Combination of HSP90 inhibitor onalespib (AT13387) with crizotinib to treat or delay resistance in NSCLC: Preclinical and Clinical Investigations.

Harold Keer, Tomoko Smyth, Aurelie Courtin, Keisha Hearn,
John Lyons, Nicola Wallis, Aram Oganesian, and Mohammad Azab.

13th International Congress on Targeted Anticancer Therapies TAT 2015

March 2, 2015

Disclosures

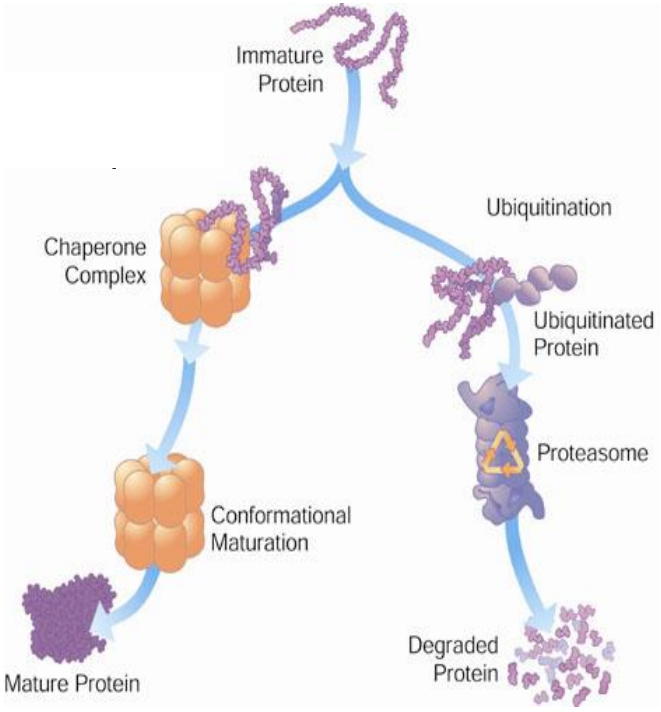
- All authors are employees of Astex Pharmaceuticals, Inc.
  (Cambridge, UK, Pleasanton, CA, USA)

- Discussion of non-approved agents (onalespib)

Introduction/Rationale: Why target HSP90? Why haven't previous approaches led to an approved drug yet?

- **HSP90 as a cancer target:**
  - Senses environmental stress and coordinates cellular responses to promote survival
  - Maintains protein homeostasis in normal cells
  - Maintains functionality/stability of mutated and/or over expressed oncogenes in cancer cells
    - ALK, MET, EGFR, HER-2, etc.
  - Inhibition of HSP90 simultaneously disrupts multiple signaling pathways

- **Clinical Approaches:**
  - Single agent relapsed/refractory
    - (RR in late setting ~15%)
  - Combinations at relapse (resensitize)
    - Chemotherapy
    - Targeted therapy



HSP90 Inhibitors and TKIs in NSCLC

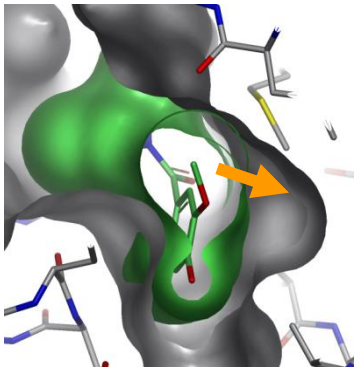
- **Resistance to Targeted Therapies (TKIs)**
  - Tyrosine kinase inhibitors used successfully to treat subsets of NSCLC
  - BUT responses are of limited duration with the development of resistance mediated by multiple mechanisms

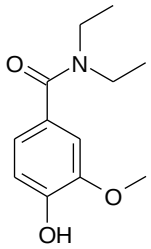
- **Hypothesis:**
  - Inhibiting HSP90 compromises cancer cell robustness and may impact resistance to other therapies

