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# ACY-1215, A SELECTIVE HISTONE DEACETYLASE (HDAC)6 INHIBITOR: INTERIM RESULTS OF COMBINATION THERAPY WITH BORTEZOMIB IN PATIENTS WITH MULTIPLE MYELOMA (MM)

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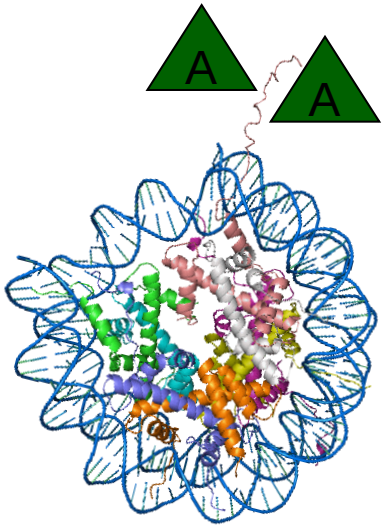
# HDAC Inhibition → Protein Acetylation

- **Targets: 11 zinc-dependent "histone deacetylase" (HDAC) enzymes present in most human cells**
  - Epigenetic regulation of gene expression → protein acetylation
  - Key regulators of protein function and degradation

- **Non-selective HDAC inhibition causes hyper-acetylation of numerous protein networks in cells**
  - Broad epigenetic modulation of nuclear chromatin / DNA
  - Acetylation of proteins in cytoplasm including microtubular proteins

*Addition of "acetyl" groups*




*Example: DNA / histone protein network*

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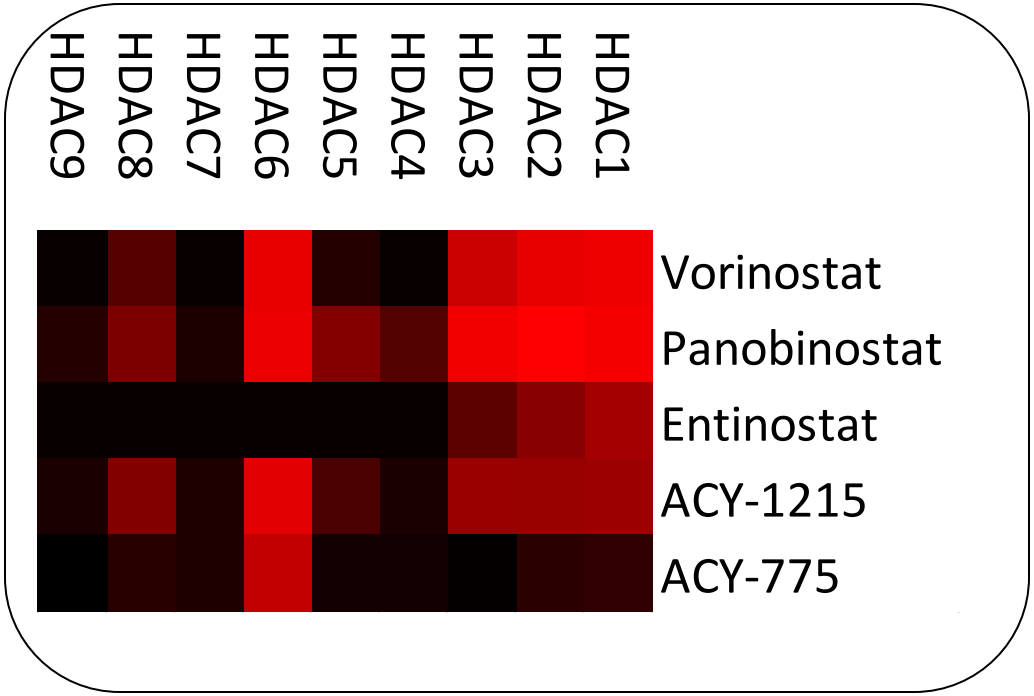
# Isoform Selectivity Profiles of HDAC Inhibitors




Relative biochemical $IC_{50}$ values across HDAC1-9

- **ACY-1215 is approximately 11-fold selective for HDAC6 over HDAC3**
- **ACY-775 (tool compound) is approximately 300-fold selective for HDAC6 over HDAC1/2, and 1500-fold selective over HDAC3**
- **Nonselective HDAC Inhibition may contribute to toxicity**

