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Discovery of ASTX295, a Potent, Next-Generation Small Molecule Antagonist of MDM2 with Differentiated Pharmacokinetic Profile

From Concept to Clinic

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Disclosure Information

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Maria Ahn

I have the following relevant financial relationships to disclose:

Employee of Astex Pharmaceuticals, Cambridge, UK

Targeting the MDM2-p53 Interaction

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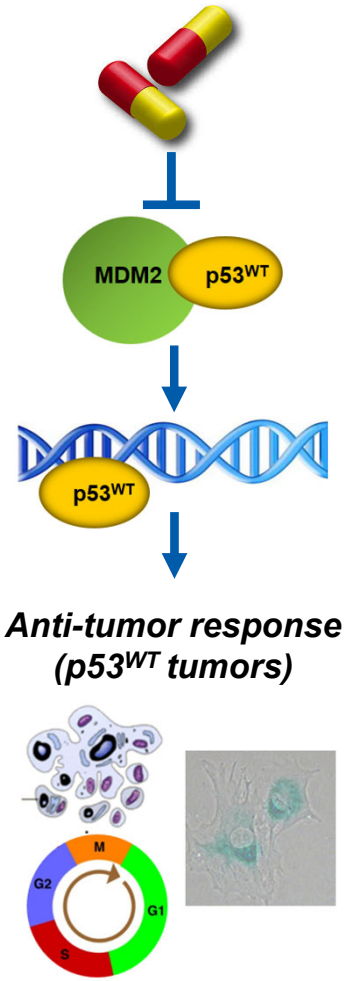
- p53 is a tumor suppressor that elicits anti-cancer response in the presence of cellular stress
- MDM2 is the main negative regulator of p53
- Disrupting the MDM2-p53 protein-protein interaction has been pursued as a promising strategy for cancer therapy
- Multiple small molecule inhibitors of the MDM2-p53 interaction remain in clinical development
- MDM2 antagonists have demonstrated clinical activity (*e.g.*, liposarcoma)



Anti-tumor response (p53^{WT} tumors)

"The Problem": Bone Marrow Toxicity

- A number of MDM2 antagonists demonstrated clinical activity
- Activation of p53 impairs thrombopoiesis (Iancu-Rubin *et al.,* 2014)
- Thrombocytopenia and neutropenia are major on-target dose limiting toxicities
- **Goal:** Develop a potent, oral, next-generation MDM2 antagonist with a different safety profile

Hematological toxicities in the RG7112 proof-of-mechanism study

	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Adverse event						
Nausea	14 (70%)	2 (10%)	11 (55%)	1 (5%)	0	0
Vomiting	11 (55%)	5 (25%)	4 (20%)	2 (10%)	0	0
Asthenia	9 (45%)	3 (15%)	6 (30%)	0	0	0
Diarrhoea	9 (45%)	7 (35%)	1 (5%)	1 (5%)	0	0
Thrombocytopenia	8 (40%)	1 (5%)	2 (10%)	2 (10%)	3 (15%)	0
Fatigue	6 (30%)	2 (10%)	4 (20%)	0	0	0
Neutropenia	6 (30%)	0	0	0	6 (30%)	0
Alopecia	4 (20%)	3 (15%)	1 (5%)	0	0	0
Constipation	3 (15%)	2 (10%)	1 (5%)	0	0	0
Decreased appetite	3 (15%)	2 (10%)	0	1 (5%)	0	0
Abdominal pain	2 (10%)	1 (5%)	1 (5%)	0	0	0
Anaemia	2 (10%)	1 (5%)	1 (5%)	0	0	0
Atrial fibrillation	2 (10%)	1 (5%)	1 (5%)	0	0	0
Back pain	2 (10%)	2 (10%)	0	0	0	0
Dysgeusia	2 (10%)	2 (10%)	0	0	0	0
Reflux	2 (10%)	1 (5%)	1 (5%)	0	0	0
Pain in extremity	2 (10%)	1 (5%)	1 (5%)	0	0	0
Pyrexia	2 (10%)	1 (5%)	1 (5%)	0	0	0
Urinary tract infection	2 (10%)	2 (10%)	0	0	0	0
Serious adverse event						
Neutropenia	6 (30%)	0	0	0	6 (30%)	0
Thrombocytopenia	3 (15%)	0	0	0	3 (15%)	0
Febrile neutropenia	1 (5%)	0	0	0	1 (5%)	0
General deterioration	1 (5%)	0	0	1 (5%)*	0	0
Haemorrhage	1 (5%)	0	0	0	0	1 (5%)*

Data are number of events (%). *Deemed unrelated to treatment.

