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# Addition of HSP90 inhibitor onalespib to crizotinib prior to progression in patients with ALK-pos NSCLC; results of a randomized Phase 2 study

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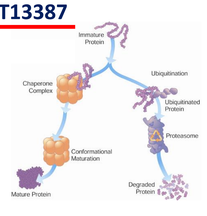
## BACKGROUND

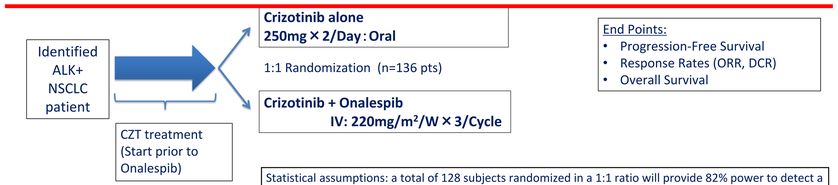
- Hsp90 is required for proper ALK function
- Onalespib (AT13387) is a second generation Hsp90 inhibitor
- Onalespib in ALK-driven pre-clinical models:
  - Displays potent antitumor activity
  - Delays the onset of resistance[1]
- In the clinic, onalespib[2]
  - Has a safety profile consistent with the class (diarrhea, mild transient visual changes)
  - PK & PD results support weekly dosing
  - Has antitumor activity (PR) at a dose of 220 mg/m$^2$ (D1,8,15 of 28 Day cycle)
- Crizotinib (CZT) has demonstrated clinical activity in ALK-pos NSCLC[3]
- AT13387-05 is a 3-part, Phase 1-2 study in ALK-pos NSCLC.
  - Part A (Phase 1 of the study demonstrated the safety of Onalespib/CZT in combination with some activity in progressing patients[4]
  - Results are presented for Part B of the study, randomization to combination of Onalespib added to CZT vs CZT alone prior to development of resistance (Fig 2)

### Figure 1: AT13387




## STUDY DESIGN

### Figure 2: AT13387-05 randomized study schema (Part B)




### Study objectives

- **Primary:**
  - To compare progression-free survival (PFS) between the administration of single-agent CZT and the combination of CZT + onalespib in subjects with NSCLC who will be treated with CZT or who were treated with CZT and have not progressed
- **Secondary:**
  - To assess the safety of onalespib in combination with CZT in subjects with NSCLC
  - To compare the OS between CZT and CZT + Onalespib
  - To compare ORR (CR + PR) between CZT and CZT + Onalespib for subjects with measurable disease at baseline
  - To assess ORR in CZT patients who crossover to CZT + Onalespib and have measurable disease at the time of crossover

### Patient population

**Major Inclusion Criteria:**

- Patients with NSCLC (ALK rearranged or other change potentially sensitive to CZT, e.g. ROS)
- Treated with or scheduled to be treated with CZT prior to first potential dose of onalespib
- Adequate organ (cardiac, renal, hepatic) function & Performance Status (ECOG 0-2)
- Controlled brain metastases allowed

**Major Exclusion Criteria:**

- Prior anticancer treatment with Hsp90 inhibitor
- Known symptomatic brain metastases
- ≥ Grade 2 bilirubin or transaminases or visual disturbances due to CZT

### Study methodology

**Dosing Regimen:**

- CZT at either 250 mg PO BID (or lower based on current tolerated dose) alone or in combination with onalespib at 220 mg/m$^2$ on Days 1, 8, 15 every 4 weeks.