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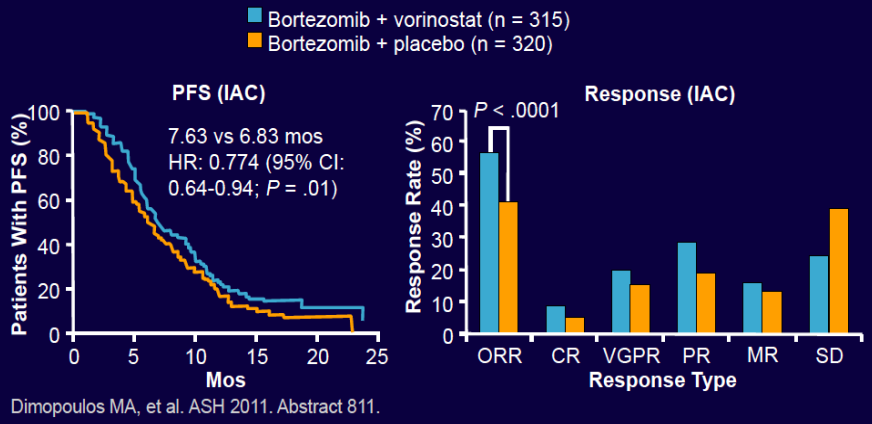
# VANTAGE 088

## VANTAGE 088: PFS, OS, and Response

- PFS significantly prolonged with addition of vorinostat to bortezomib
  - No difference in median OS (data not yet mature)




Dimopoulos MA, et al. ASH 2011. Abstract 811.

| Adverse Event | Bortezomib + Vorinostat (N=315) | | Bortezomib + Placebo (N=320) | |
|---|---|---|---|---|
| | All Grade, % | Grade 3-4, % | All Grade, % | Grade 3-4, % |
| **HEMATOLOGIC (≥15%)** | | | | |
| Anemia | 29 | 17 | 25 | 13 |
| Thrombocytopenia[a] | 55 | 45 | 33 | 24 |
| Neutropenia | 36 | 28 | 30 | 25 |
| **NONHEMATOLOGIC (≥25%)** | | | | |
| Constipation[a] | 20 | 2 | 27 | 1 |
| Diarrhea[a] | 62 | 17 | 43 | 9 |
| Nausea[a] | 61 | 8 | 39 | 4 |
| Vomiting[a] | 45 | 7 | 26 | 4 |
| **OTHER AEs OF INTEREST** | | | | |
| Neuralgia | 26 | 6 | 27 | 5 |
| Fatigue | 40 | 17 | 31 | 7 |

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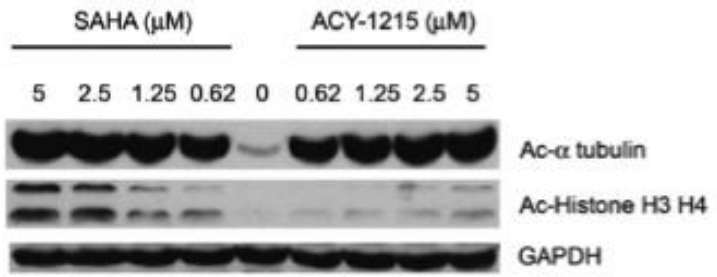
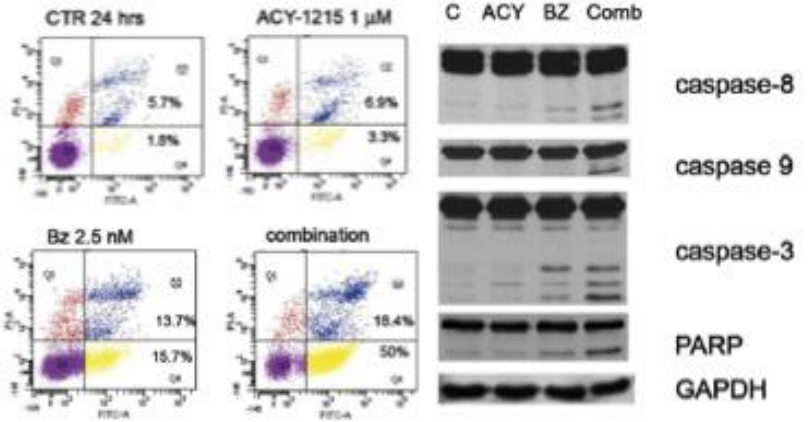
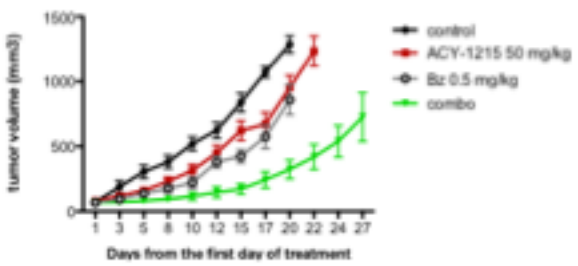
**Dimopoulos et al. Lancet Oncology 2013**