Table 2: **All adverse events and serious adverse events that occurred in at least one patient**

(Ray-Coquard *et al.*, *Lancet Onc,* 2012)

"The Hypothesis": Differential Sensitivity to p53 Activation in Normal vs. Cancer cells

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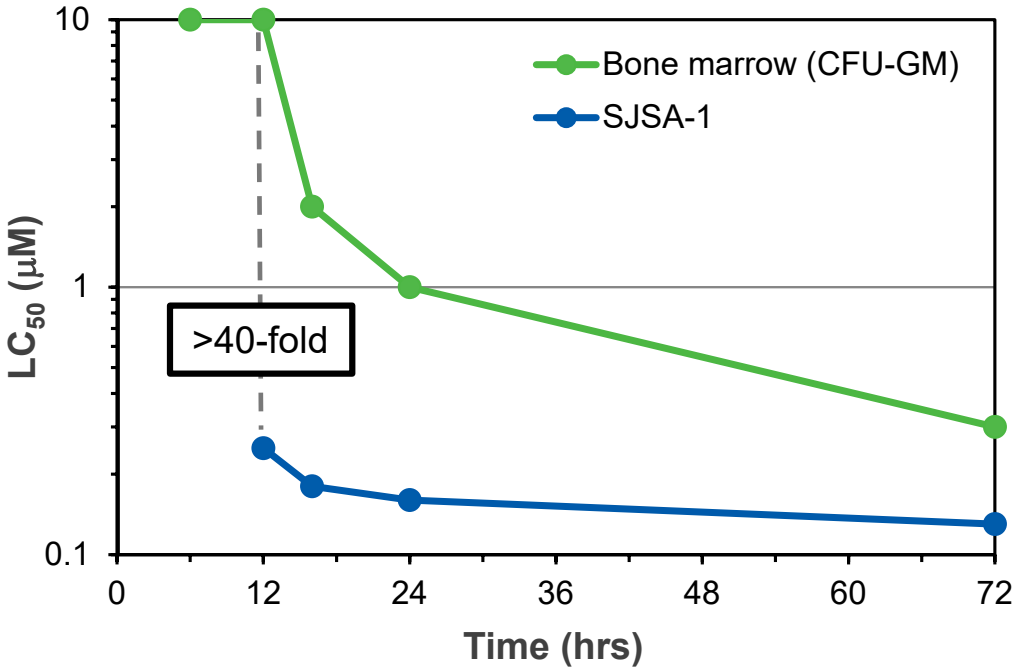
- Early *in vitro* studies indicated differential sensitivity of normal vs. cancer cells following short (<12 hours) treatment with an MDM2 antagonist
- ***Hypothesis***: Pulses of short exposures may limit p53 pathway activation in normal cells and reduce bone marrow toxicity while maintaining efficacy

Differential time-dependent sensitivity in human bone marrow vs. osteosarcoma cell line (SJSA-1)



(Abstract 3333)

