Astex Pharmaceuticals

ASTX660
CRUK CA
March 2018

astex®

Outline

1. **Astex Pharmaceuticals**

2. **Background & Profile**
   1. Differentiation of ASTX660 from other IAP inhibitors
   2. Inhibition of XIAP, in addition to cIAP1/2
   3. Optimized dual inhibition, potency, and oral administration

3. **ASTX660-01 Phase 1/2 Study**
   1. Phase 1 experience
   2. Phase 2 cohorts

4. **Opportunities for combination**
   1. Chemotherapy
   2. Immunotherapy
   3. Radiotherapy
   4. Molecularly Targeted Agents

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Astex Pharmaceuticals, Inc.

Clinical Development based in Pleasanton, California, USA (Bay Area)
~ 120 employees and consultants:

- Clinical Development
- Clinical Operations
- Regulatory Affairs
- Quality Assurance
- Manufacturing / CMC

Astex Therapeutics, Ltd.

Drug Discovery based in Cambridge, UK
~ 120 employees and consultants

- Structural Biology & Biophysics
- Computational Chemistry & Informatics
- Medicinal Chemistry
- Biology & DMPK
- Translational Research and Development

- Dedicated to small molecule drug discovery and development in oncology, hematology & CNS
- Formed in 2011 by the merger of:
  - **Astex Therapeutics Ltd**: leader in fragment-based drug discovery: Cambridge, UK: multiple targeted cancer drugs in development
  - **SuperGen, Inc.**: California, US-based public company since 1996: developed Dacogen® approved for treatment of MDS in the US and AML in EU
  - **Otsuka Acquired Astex Pharmaceuticals in 2013**

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ASTX660

Background

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ASTX660 is a potent, next generation small-molecule IAP antagonist

- **Inhibitor of apoptosis proteins (IAPs) function to limit cell death by preventing apoptosis**
- **ASTX660 is a potent, next generation, small- molecule antagonist of IAPs, discovered by fragment-based drug discovery (FBDD)**
- **Chemically distinct from 1st generation peptidomimetic SMAC mimetics**
  - Monomer, fragment derived, non-Alanine
- **ASTX660 has a balanced inhibition across the family (cIAP1, cIAP2 and XIAP)**

Presented at EORTC 2014. Abstract #380

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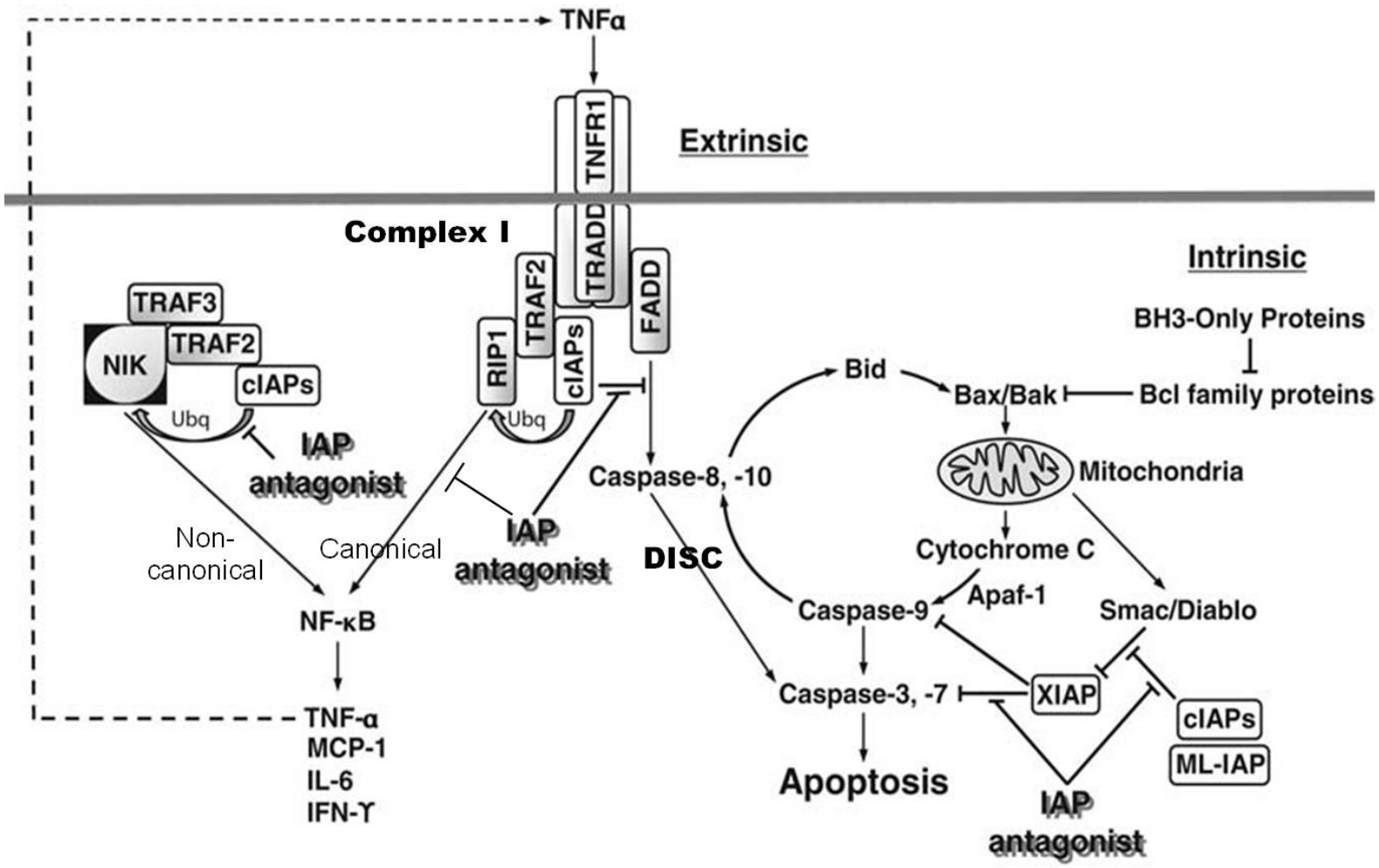
IAP antagonism leads to a switch from pro-survival signaling to apoptosis



