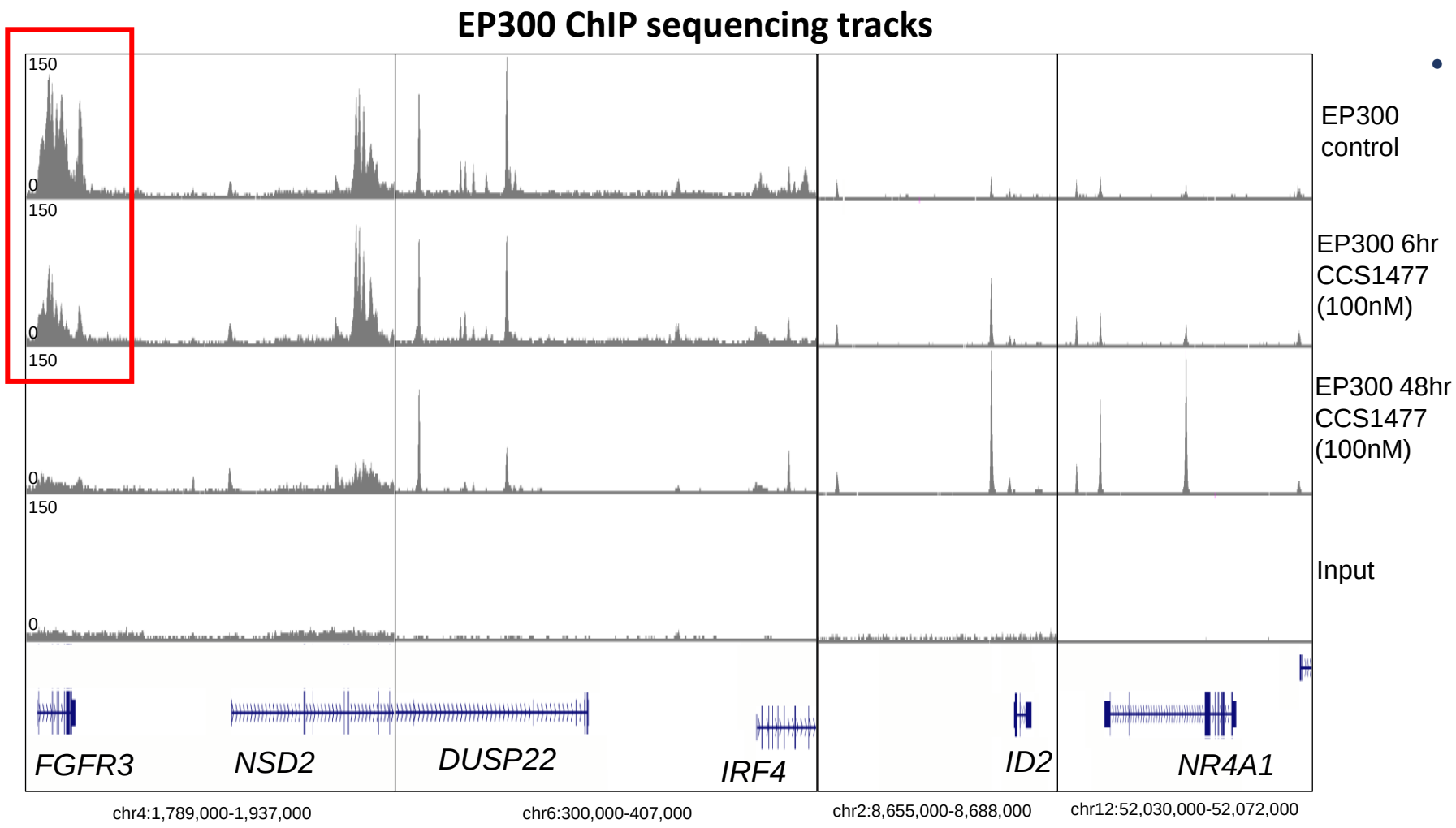

- Reduced EP300 at FGFR3/MMSET t(4;14) breakpoint within 6hrs

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