Further Validation of the Hypothesis

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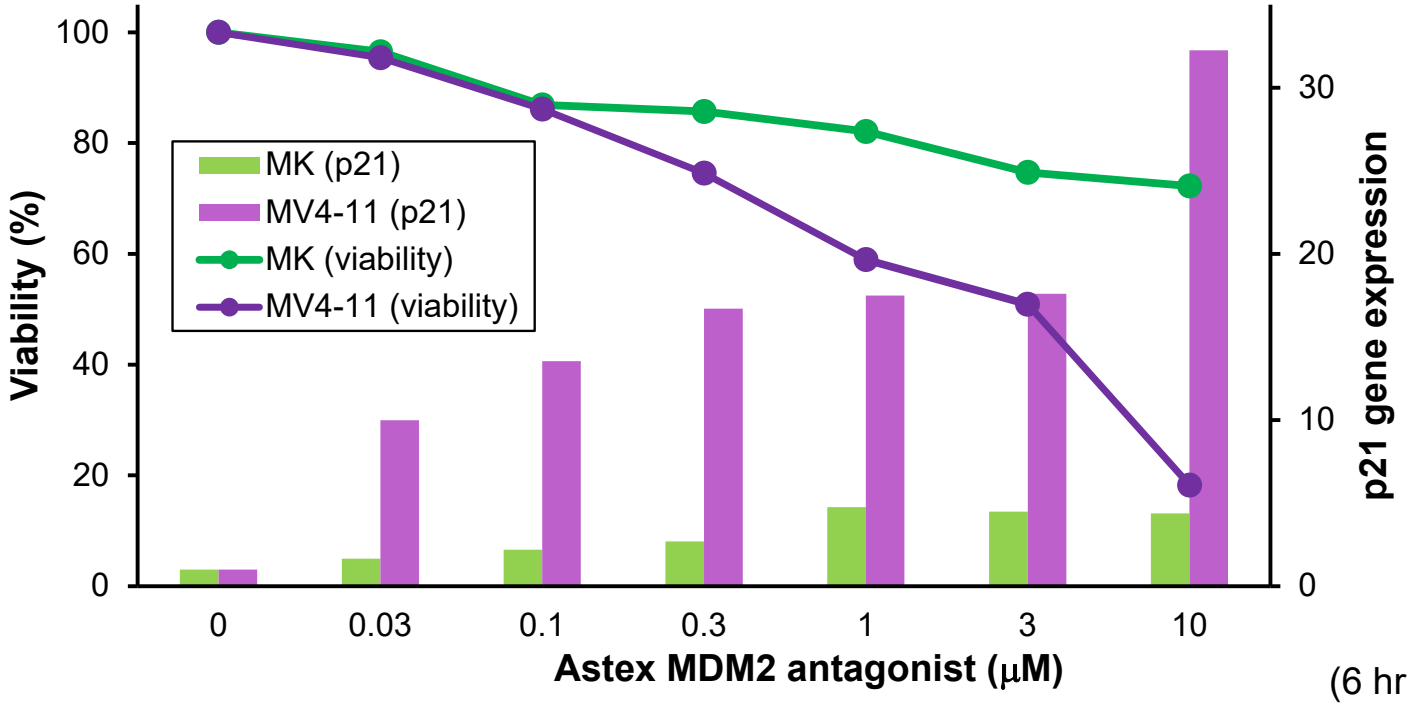
- Strong induction of pro-apoptotic genes was observed after 6 hours in cancer (primary CLL) but not in bone marrow cells
- Further studies in human megakaryocytes (MKs) supported the hypothesis



(6 hr pulse treatment QDx3)