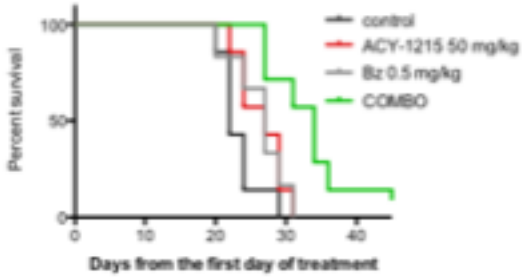
# Synergistic Anti-Myeloma Activity of ACY-1215 with Bortezomib

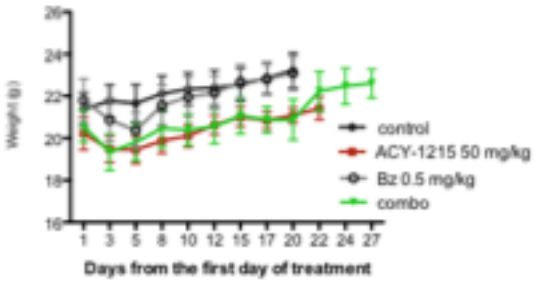


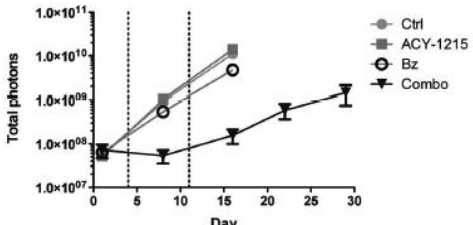

## MM Xenograft plasmacytoma model

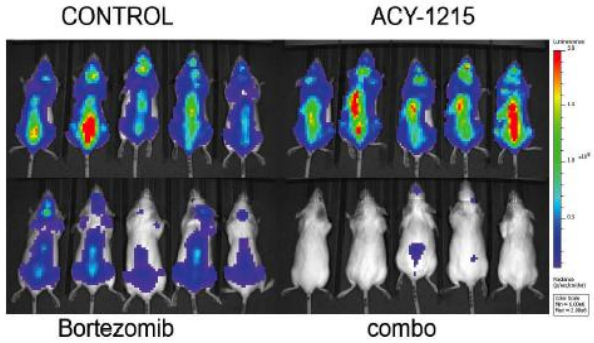



## MM Xenograft disseminated model

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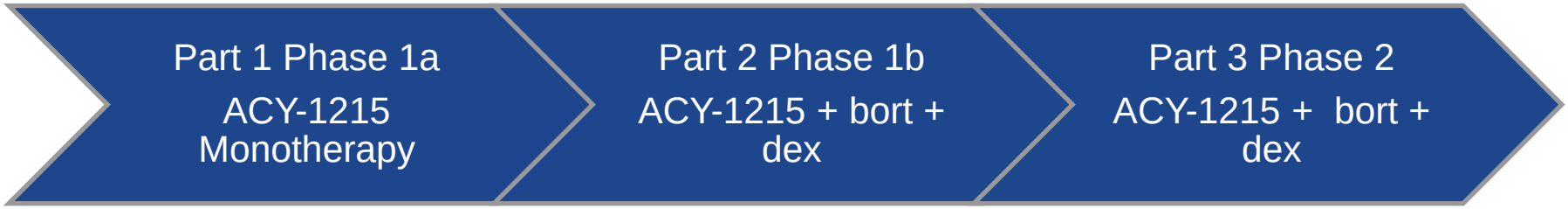
Santo et al. Blood 2012

# ACY-100 STUDY

## Study Design:




- Relapsed or refractory multiple myeloma patients with prior immunomodulatory agent, proteasome inhibitor therapy and at least two prior lines of therapy.
- Creatinine clearance >30 mL/min, adequate hepatic and bone marrow function
- Phase 1b patients receive ACY-1215 days 1-5, 8-12 with IV bortezomib days 1, 4, 8 & 11 with dexamethasone PO 20 mg days 1,2, 4 & 5 and days 8, 9, 11 & 12

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# ACY-100 STUDY

## Dose Escalation Schema

| Ph 1a Cohorts | ACY-1215 (mg) | QD ACY-1215 (mg) | BID ACY-1215 (mg) | Ph 1b Cohorts |
|---|---|---|---|---|
| | | Bortezomib (mg/m$^2$) + Dexamethasone (20 mg) | | |
| Cohort 1 | 40 | | | |
| Cohort 2 | 80 | | | |
| Cohort 3 | 160 | 40 + 1.0 | | Cohort 1 |
| Cohort 4 | 240 | 40 + 1.3 | | Cohort 2 |
| Cohort 5 | 360 | 80 + 1.3 | | Cohort 3 |
| | | 160 + 1.3 | | Cohort 4 |
| | | 240 + 1.3 | | Cohort 5 |
| | | | 160 + 1.3 | Cohort 6 |