- **HSP90 in combination with TKI may:**
  - **Delay the development of resistance to a TKI**
  - **Overcome acquired resistance to TKIs regardless of mechanism**

Discovery of Onalespib: A Potent HSP90 Inhibitor

Fragment

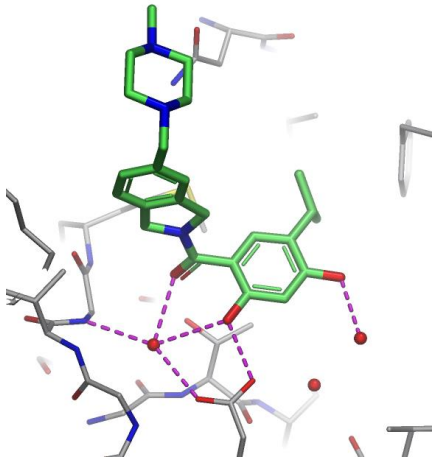


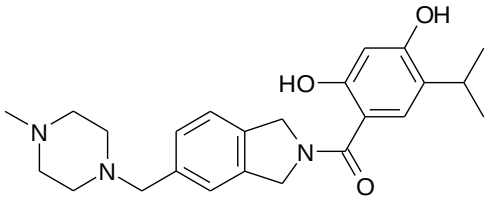


K_d (ITC) = 790 μM
LE = 0.26

- Potency increase
- Modification of physical properties to improve efficacy
- Rational SAR to modify hERG activity

Candidate (AT13387)





K_d (ITC) = 0.00071 μM
LE = 0.42

Murray et al J Med Chem 2010
Woodhead et al J Med Chem 2010

Onalespib Phase 1 Experience

- **Onalespib is well tolerated. MTD defined with:**
  - Twice weekly regimen: 120 mg/m^2/ Dose Days 1,4 for 3 weeks
  - **Once weekly regimen: 260 mg/m^2/dose for 3 weeks**

- **Few patients had Gr 3 toxicities and no Gr 4 AEs reported.**
  - DLTs were mainly Gr 2 GI AEs (diarrhea, vomiting) and fatigue.
  - Visual disturbances were almost all Gr 1
    - All were transient and reversible, and not dose-limiting
    - On-target class effects of potent HSP90 inhibition with good tissue distribution

- **PK exposures were dose-dependent and linear**

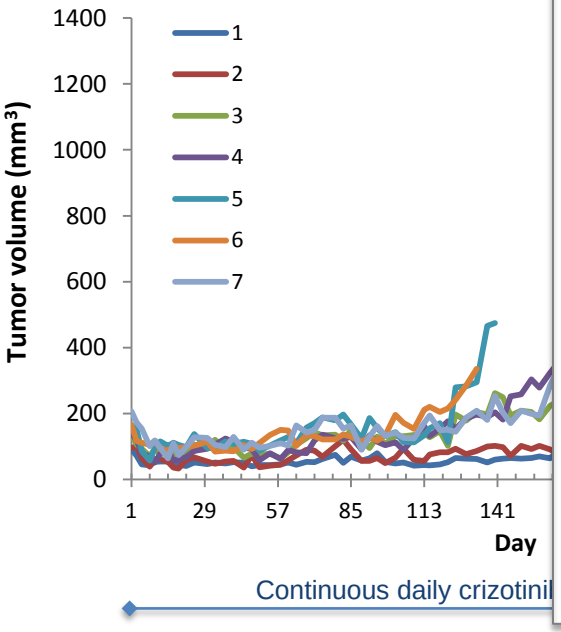
- **HSP70 induction of 2-11 fold magnitude confirming PD evidence of target engagement**