After Flygare & Fairbrother, 2010

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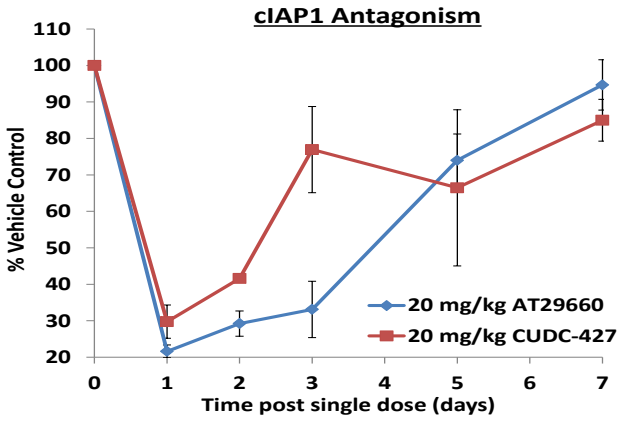
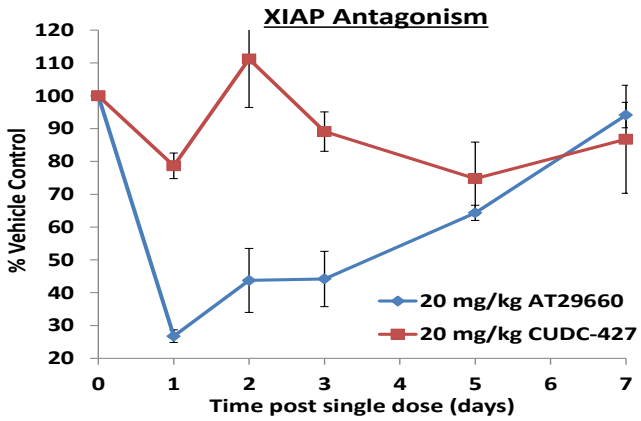
ASTX660 is a balanced dual cIAP/XIAP antagonist

- **ASTX660 demonstrates low nM XIAP inhibition and more balanced selectivity of cIAP1 over XIAP compared to 1st generation peptidomimetics**

in vitro Cell Assays	IC_{50} values in nM*	ASTX660	CUDC-427 (Curis)	LCL-161 (Novartis)	Debio-1143 (Debiopharm)	Birinapant (Tetralogic)
cIAP1 (cellular activity)	MDA-MB-231 (cIAP1 degradation)	**0.22**	**0.044**	**0.40**	**0.92**	**0.23**
XIAP (cellular activity)	HEK293-XIAP-Caspase9 (binding assay)	**2.8**	**10**	**35**	**34**	**23**
Selectivity	**cIAP1/XIAP**	**13**	**230**	**88**	**37**	**100**
Proliferation	MDA-MB-231 (cIAP1 driven model)	**1.8**	**3.0**	**7.8**	**18.0**	**0.98**
Administration Route		**Oral**	**Oral**	**Oral**	**Oral**	**Intravenous**



IAP pharmacodynamics in MDA-MB-231 tumor xenografts



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ASTX660-01
Phase 1/2
Study

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ASTX660-01 Phase 1: Summary

1. **Enrollment in the Phase 1 is completed**
   - Dosed from 15 mg to 270 mg (fixed daily dose)
   - Maximum tolerated dose (MTD): 210 mg
   - Recommended Phase 2 dose (RP2D): 180 mg
   - Dose limiting toxicities (DLT): Asymptomatic grade 3 lipase with or without Grade 3 increased amylase elevation
   - Common adverse events included anemia, nausea, vomiting, rash, lipase and amylase elevation, ALT elevation, lymphopenia

2. **Target exposures achieved at the 180 mg RP2D**
   - PK becomes non-proportional at and above 210 mg

3. **Biological and preliminary clinical activity observed at 180 mg**
   - cIAP1 suppression in PBMC - deep and sustained
   - Clinical response seen in cutaneous T cell lymphoma

4. **Phase 2 is currently ongoing (USA, Europe)**

Presented at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics 2017, Abstract #A091

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ASTX660-01 Phase 1: Dose Escalation Summary

- **45 patients received at least one dose of ASTX660**
- **DLTs were reported in 4 subjects (asymptomatic G3 lipase elevation with or without amylase elevation)**
- **Most DLTs resolved on dose interruption and rechallenge was successful at a lower dose**
- **One subject discontinued study treatment due to a study drug related AE (Grade 3 lipase elevation)**

Cohort	Dose (mg QD)	Form	N pts	DLTs
1	15	Powder In Bottle	3	-
2	30		3	-
3	60		4	-
4	120		3	-
5	180		3	-
6	180	Capsule	6	-
7	270		6	3 (G3 lipase elevation)
8	210 MTD		9	1 (G3 lipase elevation)
Dose Expansion	180 RP2D		8	-

Presented at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics 2017, Abstract #A091

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ASTX660-01 Phase 1: Adverse Events Regardless of Relationship in ≥10% Subjects