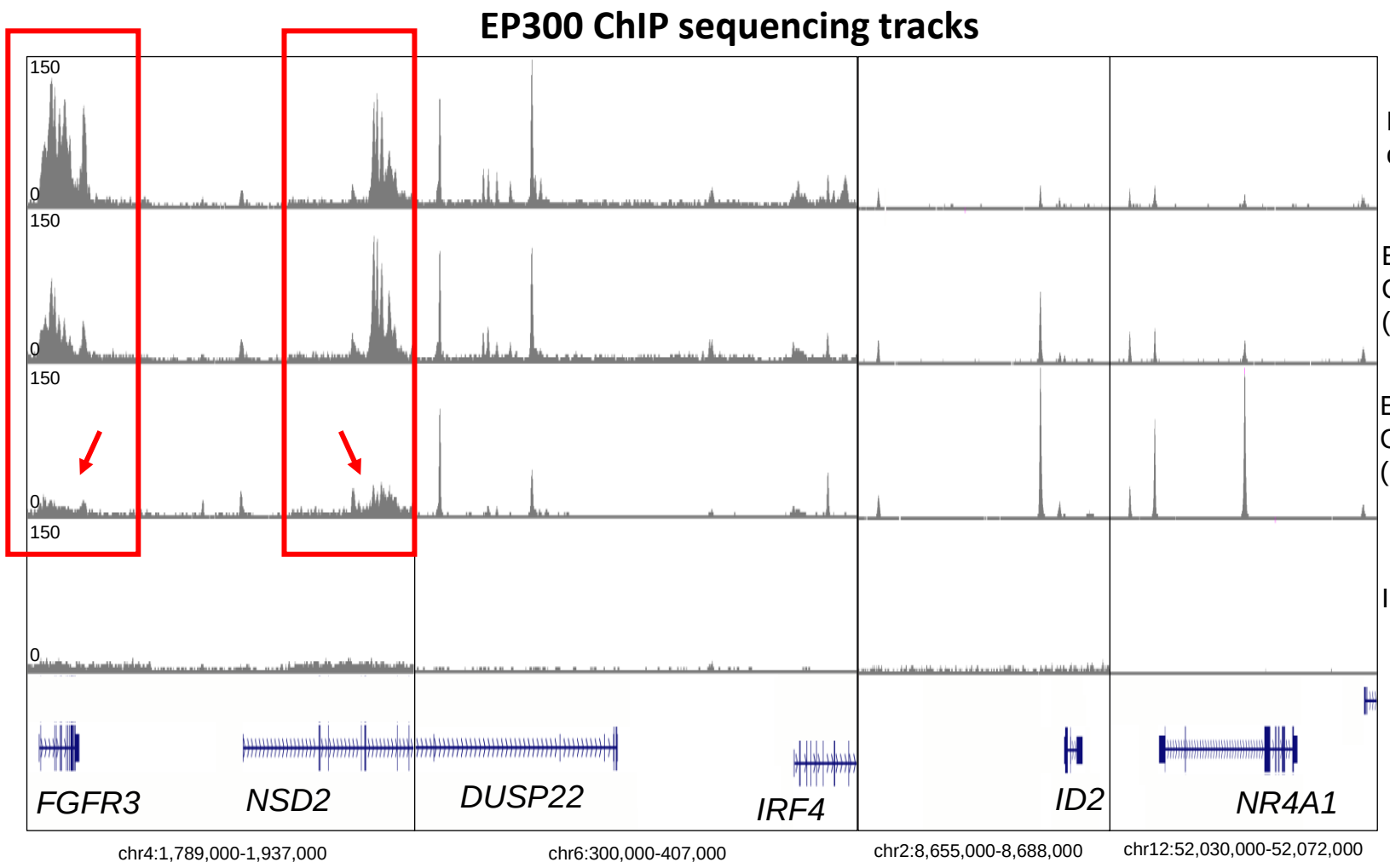

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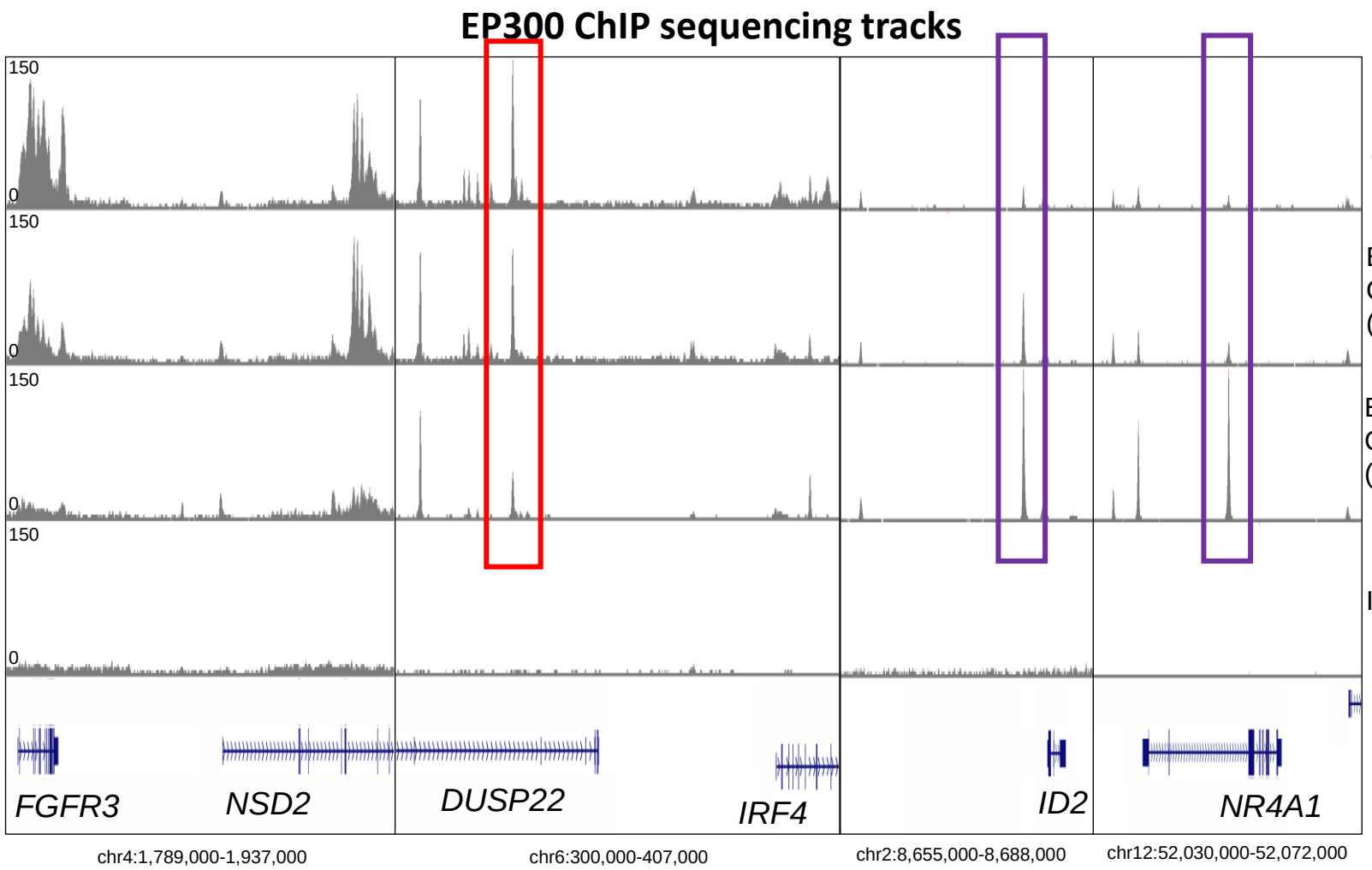