- **Early evidence of activity with objective PR at 220 mg/m^2 dose level**

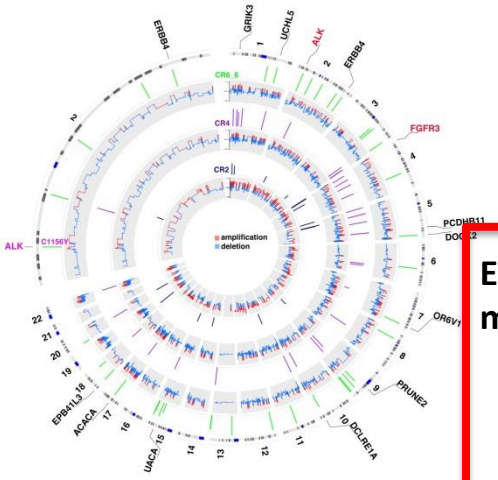
(Shapiro, et al., Clinical Cancer Research 2015)

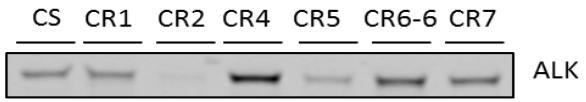
AT13387 Overcomes Acquired Resistance in an ALK-Positive Crizotinib-Resistant Xenograft

H2228 tumor xenografts treated with crizotinib



EML4-ALK NSCLC xenografts acquired resistance to crizotinib through different mechanisms



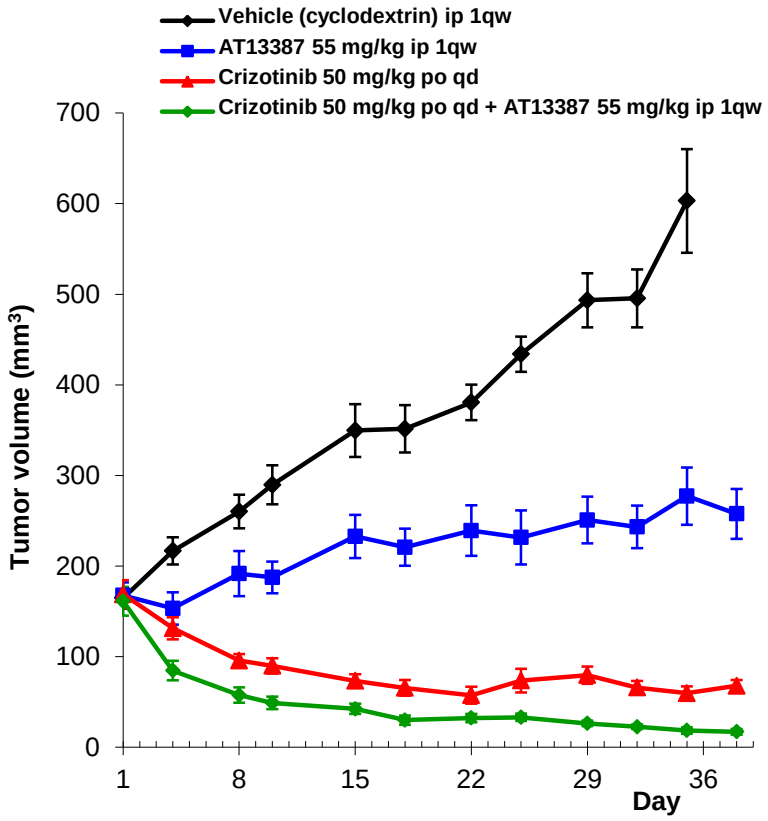


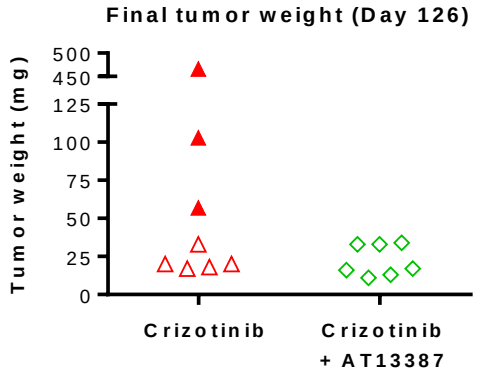
Exome sequencing revealed various gene modifications also reported in the clinic:

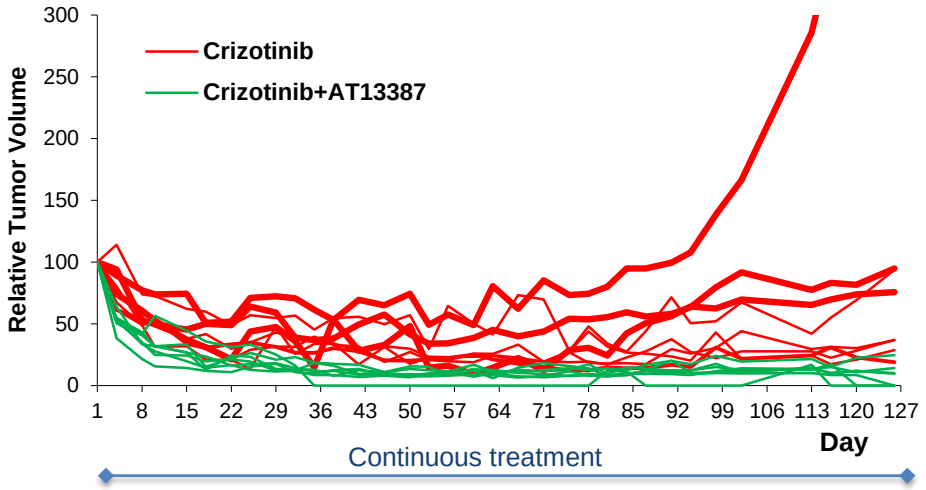
- ✓ Amplification of ALK gene (CR4 and CR6-6)
- ✓ Deletion of ALK gene (CR2)
- ✓ C1156Y ALK mutation (CR6-6)
- ✓ Amplification of FGFR3 gene (CR6-6)
- ✓ Mutation in ERBB4 gene (CR1, CR5 and CR6-6)

- **AT13387 treatment inhibits the growth of an ALK-dependent tumour xenograft with acquired resistance to crizotinib (Wallis, et al AACR 2014)**
- **Exome sequencing of resistant tumors revealed clinically relevant gene changes (Courtin, et al, ESMO 2014)**

“Front-Line” combination of onalspib with crizotinib delays the development of resistance in an ALK-dependent xenograft