Preferred Term	Grade 1-2	Grade 3-4	All
Fatigue	15 (33%)	0	15 (33%)
Anemia	8 (18%)	6 (13%)	14 (31%)
Lipase increased	8 (18%)	6 (13%)	14 (31%)
Vomiting	14 (31%)	0	14 (31%)
Nausea	13 (29%)	0	13 (29%)
Lymphocyte count decreased/lymphopenia	5 (11%)	7 (16%)	12 (27%)
Pruritus	10 (22%)	0	10 (22%)
Hypocalcaemia	9 (20%)	0	9 (20%)
ALT increased	8 (18%)	0	8 (18%)
Decreased appetite	7 (16%)	1 (2%)	8 (18%)
AST increased	7 (16%)	0	7 (16%)
Edema peripheral	7 (16%)	0	7 (16%)
Rash maculo-papular	7 (16%)	0	7 (16%)
Amylase increased	5 (11%)	1 (2%)	6 (13%)
Diarrhea	6 (13%)	0	6 (13%)
Hypokalemia	5 (11%)	1 (2%)	6 (13%)
Hyponatremia	3 (6.7%)	3 (6.7%)	6 (13%)
Cough	5 (11.1%)	0	5 (11.1%)
Headache	4 (8.9%)	1 (2.2%)	5 (11.1%)
Hypoalbuminemia	5 (11.1%)	0	5 (11.1%)
Hypotension	5 (11.1%)	0	5 (11.1%)

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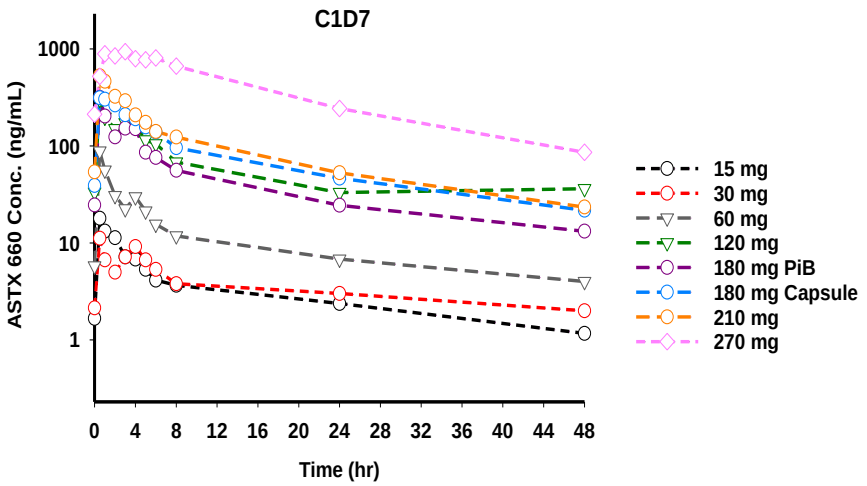
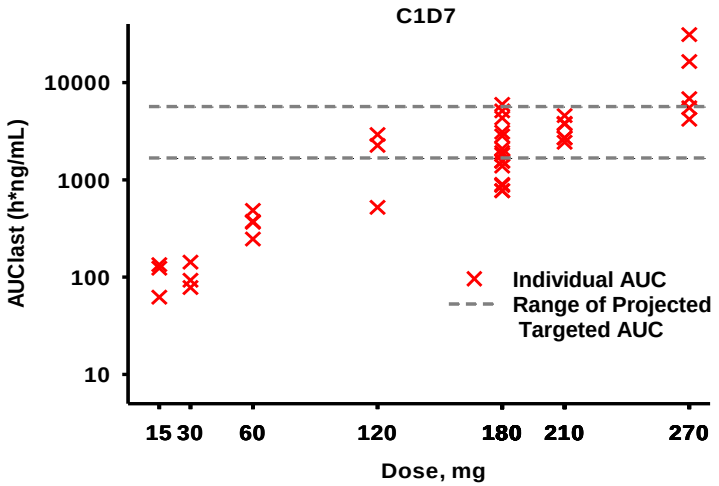
ASTX660-01 Phase 1: Pharmacokinetics





1. **180 mg** achieves **targeted therapeutic range exposures** (based on xenografts)

2. PK becomes non-proportional above 180 mg
   - Supraproportionally at higher exposures at 210 and 270 mg

Presented at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics 2017, Abstract #A091