- Reduced EP300 at FGFR3/MMSET t(4;14) breakpoint within 6hrs
- More extensive loss by 48hrs
- By 48hrs – ***redistribution*** of EP300; reduced binding at some sites, increased binding at others

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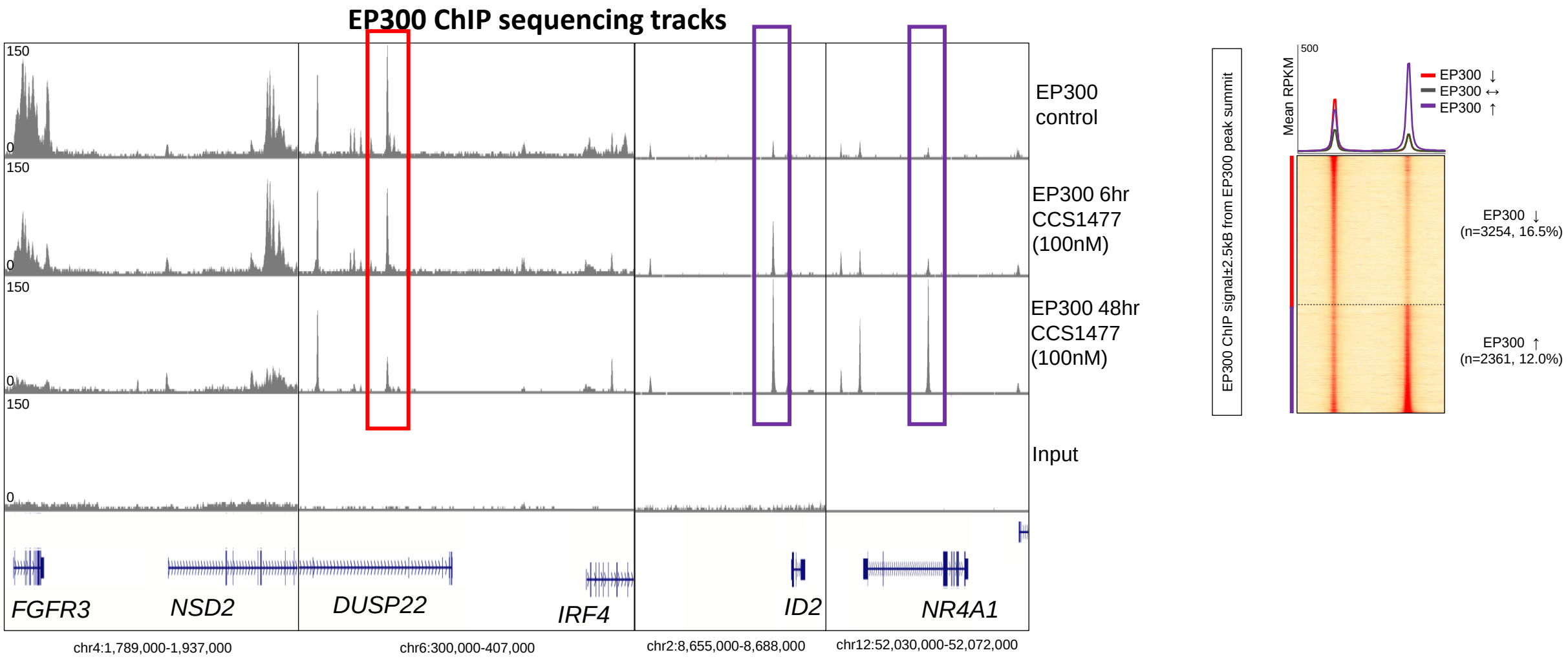