Targeting the Desired PK Profile

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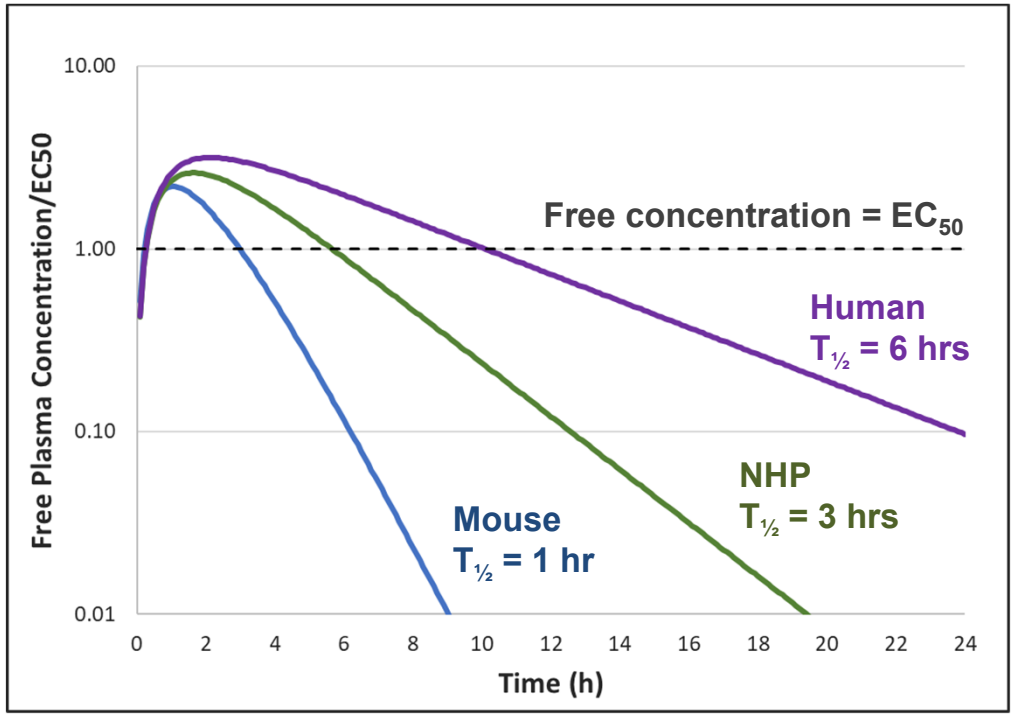
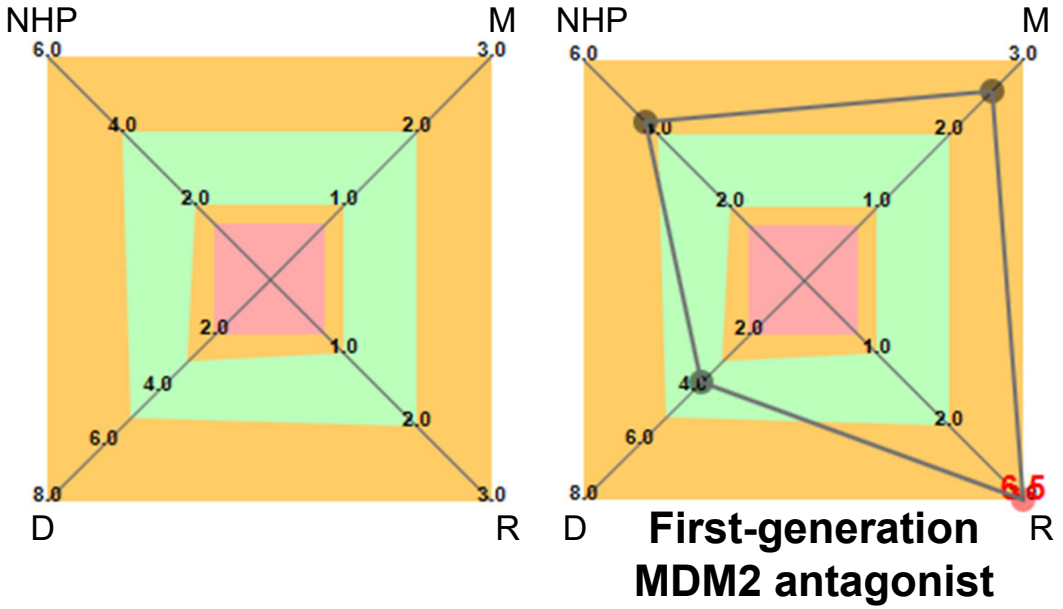
- Lead optimisation focused on targeting a specific human PK profile ($T_{1/2}$=3-12 hours)
- All other MDM2 antagonists in clinical development at the time retained $T_{1/2}$ >14 hours



Cross-species half-life comparison



(NHP, non-human primate; M, mouse; R, rat; D, dog)

Concept to Clinical Candidate: ASTX295

Short Exposure to Limit Bone Marrow Toxicity

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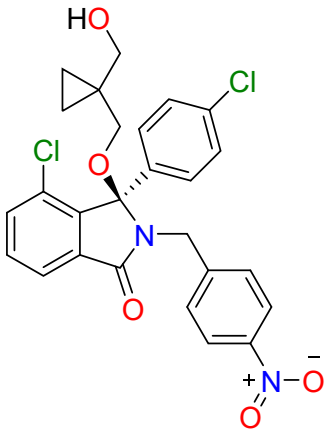
- Lead optimisation using structure-based drug design (SBDD) generated potent compounds with three different profiles