**Study Assessments:**

Safety:

- AEs assessed at D1,8,15,22 for cycle 1
- Triplicate ECGs pre- and post-onalespib infusion
- Chemistry and Hematology prior to Days 1,8, and 15
- PK: Blood samples at various time points D1 for onalespib and CZT
- Efficacy: Assessment of ORR and PFS by RECIST every 2 cycles

**Study Endpoints:**

**Primary:**

- The comparison of PFS between CZT alone and the combination of CZT + Onalespib

**Secondary:**

- The comparison of OS and between CZT alone and the combination of CZT + onalespib
- The comparison of AEs between CZT alone and the combination of CZT + onalespib
- The comparison of ORR (CR + PR) between CZT alone and CZT + onalespib for subjects with measurable disease at baseline
- The comparison of ORR (CR + PR) in CZT patients who cross over to CZT + onalespib for subjects with measurable disease at the time of crossover

### Table 1: Patient characteristics and prior therapy

| Characteristic | | CZT (N=66) | CZT + Onalespib (N=67) | Total (N=133) |
|---|---|---|---|---|
| **Age (years)** | Median (range) | 51.0 (20-80) | 58.0 (29-85) | 54.0 (20-85) |
| **Gender** | M/F (%F) | 33/33 (50%) | 23/44 (65.7%) | 56/77 (57.9%) |
| **ECOG** | 0 (%) | 11 (16.7%) | 25 (37.3%) | 36 (27.1%) |
| | 1 (%) | 52 (78.8%) | 39 (58.2%) | 91 (68.4%) |
| | 2 (%) | 3 (4.5%) | 3 (4.5%) | 6 (4.5%) |
| **Treatment** | | CZT (N=66) | CZT + Onalespib (N=67) | Total (N=-133) |
| **Prior systemic chemotherapy** | Y/N (%Y) | 48/18 (72.7%) | 46/21 (68.7%) | 94/39 (70.7%) |
| **Prior CZT** | Y/N (%Y) | 28/38 (42.4%) | 25/42 (37.3%) | 53/80 (39.8%) |
| **Duration of prior CZT** | 0-2 months | 5 (17.9%) | 7 (28.0%) | 12 (23.1%) |
| | > 2 – 4 months | 12 (42.3%) | 7 (28.0%) | 19 (36.5%) |
| | > 4 months | 11 (39.3%) | 11 (44.0%) | 22 (42.3%) |
| **Response to CZT** | CR | 1 (3.6%) | 1 (4.0%) | 2 (3.8%) |
| | PR | 13 (46.4%) | 10 (40.0%) | 23 (43.4%) |
| | SD | 10 (35.7%) | 8 (32.0%) | 18 (34.0%) |
| | PD | 0 (0%) | 0 (0%) | 0 (0%) |
| | NE | 2 (7.1%) | 3 (12.0%) | 5 (9.4%) |
| | Unk | 2 (7.1%) | 3 (12.0%) | 5 (9.4%) |
| **Brain Metastases** | Y/N (%Y) | 33/33 (50.0%) | 28/39 (41.8%) | 61/72 (45.9%) |

- CZT alone and CZT + Onalespib arms were reasonably balanced for most factors: (age, ECOG PS, Prior systemic chemotherapy, Prior CZT and duration)

## SAFETY SUMMARIES

### Table 2: AEs grade 3 and higher occurring in >5% of subjects, independent of relationship

| Event | CZT alone | | | Onalespib + CZT | | | All Patients | | |
|---|---|---|---|---|---|---|---|---|---|
| | G3 | G4 | **Total** | G3 | G4 | **Total** | G3 | G4 | **Total** |
| Diarrhoea | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 10 (14.9%) | 0 (0.0%) | 10 (14.9%) | 10 (7.5%) | 0 (0.0%) | 10 (7.5%) |
| Nausea | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 7 (10.4%) | 0 (0.0%) | 7 (10.4%) | 7 (5.3%) | 0 (0.0%) | 7 (5.3%) |
| Fatigue | 1 (1.5%) | 0 (0.0%) | 1 (1.5%) | 7 (10.4%) | 0 (0.0%) | 7 (10.4%) | 8 (6.0%) | 0 (0.0%) | 8 (6.0%) |
| ALT increased | 1 (1.5%) | 3 (4.5%) | 4 (6.0%) | 2 (3.0%) | 0 (0.0%) | 2 (3.0%) | 3 (2.3%) | 3 (2.3%) | 6 (4.6%) |
| AST increased | 3 (4.5%) | 1 (1.5%) | 4 (6.0%) | 1 (1.5%) | 0 (0.0%) | 1 (1.5%) | 4 (3.0%) | 1 (<1.0%) | 5 (3.8%) |
| Blood CPK increased | 3 (4.5%) | 1 (1.5%) | 4 (6.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 3 (2.3%) | 1 (<1.0%) | 4 (3.0%) |