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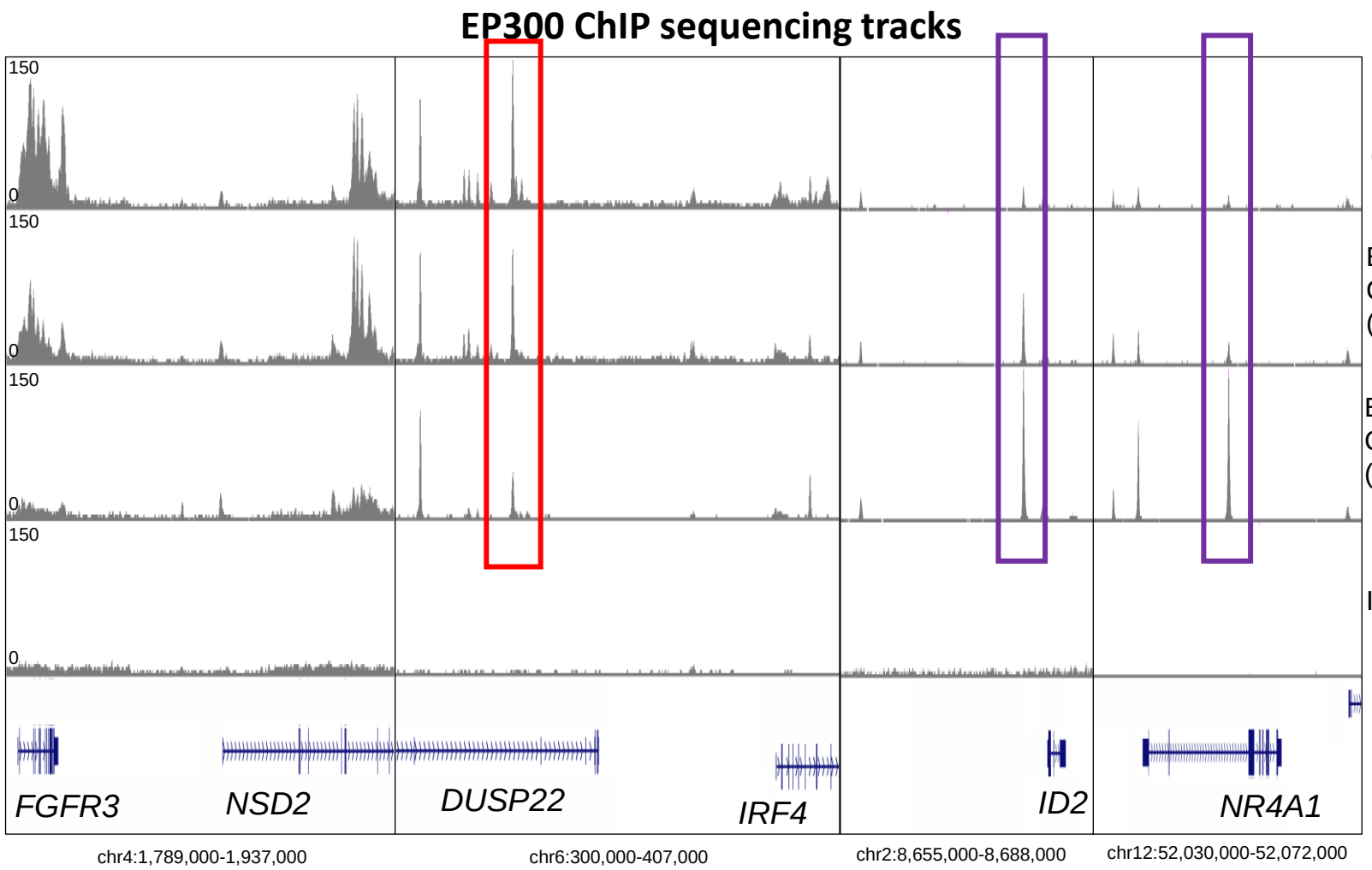

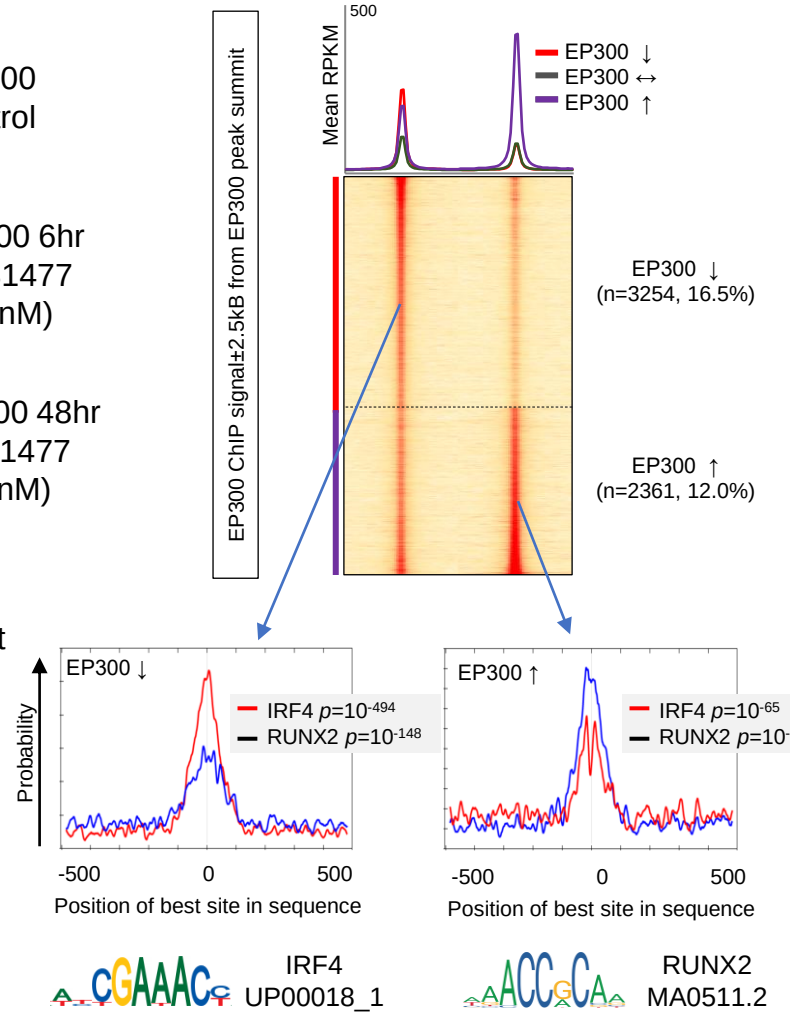

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A Phase 1/2a study of CCS1477 in haematological malignancies (NCT04068597)