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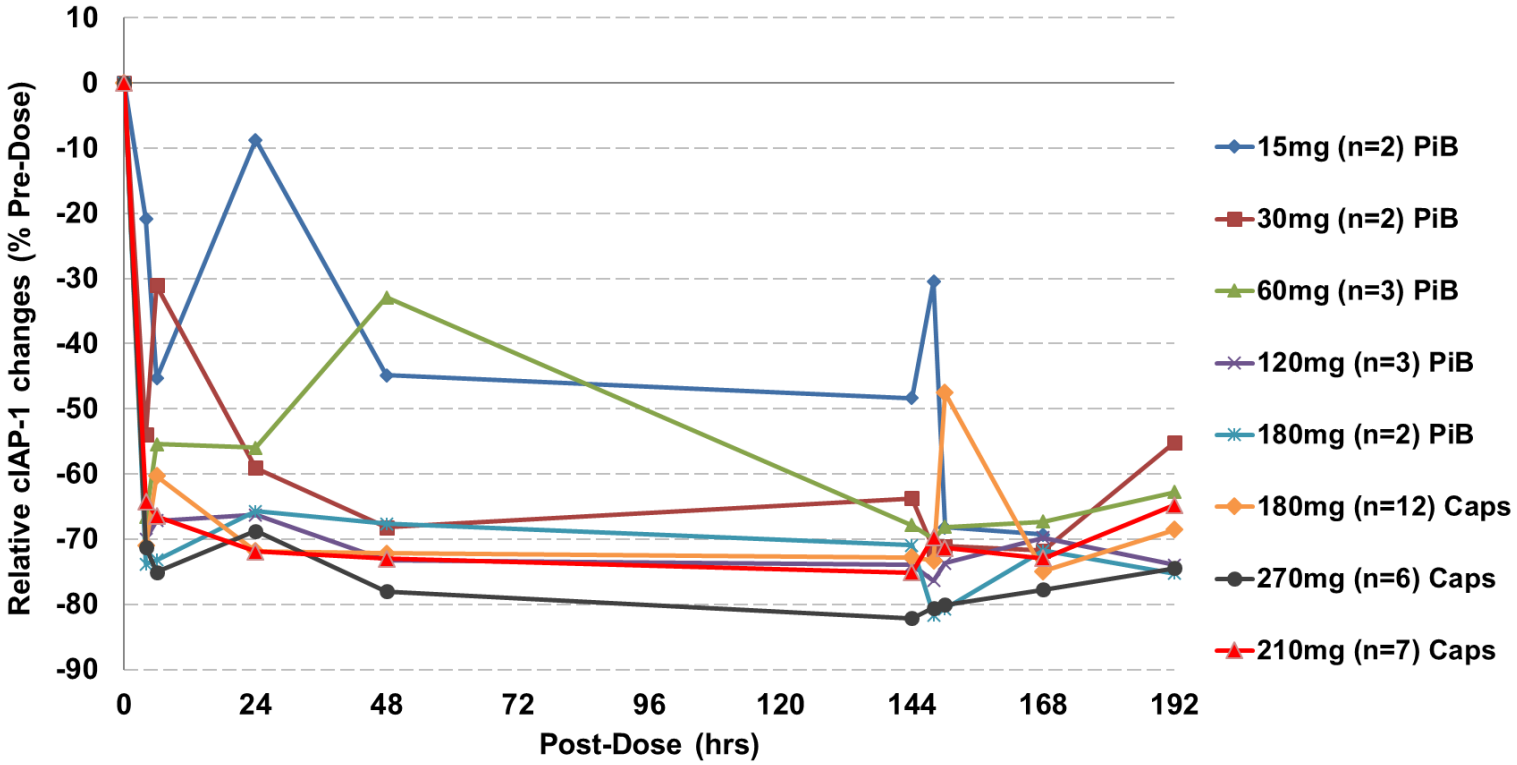
ASTX660-01 Phase 1: cIAP1 Target Engagement



- **Rapid, sustained, dose-dependent decreases in PBMC cIAP-1 with 180mg**
- **Prolonged cIAP-1 degradation in cycle 2 with ≥180mg ASTX660**

Presented at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics 2017, Abstract #A091

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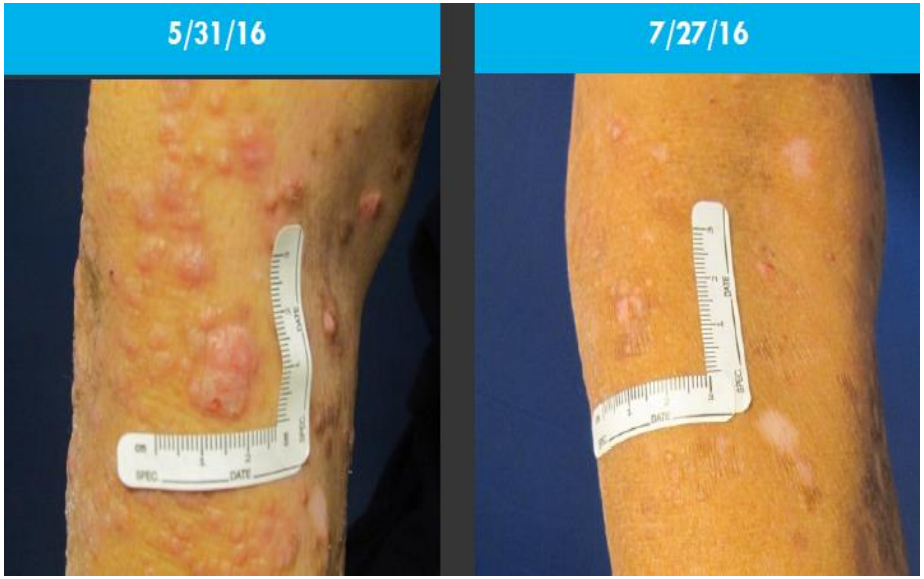
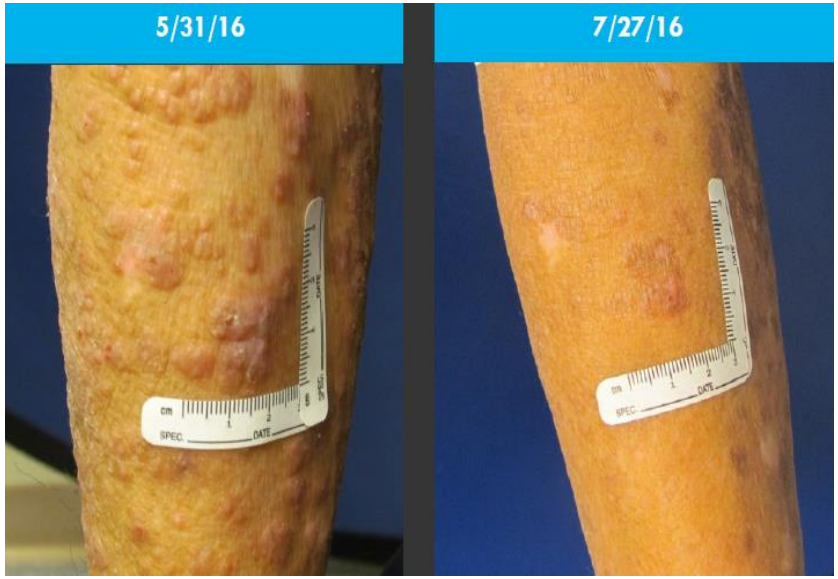
ASTX660-01 Phase 1: Clinical Activity

- **One clinical response was observed at the 180 mg dose in a subject with folliculotropic mycosis fungoides**





Presented at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics 2017, Abstract #A091