### Results

Treatment-emergent AEs grade 3 or higher, reported in more than 5.0% of subjects are presented in Table 2. Addition of onalespib to CZT did not appear to worsen the tolerability based on grade 3 or higher events though a higher percentage of combination treated subjects (60% vs. 36%) experienced grade 3 or higher events. Two subjects (3%) (both in combination arm) discontinued treatment due to AEs.

### Table 3: All AEs occurring in >10% of subjects, independent of relationship

| | CZT | Onalespib + CZT | Total |
|---|---|---|---|
| | (N=66) | (N=67) | (N=133) |
| Number (%) of Subjects Experiencing Any TEAEs | 66 (100.0%) | 67 (100.0%) | 133 (100.0%) |
| Diarrhoea | 34 (51.5%) | 55 (82.1%) | 89 (66.9%) |
| Nausea | 35 (53.0%) | 53 (79.1%) | 88 (66.2%) |
| Vomiting | 26 (39.4%) | 44 (65.7%) | 70 (52.6%) |
| Constipation | 23 (34.8%) | 27 (40.3%) | 50 (37.6%) |
| Fatigue | 15 (22.7%) | 34 (50.7%) | 49 (36.8%) |
| Oedema Peripheral | 17 (25.8%) | 23 (34.3%) | 40 (30.1%) |
| Decreased Appetite | 16 (24.2%) | 23 (34.3%) | 39 (29.3%) |
| Headache | 17 (25.8%) | 18 (26.9%) | 35 (26.3%) |
| Cough | 15 (22.7%) | 17 (25.4%) | 32 (24.1%) |
| Dysgeusia | 11 (16.7%) | 20 (29.9%) | 31 (23.3%) |
| Dizziness | 15 (22.7%) | 16 (23.9%) | 31 (23.3%) |
| Insomnia | 8 (12.1%) | 20 (29.9%) | 28 (21.1%) |
| Alanine Aminotransferase Increased | 13 (19.7%) | 13 (19.4%) | 26 (19.5%) |
| Photopsia | 13 (19.7%) | 12 (17.9%) | 25 (18.8%) |
| Visual Impairment | 12 (18.2%) | 12 (17.9%) | 24 (18.0%) |
| Dyspepsia | 8 (12.1%) | 14 (20.9%) | 22 (16.5%) |
| Dyspnoea | 9 (13.6%) | 13 (19.4%) | 22 (16.5%) |
| Rash | 9 (13.6%) | 13 (19.4%) | 22 (16.5%) |
| Aspartate Aminotransferase Increased | 11 (16.7%) | 9 (13.4%) | 20 (15.0%) |
| Productive Cough | 9 (13.6%) | 11 (16.4%) | 20 (15.0%) |
| Pyrexia | 9 (13.6%) | 10 (14.9%) | 19 (14.3%) |
| Abdominal Pain Upper | 8 (12.1%) | 11 (16.4%) | 19 (14.3%) |
| Abdominal Pain | 4 (6.1%) | 14 (20.9%) | 18 (13.5%) |
| Dry Mouth | 3 (4.5%) | 14 (20.9%) | 17 (12.8%) |
| Anaemia | 6 (9.1%) | 11 (16.4%) | 17 (12.8%) |
| Asthenia | 6 (9.1%) | 10 (14.9%) | 16 (12.0%) |
| Electrocardiogram Qt Prolonged | 5 (7.6%) | 11 (16.4%) | 16 (12.0%) |
| Myalgia | 3 (4.5%) | 12 (17.9%) | 15 (11.3%) |
| Chills | 7 (10.6%) | 8 (11.9%) | 15 (11.3%) |
| Urinary Tract Infection | 5 (7.6%) | 9 (13.4%) | 14 (10.5%) |