- Safety, tolerability, PK and biological activity
- Myeloma, Lymphoma, AML & Higher Risk MDS.
- Identified the recommended phase 2 dose and schedule: 35mg BID, 4 days on/3 days off
- Treatment generally well-tolerated with majority of on-target toxicities mild/moderate
- Safety profile consistent with cumulative data in solid tumours (NCT03568656)
- Patient population: heavily pretreated relapse/refractory myeloma, incl. triple class refractory

Monotherapy CCS1477

Part A, C1, D1

- 26 MM dosed (7 dosed at RP2D)
- Dose/schedule optimised

CCS1477 + pomalidomide + dex

Part D2, D3, D4

- Three patients completed cycle 1
- Good initial tolerability and efficacy

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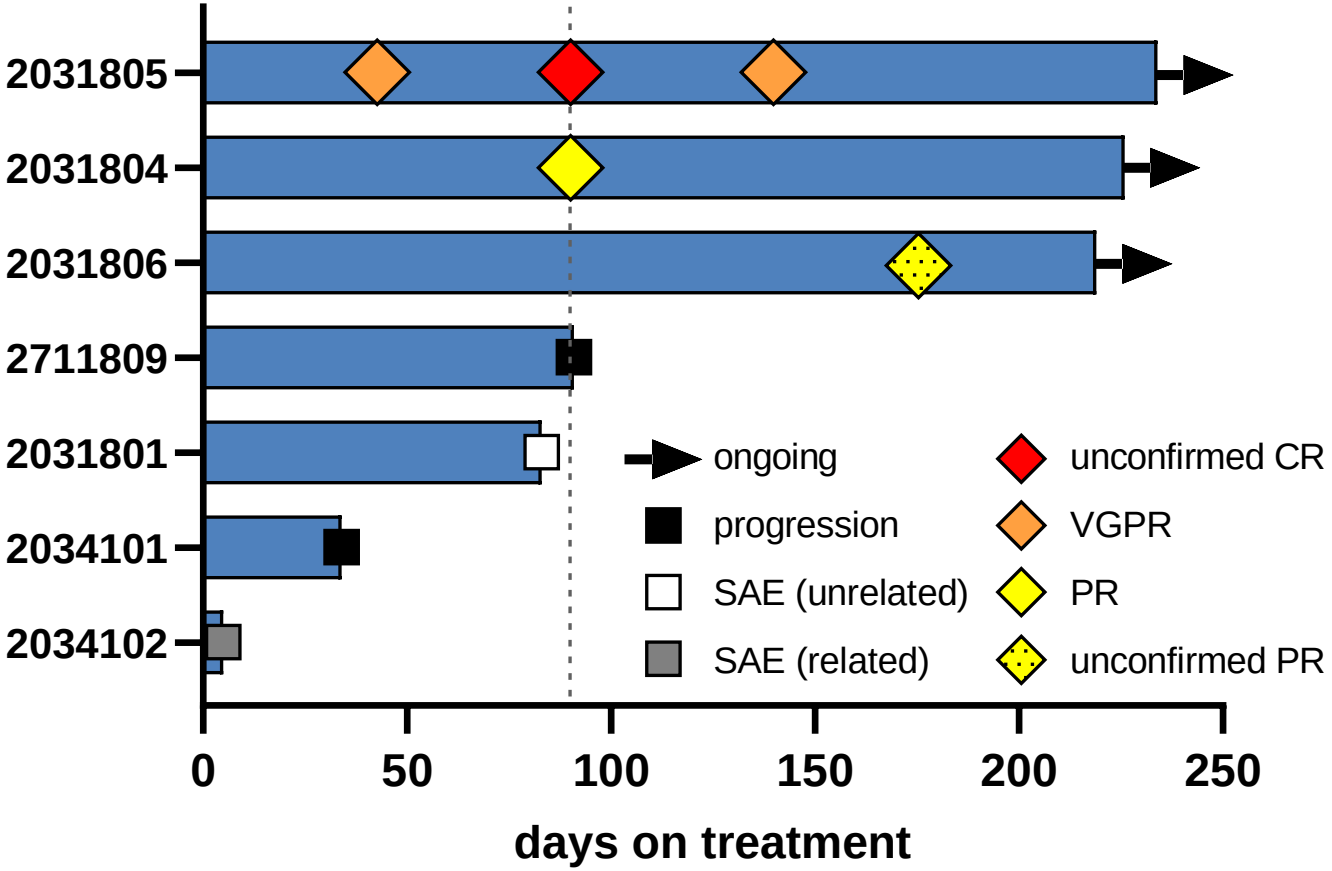
CCS1477 monotherapy efficacy at recommended phase 2 dose

All patients heavily pre-treated (and len/pom resistant)
Triple-class exposed (6 of 7)
3 of 7 triple-class refractory
4-8 lines of prior therapy