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ASTX660-01 Phase 2 Cohorts

Phase 2 part of the study will explore the single-agent antitumor activity of ASTX660 in selected tumor types with molecular features that potentially may confer sensitivity to ASTX660

#	Cohort
1	Head and neck squamous cell cancer (**HNSCC**)[1]
2	Diffuse Large B Cell Lymphoma (**DLBCL**)[2-4]
3	Peripheral T Cell Lymphoma (**PTCL**) [2-4]
4	Cutaneous T Cell Lymphoma (**CTCL**) [2-4]
5	Feature that may confer sensitivity (**Molecular**)
6	Cervical carcinoma (**Cervical**) [1]

1. Eytan, DF, et al. 2016. *Cancer Research* **76**: 5442-5454; 2. Yang, Y, et al. 2016. *Cancer Cell* **29**: 294-507; 3. Izban, KF, et al. 2000 *Human Pathology* **31**: 1482-1490.4. Quesada, AE, et al. 2014. *International Journal of Clinical and Experimental Pathology* **7**: 8732-8739.

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Combination Opportunities

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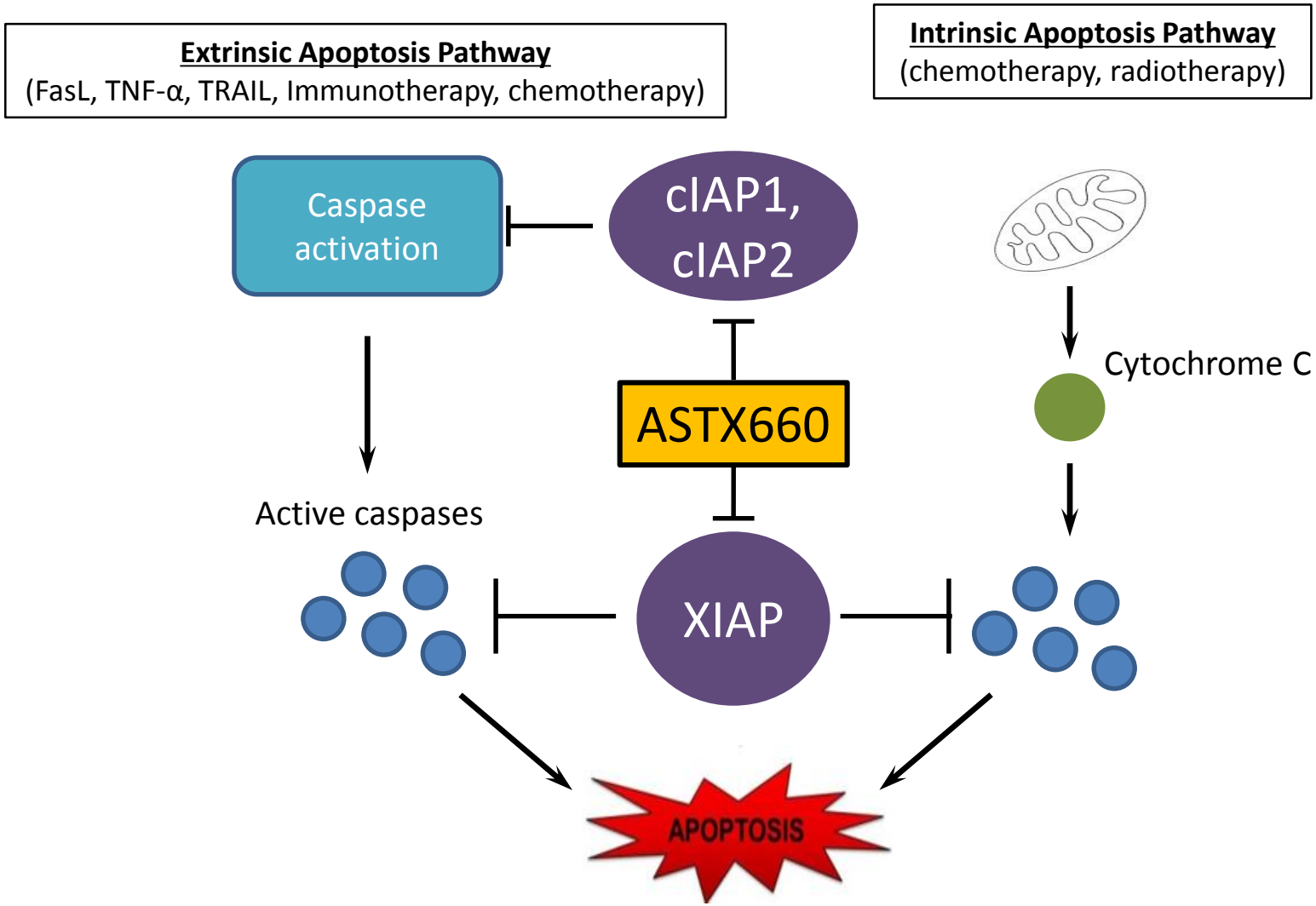
ASTX660 offers dual antagonism of cIAP and XIAP anti-apoptotic effects