Early Lead

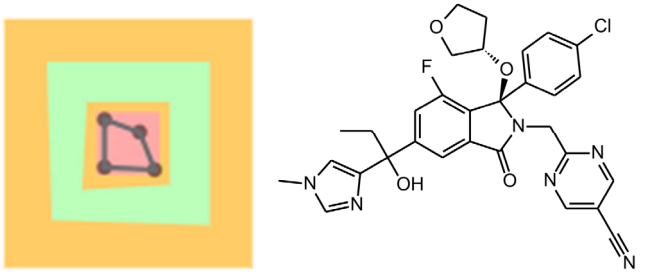


Lead Optimisation

SBDD

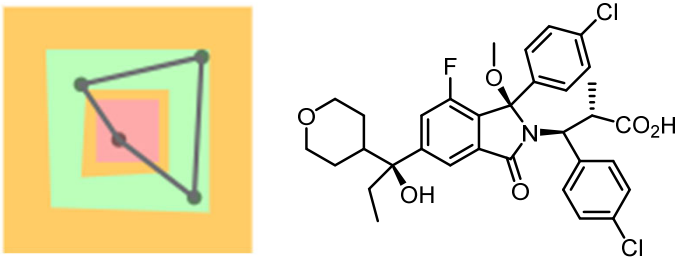
Improve potency
Optimise PK

Neutral



SJSA1 GI_{50}=85 nM
Metabolically unstable

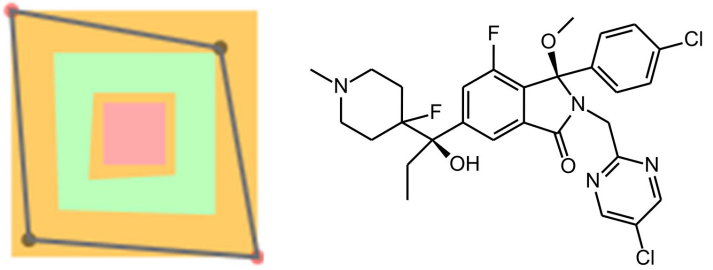
Acid



ASTX295

SJSA1 GI_{50}=23 nM
Desired predicted $T_{1/2}$

Basic



SJSA1 GI_{50}=27 nM
Longer predicted $T_{1/2}$

Hardcastle *et al.*, *J Med Chem* 2011
Chessari *et al.*, *J Med Chem* 2021

ASTX295 Activates p53 and Induces Cell Death

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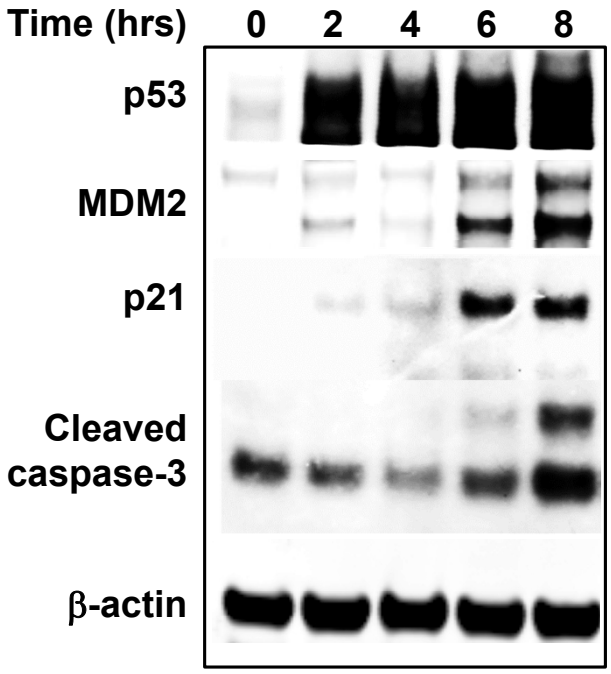
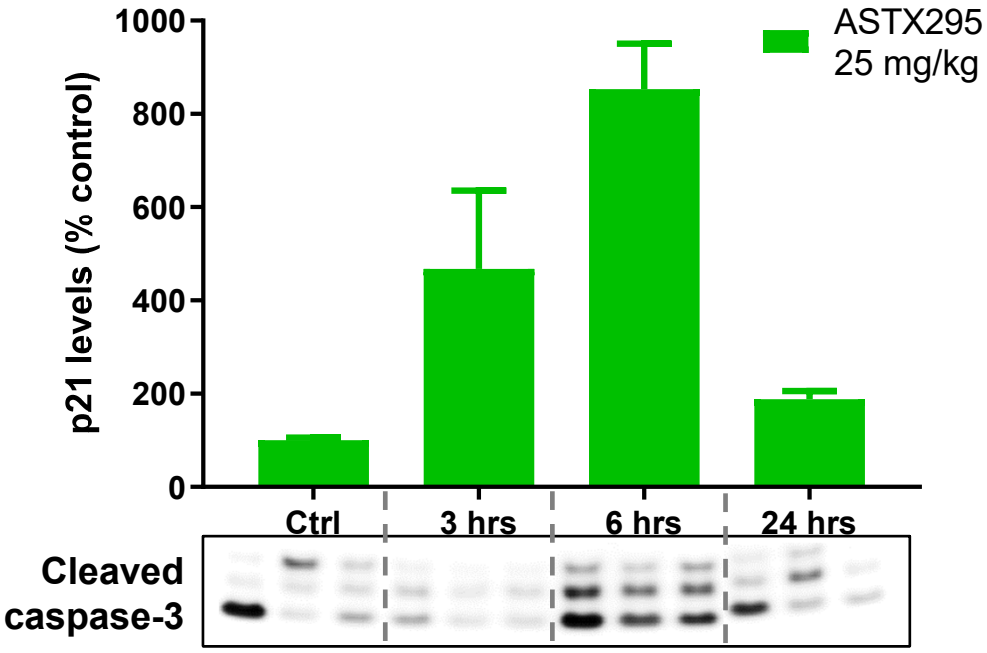
- ASTX295 activity is specific for cells carrying wild-type p53
- ASTX295 shows the desired, shorter duration of p53 pathway modulation *in vivo*