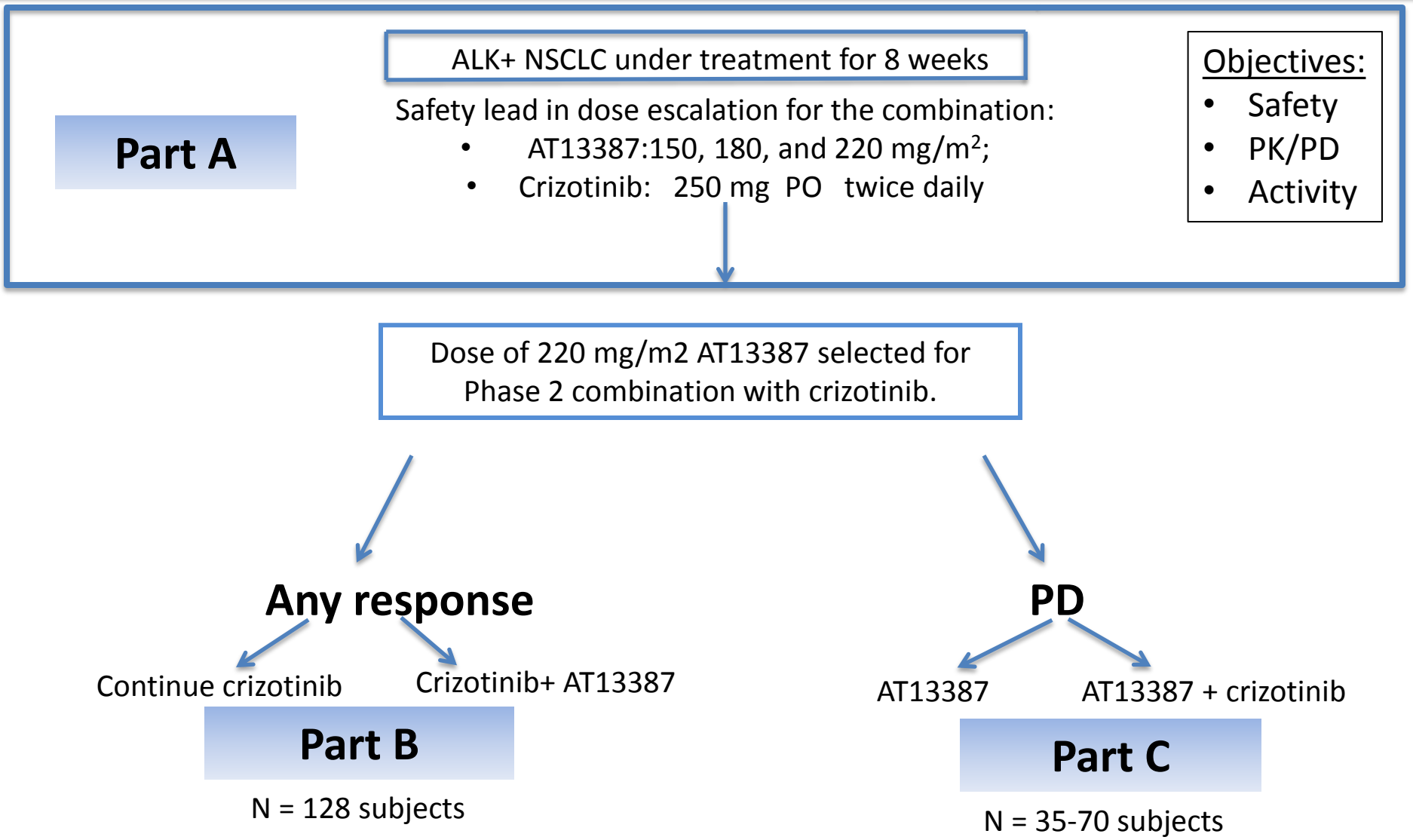






- **Combination of AT13387 and crizotinib shows improved inhibition of tumor growth over monotherapies**
- **Combining crizotinib upfront with AT13387 delays the emergence of resistance in vivo (Wallis, et al, WLC 2013)**

AT13387-05 Study Schema



Demographics

Characteristic		Dosing Cohort			
		150 mg/m2 (n=8)	180 mg/m2 (n=9)	220 mg/m2 (n=15)	Total (n=32)
Age (yrs) mean (range)		52 (32-64)	57 (30-75)	59 (36-74)	57 (30-75)
Gender (M/F)		4/4 (50/50%)	3/6 (33/67%)	7/8 (47/53%)	14/18 (44/56%)
Histology (Adenocarcinoma/Other)		7/1	9/0	15/15	31/1
Prior ALK inhibitor					
	Crizotinib	8	9	15	32
	Ceritinib	0	0	1	1
	Alectinib	0	2	2	4

(Besse, et al, ESMO 2014)