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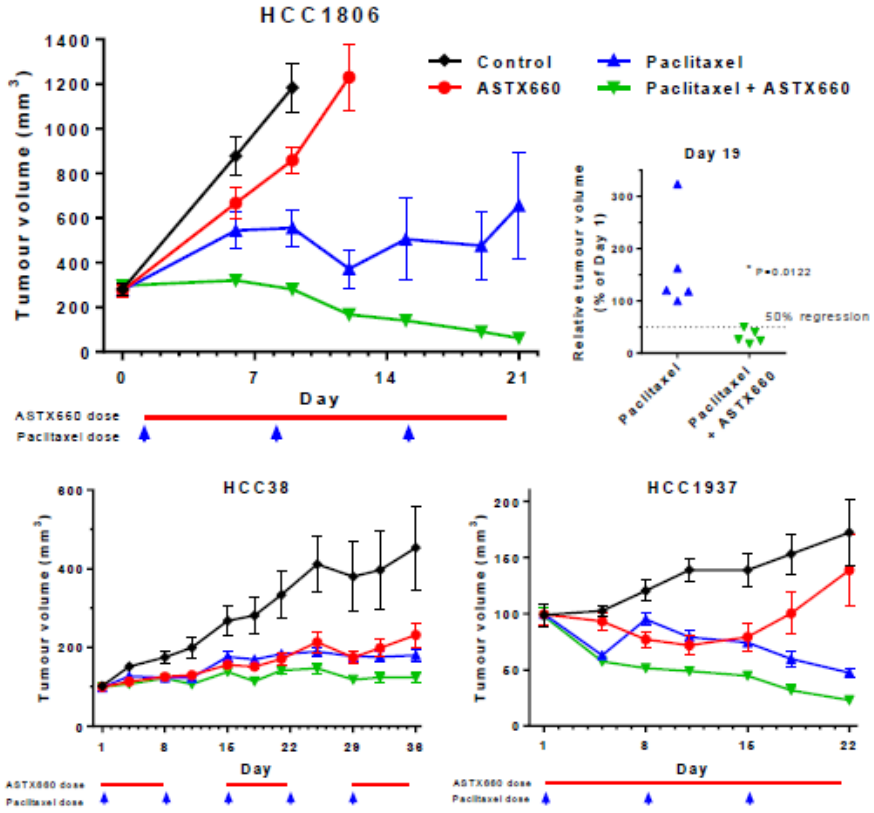
ASTX660 Combination with Chemotherapy

- **Combination of Paclitaxel and ASTX660 enhanced tumour growth inhibition in vivo in triple negative breast cancer (TNBC) models**



Presented at the AACR Annual Meeting 2016. Abstract #1287

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Dual cIAP/XIAP antagonism may exhibit positive immuno-stimulatory activities

- **Dendritic cell maturation and antigen presentation**
  - IAP antagonist (LCL-161) promotes dendritic cell maturation (Knights 2012)
    - Increases population expressing DC markers
    - Increases marker density
    - Protects from apoptosis
- **Direct effects on T cells**
  - IAP antagonists (M1, LCL-161) enhance the stimulation of multiple immune effectors in vitro (Dougan 2010, Knights 2012)
    - Increased cytokine production in CD8+ T cells treated with IAP antagonist + stimuli such as anti-CD3/CD28
    - Similar observation for CD4+, splenocytes & lymph node and NK cells
    - Increases cytokine-producing CD8+ cells (similar data on CD4+)
- **Dual cIAP/XIAP antagonism may be advantageous**
  - High expression of XIAP renders tumour cells resistant to ADCC through inhibition of caspase and ROS suppression (Evans et al 2016)
  - Defects in mithocondrial apoptotic pathways and elevated XIAP expression confer resistance to CTL-mediated killing (Kashkar et al, Blood 2006)

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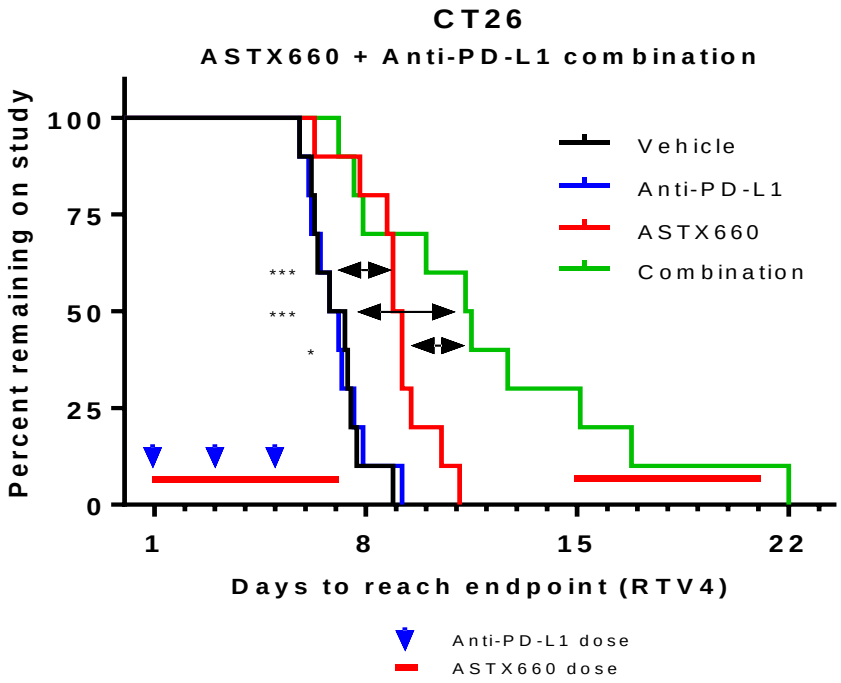
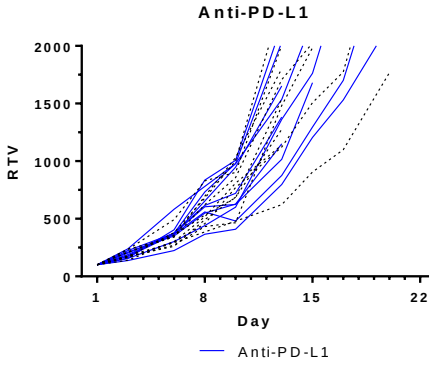
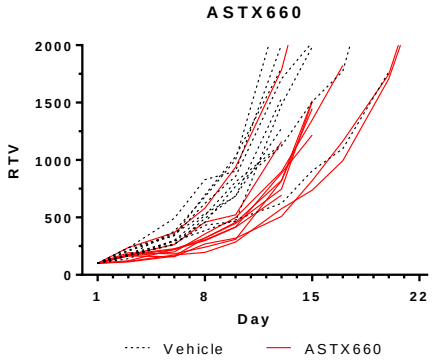
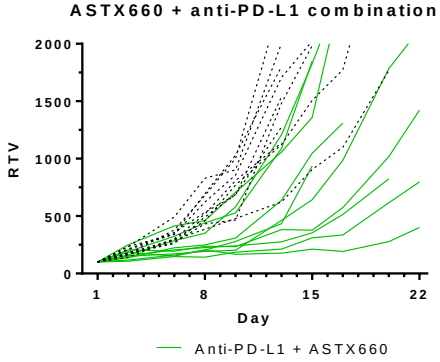
ASTX660 Combination with Anti-PD-L1 Therapy