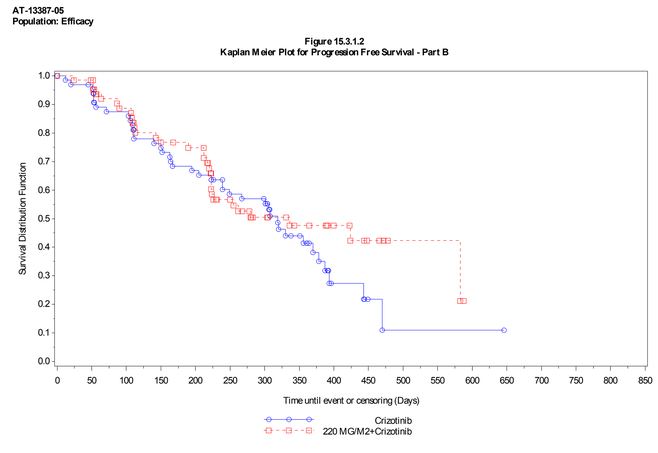
Treatment-Emergent AEs of any grade, reported in >10% of subjects, independent of relationship, are presented in Table 3. The safety profiles were generally consistent with those expected based on single agent data. Notably, a high percentage of subjects receiving onalespib experienced GI AEs (diarrhoea, nausea, vomiting, etc.), though these were generally grade 2 or lower and were self-limited or resolved with symptomatic treatment. Elevated hepatic transaminases and visual impairment which can be seen with CZT did not appear to be worsened by the addition of onalespib.

### Table 4: Analysis of objective response rates

| | CZT (N=65) | Onalespib + CZT (N=65) |
|---|---|---|
| **Response Category** | | |
| Complete Response (CR) | 2 (3.1%) | 0 (0.0%) |
| Partial Response (PR) | 31 (47.7%) | 38 (58.5%) |
| Stable Disease (SD) | 24 (36.9%) | 23 (35.4%) |
| Progressive Disease (PD) | 6 (9.2%) | 3 (4.6%) |
| Not Evaluable (NE) | 2 (3.1%) | 1 (1.5%) |
| Objective Response (ORR) | 33 (50.8%) | 38 (58.5%) |

95% CIs of ORR for CZT alone and CZT + onalespib were 40-64.7 and 47.3-71.4, respectively. The p-value is 0.43 for comparing the two ORR rates

### Figure 3: Analysis of progression-free survival

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PFS analysis was based on 40 CZT events and 31 Combination events.

Median PFS estimates:

- CZT alone 319 days (239-378)
- CZT + Onalespib 336 days (223- NE)
- P-value = 0.35
- HR = 0.78 (0.5-1.3)

### Table 5. Analyses of PFS based on presence or absence of CNS mets

| | CZT alone | | | CZT + onalespib | | |
|---|---|---|---|---|---|---|
| | No. subjects | Events | Median PFS (95% CI) | No. subjects | Events | Median PFS (95% CI) |
| CNS Mets present | 32 | 24 | 231 (111-308) | 27 | 18 | 224 (212-424) |
| No CNS present | 33 | 16 | 387 (320-470) | 38 | 13 | NE (223-NE) |

## CONCLUSIONS

- Onalespib can be combined with standard dose CZT (250 mg BID) with good tolerability
- More objective responses were seen in the combination (onalespib + CZT) arm, however the difference was not significant
- The response rate did not translate into an improvement in progression-free survival despite encouraging pre-clinical data and the lack of effect was independent of the presence or absence of CNS metastases
- The data for overall survival are premature to draw conclusions at present
- The data do not support use early use of onalespib in combination with CZT to delay the emergence of resistance

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