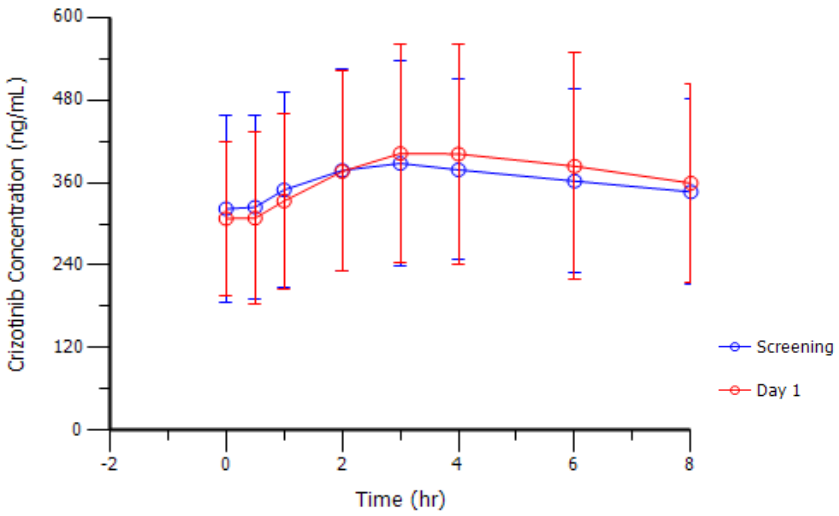
Adverse Events Grade 3 or higher related to onalespib + CZT treatment

Cohort (AT13387 dose level, CZT at 250 mg BID)	150 MG (N=8)	180 MG (N=9)	220 MG (N=15)	Total (N=32)
Anaemia	0	1 (11%)	0	1 (3%)
Diarrhoea	0	3 (33%)	3 (20%)	6 (19%)
Fatigue	0	0	1 (7%)	1 (3%)
Pneumonia	1 (13%)	0	0	1 (3%)
Alanine aminotransferase increased	0	0	1 (7%)	1 (3%)
Neutrophil count decreased	0	0	1 (7%)	1 (3%)
Dehydration	0	1 (11%)	0	1 (3%)
Hyperkalaemia	0	0	1 (7%)	1 (3%)
Muscular weakness	0	1 (11%)	0	1 (3%)
Syncope	0	1 (11%)	0	1 (3%)
Pneumonitis	1 (13%)	0	0	1 (3%)
Pulmonary embolism	0	0	1 (7%)	1 (3%)

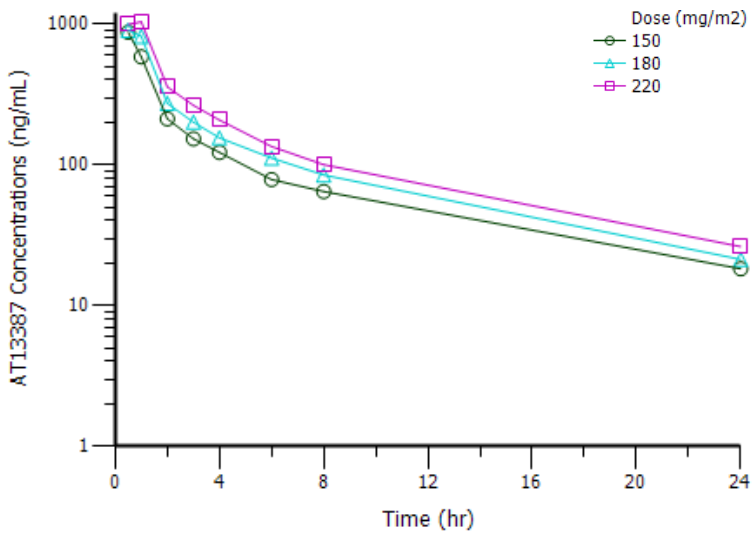
Note: one event at the 180 mg/m2 dose level was uncoded and is omitted from this table

(Besse, et al, ESMO 2014)

PHARMACOKINETICS



Pharmacokinetics of Crizotinib with and without onalespib



Pharmacokinetics of onalespib combined with Crizotinib

Day	$AUC_{0\text{-}8hr}$ (ng*hr/mL)	C_{max} (ng/mL)	T_{max} (hr)
Screening (n=31)	2905 (1056)	421 (143)	3.8 (2.1)
Day 1 (n=30)	2966 (1188)	427 (164)	4.0 (1.9)

Dose (mg/m^2)	$AUC_{0\text{-}last}$ (ng*hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$T_{1/2}$ (hr)
150 (N=8)	2297 (368)	930.5 (335.8)	0.6 (0.2)	8.6 (1.3)
180 (N=8)	2923 (846)	1053 (740)	0.8 (0.3)	7.9 (1.3)
220 (N=14)	3585 (919)	1164.0 (742)	0.8 (0.2)	7.9 (1.5)