- **ASTX660 in combination with anti-PD-L1 induced tumor regression and enhances survival in vivo in CT26 syngeneic colorectal cancer model**









*Astex in-house data presented at Tumor Immunology and Immunotherapy, 20-23 Oct 2016, Boston, USA

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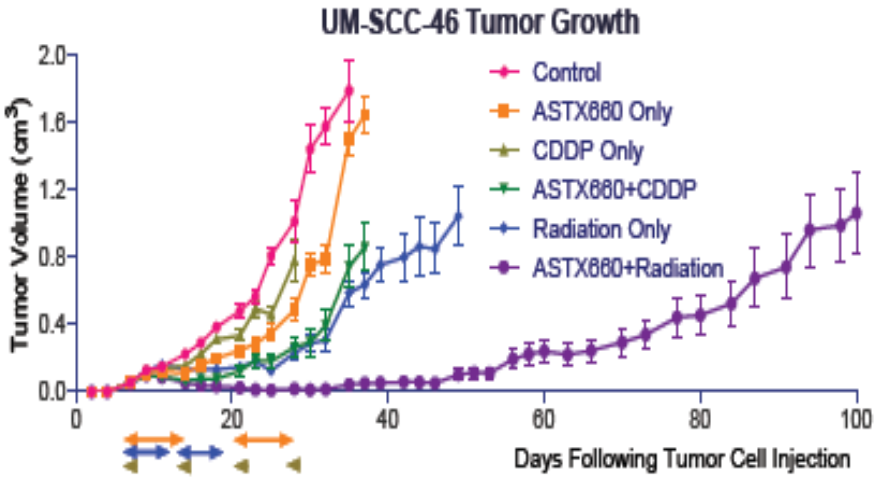
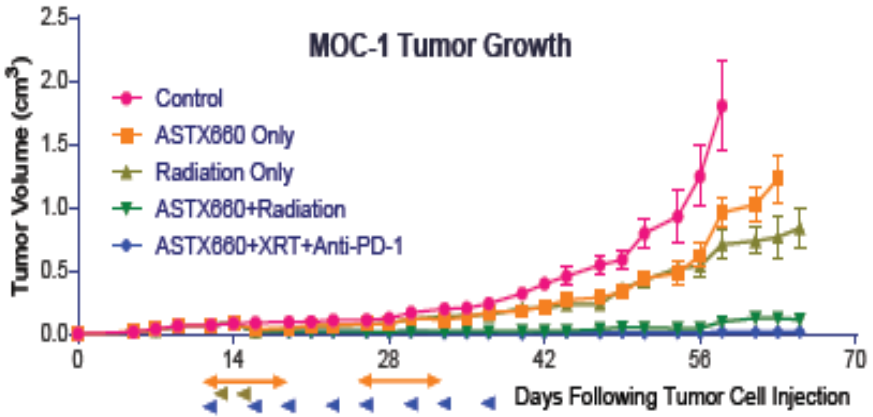
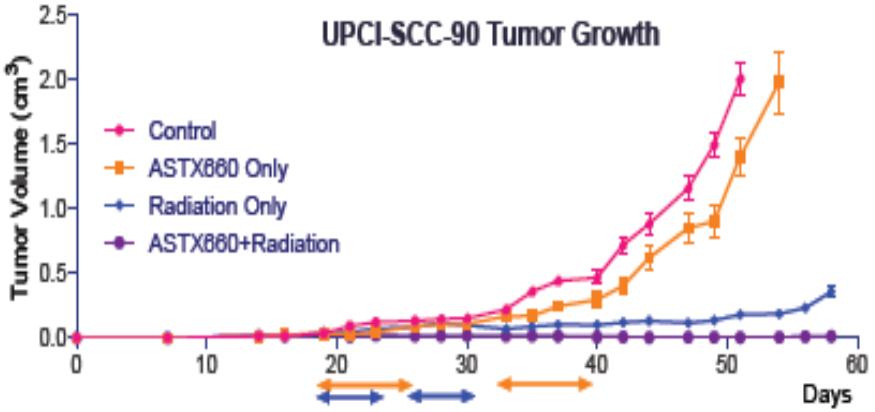
ASTX660 Combination with Radiotherapy and Anti-PD1

- ASTX660 combined with cisplatin and radiation induced tumor growth inhibition and enhanced survival in HPV- and HPV+ HNSCC models
- The greatest inhibition of syngeneic MOC-1 tumors was observed in when ASTX660 was combined with both radiation and anti-PD-1 therapy