Best % SFLC change
-99%
-86%
-19%
-1%
+329%
-13%
-42%

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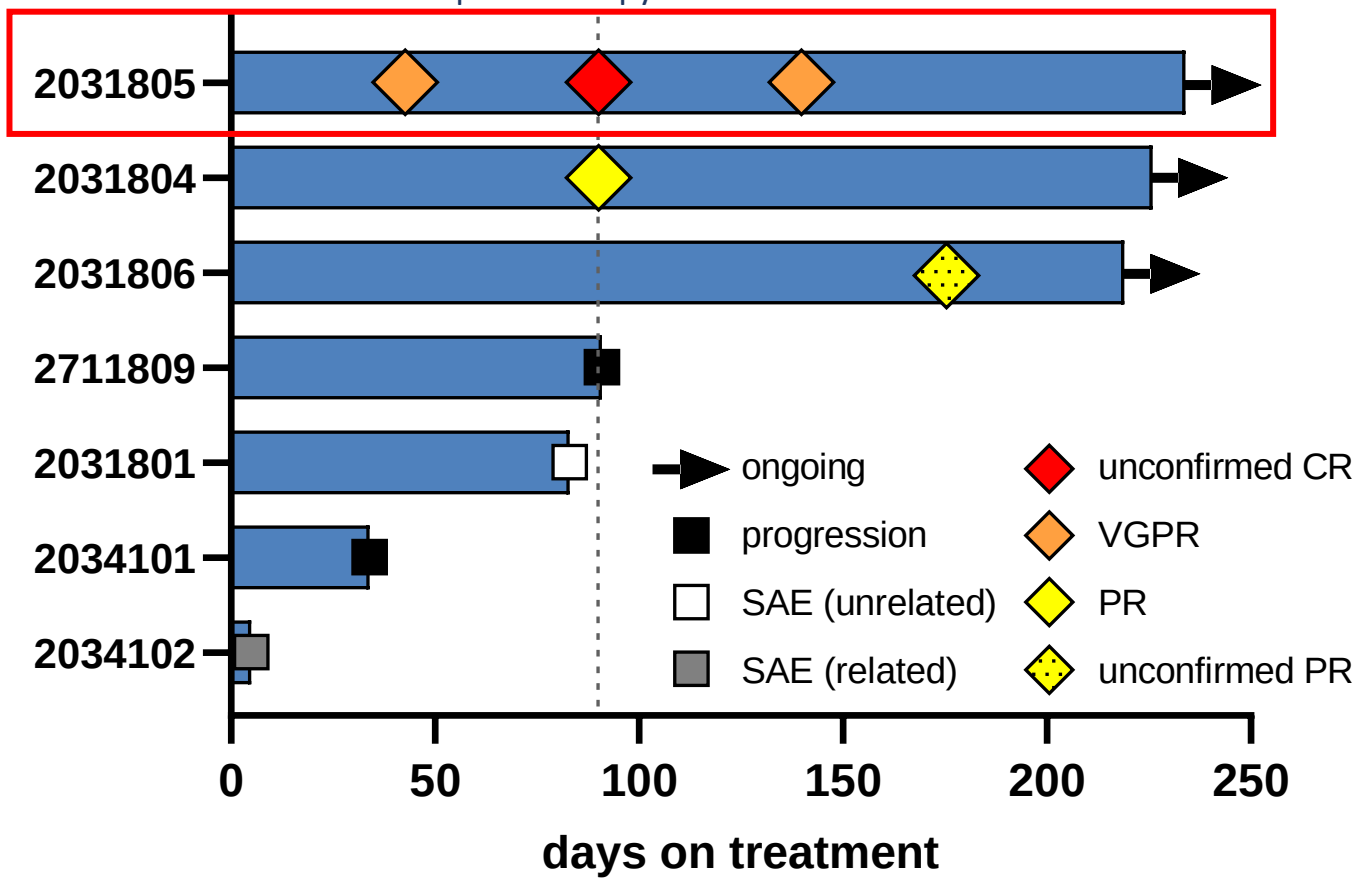

Best % SFLC change
-99%
-86%
-19%
-1%
+329%
-13%
-42%

6 of 7 patients had stabilization of SFLCs

Patient 2031805 – 50s

Extensive prior therapy:

- 2013-14 VCD (VGPR) + AutoSCT
- 2016 CTD (VGPR) + AutoSCT
- 2018-21 Ixa-Len-Dex (VGPR)
- 2021-22 Isa-Pom-Dex (VGPR)

Clinical activity:

- Urine BJ protein negative by immunofixation
- Normalization of SFLC ratio
- Good tolerability >7m