Data are presented as mean (±SD)

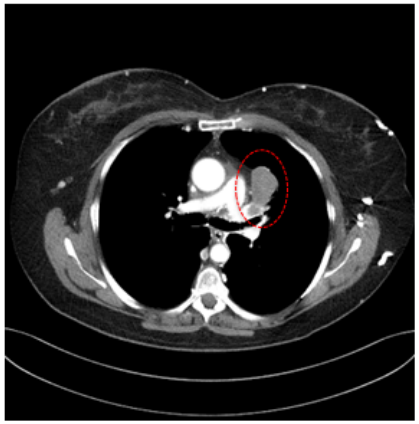
(Besse, et al, ESMO 2014)

Clinical Activity

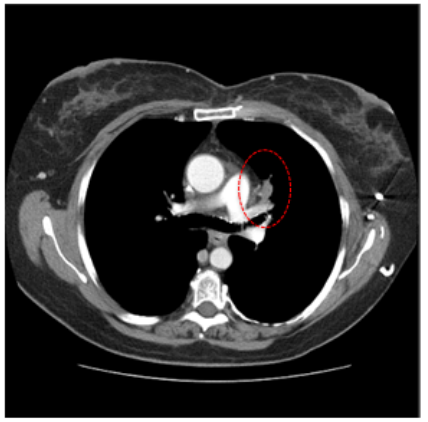
Trend toward increased activity with higher onalespib dose:

- onalespib at 150 mg/m2
  - (0 PR, 2/5 with tumor reduction)
- onalespib at 180 mg/m2
  - (1 PR, 4/6 with tumor reduction)
- onalespib at 220 mg/m2
  - (3 PR, 9/11 with tumor reduction)

Pt dx'd in 2010, treated with BEV/carbo/paclitaxel, then PEM, then crizotinib, progressed on crizotinib, put on study, assigned to 180 mg/m2 cohort.



Screening (pre-cycle 1D1)