Carter VanWaes Group, presented at AACR 2017, Abstract #1086

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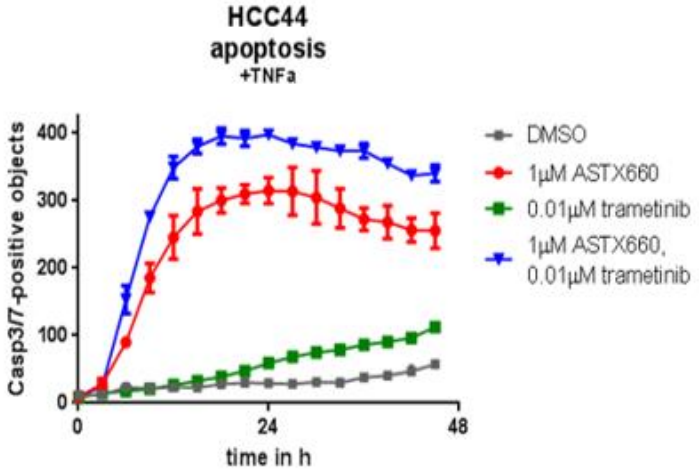
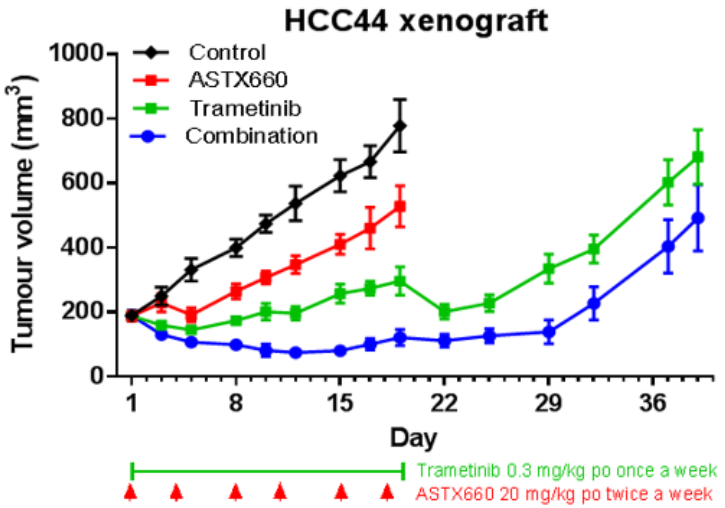
ASTX660 potentiates trametinib (MEKi) activity *in vitro* and *in vivo*





- **Cells treated with a combination of ASTX660 and trametinib show an increase in caspase activation over either single-agent treatment.**
- **ASTX660 and trametinib have moderate single-agent activity on HCC44 (KRAS mutant NSCLC) xenograft**
- **The combination of ASTX660 and trametinib caused regression and this persisted 1 week after treatment withdrawal**

Presented at the 23rd Conference of the European Cell Death Organization 'Death pathways and beyond'", Geneva, Switzerland, October 7-10, 2015.

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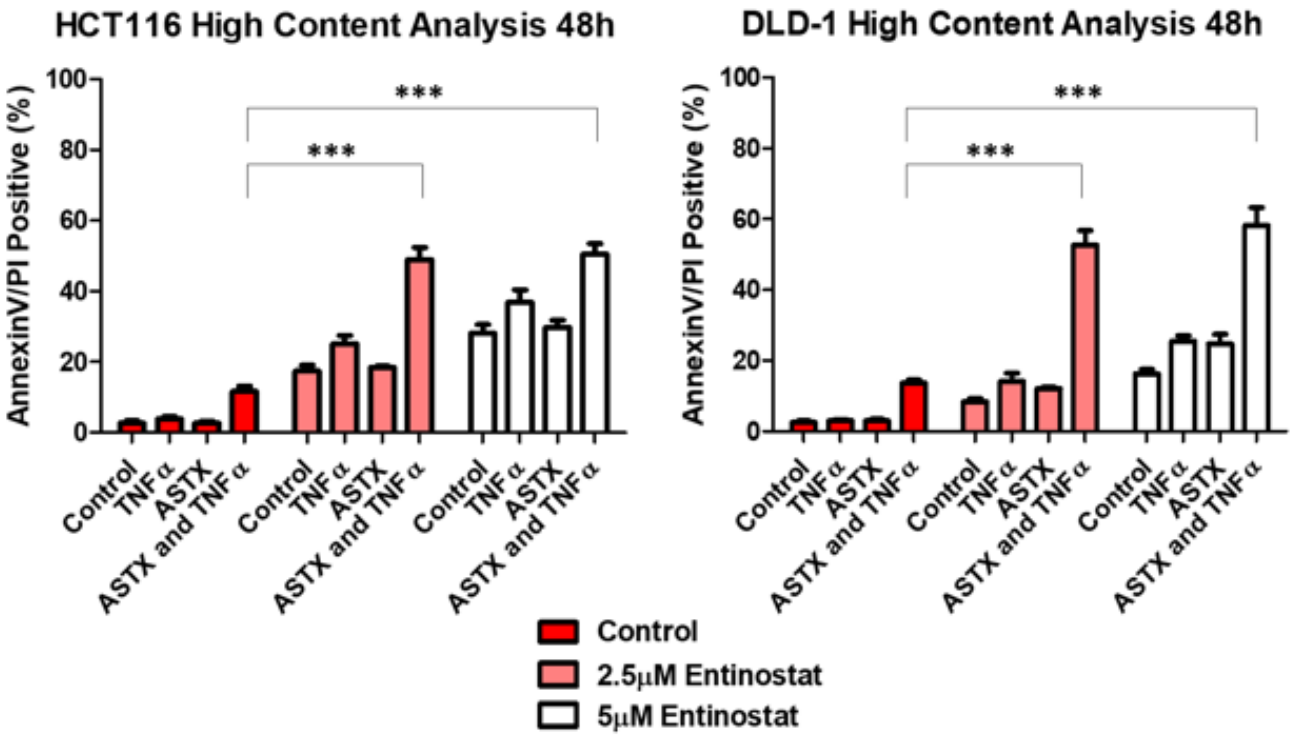
HDAC inhibitors can sensitise cancer cells to ASTX660 treatment



- **Entinostat-induced FLIP downregulation sensitises CRC cells to ASTX660**
- **Entinostat and ASTX660 combination reduces CRC cell viability**

Presented at the 2017 NCRI Cancer Conference, Liverpool UK, November 5 - 8 – K Stott et al

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Thank you