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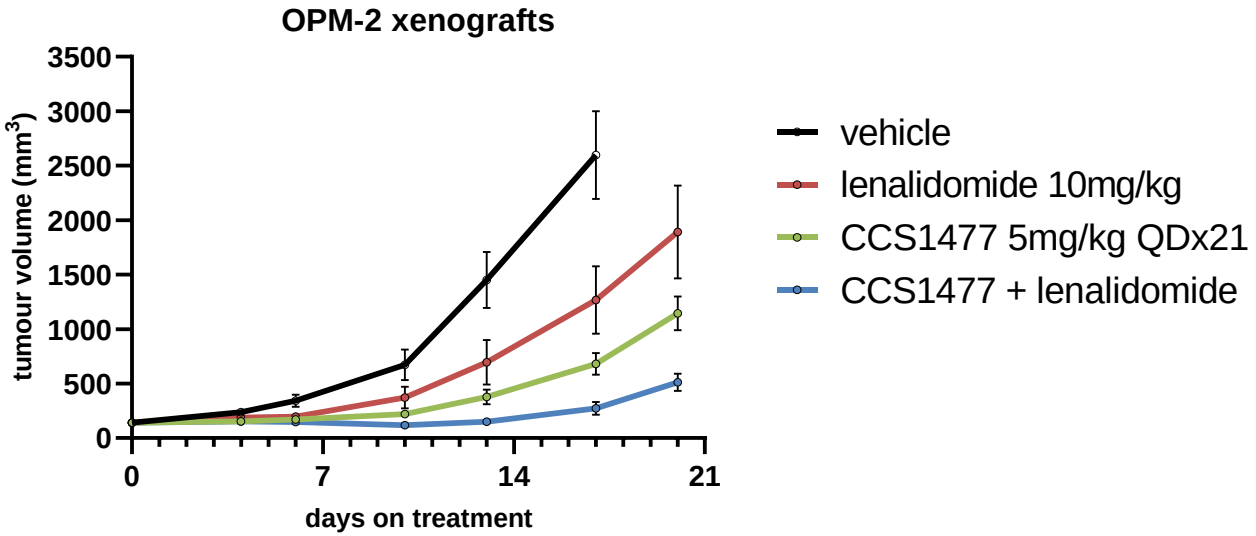
Choice of drug for combinatorial evaluation: CCS1477 effective in IMiD-resistant myeloma lines; evidence of synergy *in vivo*

CCS1477 has efficacy in Len-sensitive and -resistant cells

	Cell Line	Lenalidomide GI50 (µM)	CCS1477 GI50 (µM)
Lenalidomide resistant	RPMI-826	>10	0.006
	LP1	>10	0.006
	KMS-11	>10	0.041
	OPM-2 (AR)	>10	0.020
Lenalidomide sensitive	OPM-2	0.102	0.005

In vivo CCS1477 + Len combination efficacy



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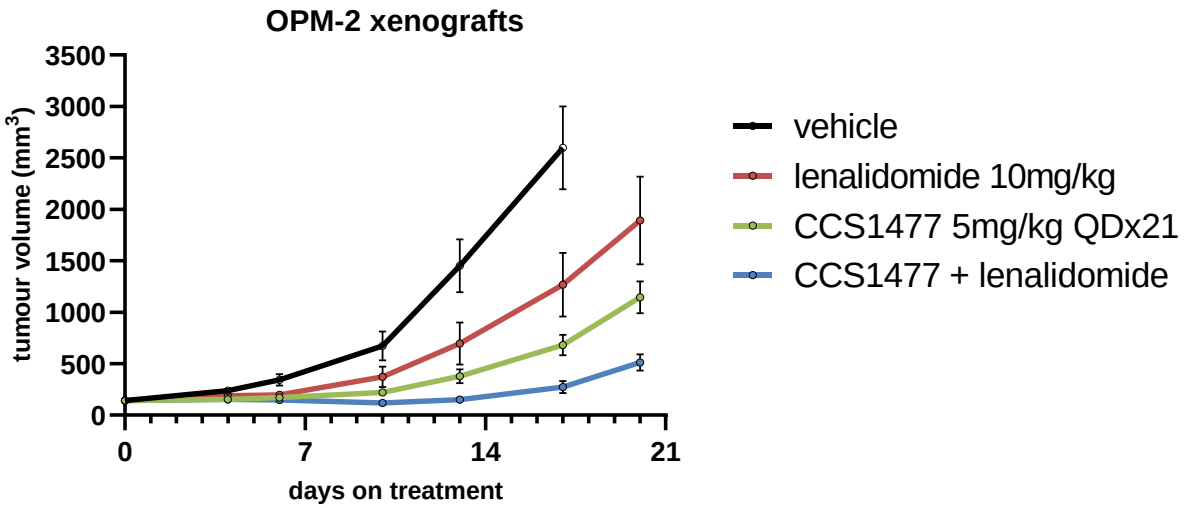
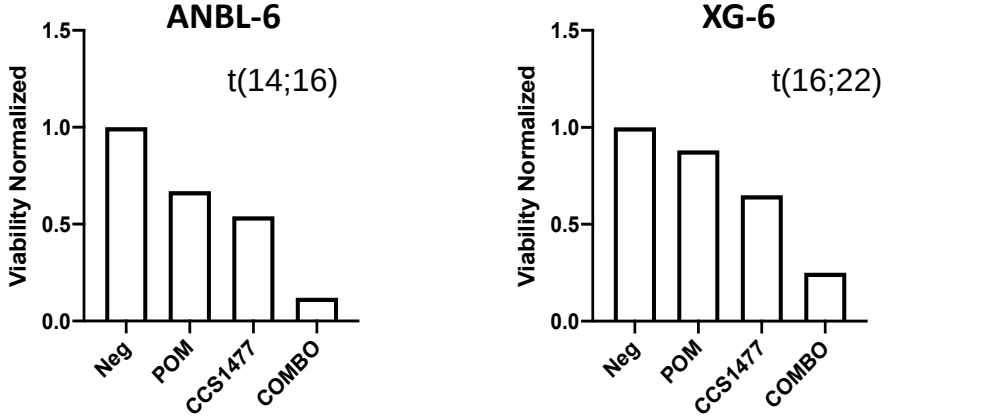
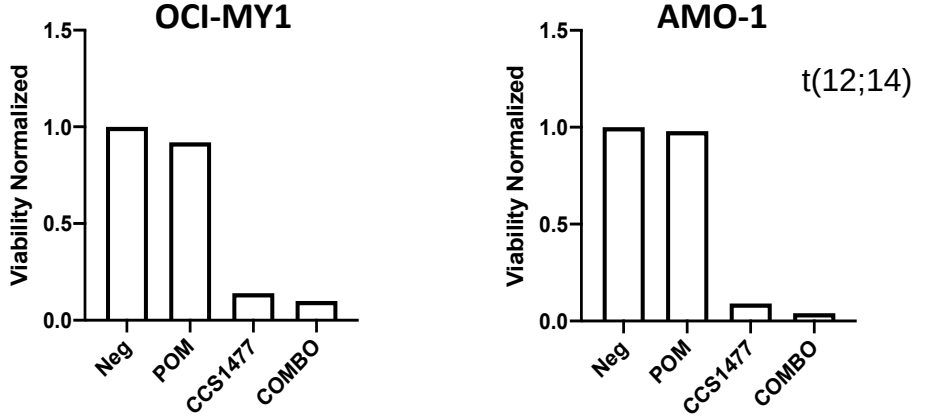