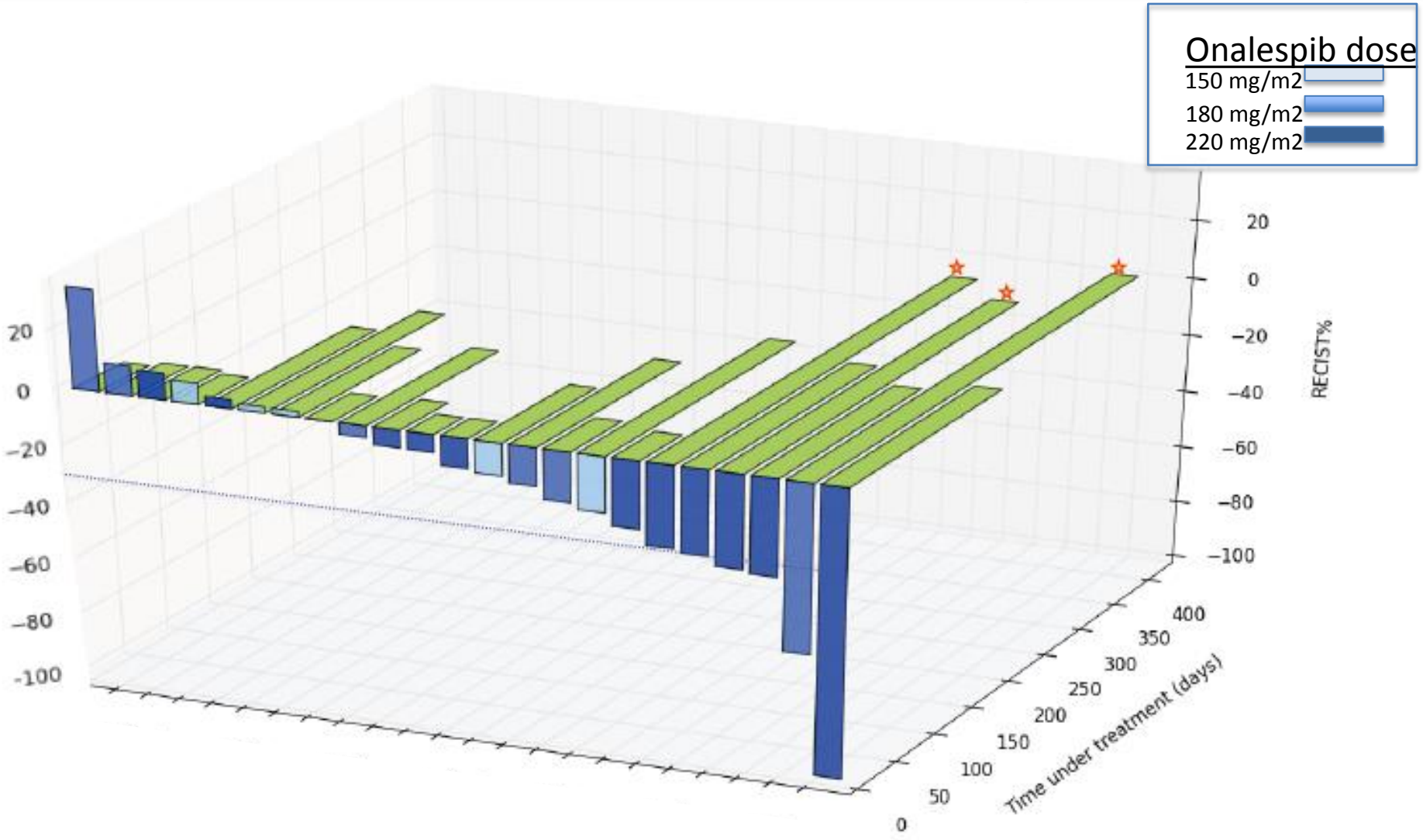
After 2 cycles of treatment.

RECIST - **55% decrease= PR**

Cohort (Onalespib Dose level)	150 mg/m2 (n=8)	180 mg/m2 (n=9)	220 mg/m2 (n=15)	Total (n=32)
Assessable (n)	5	8	12	25
CR/PR (n, %)	0 (0%)	1 (12.5%)	3 (25%)	4 (16%)
SD (n,%)	5 (100%)	4 (50%)	5 (41.7%)	14 (56%)
PD (n,%)	0 (0%)	3 (37.5%)	4 (33.3%)	7 (28%)

(Besse, et al, ESMO 2014)

Waterfall Plot of Subjects with measurable disease and at least 1 follow up scan



* Indicates subject still receiving treatment on study

(Besse, et al, 2014)

Summary/Conclusions

- **Preclinical data demonstrate early combination (crizotinib + onalespib) delays regrowth of ALK-driven tumors**
  - Alterations seen in progressing tumors reflect those seen clinically
- **Onalespib is well tolerated at a dose up to 220 mg/m2 given weekly 3 of 4 weeks in combination with full dose CZT**
- **Administration of the agents in combination does not appear to change the pharmacokinetics of either agent**
- **Encouraging activity has been seen in the dose-escalation part of the study**
  - 4 Objective PR by RECIST
  - More antitumor activity at higher dose
  - Over 50% patients with decrease in tumor size
- **Arms B (prior to progression on CZT) and C (following progression on CZT are open and enrolling**

Acknowledgements

- **Patients and their families**

- Multiple sites, Investigators, coordinators, and staff:
  - B. Besse
  - E. Bertino
  - N.A. Pennell,
  - A. Wozniak
  - D. Mahadevan,
  - A. Spira,
  - J.-C. Soria
  - D.R. Camidge

- Astex personnel in Cambridge, UK , and Pleasanton, CA