p53 activation *in vitro*



Pharmacodynamic (p21) modulation *in vivo*



ASTX295 is Potent *In Vitro* and *In Vivo*

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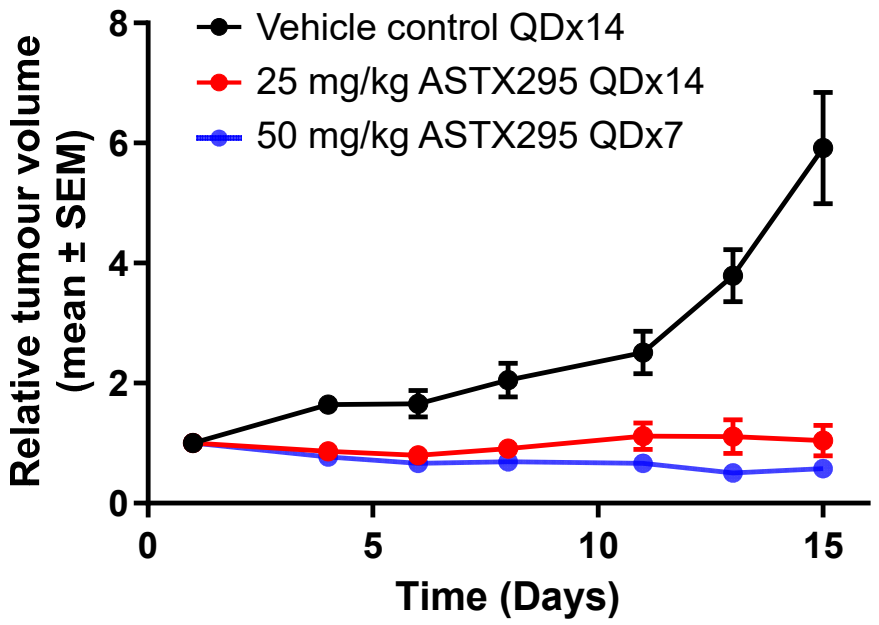
- Antiproliferative activity of ASTX295 demonstrated in 219 p53 wild-type cell lines
- ASTX295 maintains efficacy *in vivo*
- *No significant hematological changes observed in pre-clinical studies*

Property	Targeted profile	ASTX295	
MDM2 IC_{50}	<1 nM	< 1 nM	Potent
SJSA1 GI_{50}	<50 nM	27 nM	
SJSA1 p53 IC_{50}	<10 nM	10 nM	
P450	<50% at 10 μM	20% @ 20 μM (3A4)	Clean CYP/hERG
hERG	>30 μM	> 100 μM	
In vivo PD 6 hrs	p21 high	high (25 mg/kg)	Short PD duration
In vivo PD 24 hrs	p21 low	low (25 mg/kg)	
Efficacy	SD	25 mg/kg QDx14	
Human $T_{1/2}$	3 - 12 hrs	2-8 hrs (predicted) 4-6 hrs (Phase 1)	Shorter $T_{1/2}$



(SJSA-1 tumor xenograft)

Summary and Future Outlook

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- ASTX295 is a potent, next-generation MDM2 antagonist with a PK profile aimed at reducing on-target bone marrow toxicity
- ASTX295 Phase 1 study completed (NCT03975387) and RP2D identified
- ***In the clinical study, ASTX295 demonstrated a half-life of 4-6 hours and a differentiated safety profile with no significant thrombocytopenia***
- MDM2 antagonists show a wide range of sensitivity in p53 wild-type tumors. *Could patient stratification be further refined?*
  1) Identification of biomarkers predictive of sensitivity in p53 wild-type cancers
  2) Combination with chemotherapy or other targeted agents
- Differentiated safety profile of ASTX295 may offer opportunities for improved combination therapies

Preliminary Phase 1 data: Abstract CT066
Identification of predictive biomarkers: Abstract 666, Abstract 667

Thank you!

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12 years of collaboration and still going…

astex pharmaceuticals

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