CCS1477 can synergize with Pom in sensitive cells



Data from Leif Bergsagel

CCS1477 has efficacy in Pom-resistant cells



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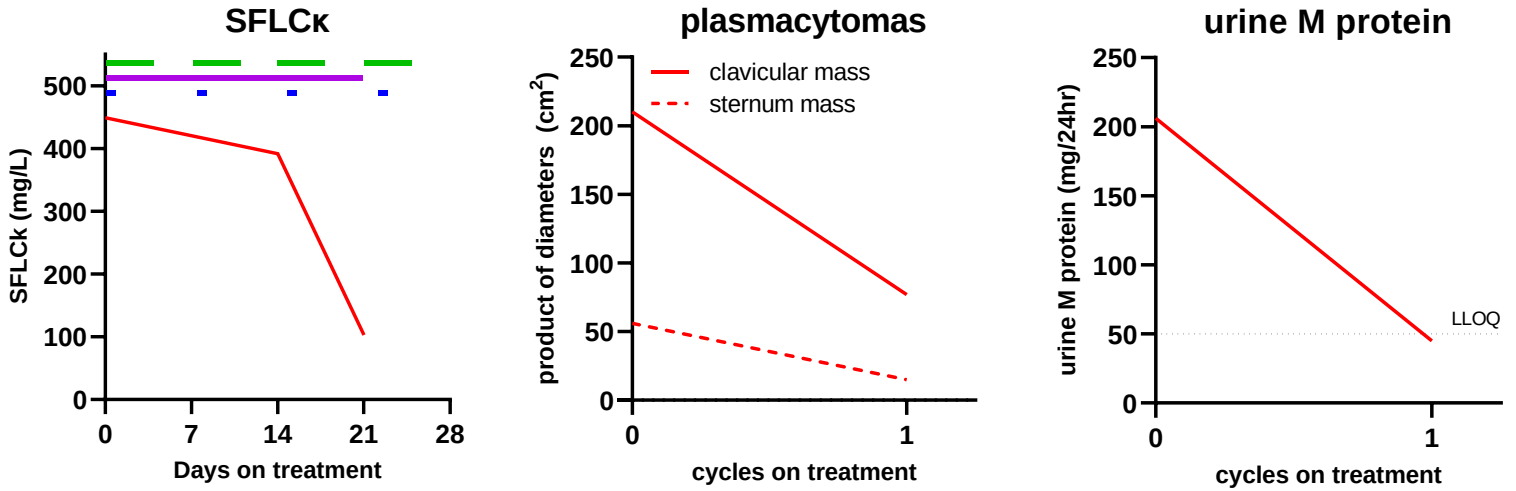
Inobrodib + pom/dex: early signs of activity

- First cohort initiated, dosing inobrodib one step below monotherapy RP2D
- First 3 patients:
  - no exacerbation of overlapping toxicities, combination generally well tolerated with predicted PK
  - **3/3 responses in cycle one: 1 VGPR, 1 PR, 1 MR**

Pt ID	Prior treatment	Measurable disease	C2D1 response
4201	6 lines Triple-class (inc. pom) refractory	urine M-protein plasmacytomas SFLC	**VGPR**
4203	TBC Pom-refractory	SFLC	**PR**
4204	TBC Pom-refractory	serum M-protein SFLC	**MR**

patient 2034201 - male, 80s, PS1



25mg inobrodib BID 4on / 3off
pomalidomide + dexamethasone

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Summary

EP300/CBP bromodomain inhibitor CCS1477:

- **Shows low nanomolar efficacy in *in vitro* and *in vivo* pre-clinical models**
- **Induces rapid, extensive transcriptional changes & EP300 redistribution on chromatin away from IRF4 binding sites**
- **Is an oral first-in-class agent which shows good long term tolerability at recommended phase 2 dose**
- **Delivers objective responses in heavily pre-treated R/R myeloma**
- **Next phase of trial seeks to evaluate CCS1477 in combination with pomalidomide and dexamethasone with initial pomalidomide-refractory patients showing early signs of clinical activity**

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Patients and their families

Clinical sites

The Christie Hospital
The Royal Marsden
University Hospital of Wales
Western General Hospital
Gartnavel General Hospital
Leicester Royal Infirmary
University College London
Oxford Cancer and Haematology Centre
University Hospital of Southampton

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Steve Salomon
Kate Fisher
Laura Johnson
Ruth Tysoe

Carrie Walker
Gill Fairweather