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# ACY-1215 as Monotherapy (n=15)

- Fifteen patients with advanced multiple myeloma treated at doses up to 360 mg orally on day 1-5, 8-12 schedule of 21 day cycle
- No maximum tolerated dose (MTD) was identified
- Adverse events reported were elevated creatinine, fatigue, hypercalcemia and upper respiratory infection NOT attributed to ACY-1215
- Grade 3 anemia and neutropenia in one patient each were considered POSSIBLY related to ACY-1215
- Best response was SD in 6 patients (Median # cycles 2, 1-10)

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**Raje, Blood, V20(21):4061**

# ACY-1215, Bortezomib and Dexamethasone n=22

## Patient Demographics and Disease Characteristics

| Characteristic | | N (%) |
|---|---|---|
| Patients Enrolled | | 22 |
| Age, years | Median (range) | 61 (46 - 82) |
| Sex | Male / Female | 14 (63.6) / 8 (36.4) |
| Race | White | 15 (68.2) |
| | Black | 4 (18.2) |
| | Asian | 1 (4.5) |
| Prior Therapies | 2 | 2 ( 9.1) |
| | 3 | 3 (13.6) |
| | 4 | 4 (18.2) |
| | >4 | 15 (58.9) |
| Relapsed | | 6 (27) |
| Refractory | | 16 (73) |

Data cut off (Nov 8, 2013)

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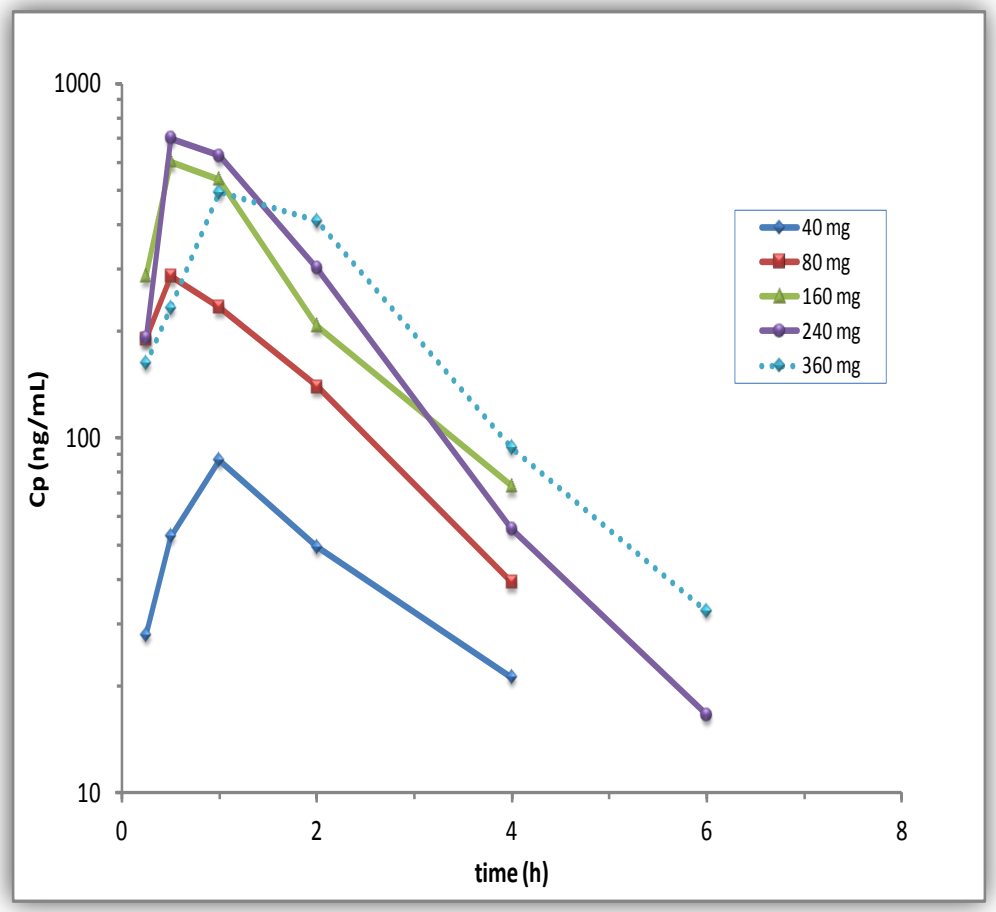
# Pharmacokinetics of ACY-1215 Monotherapy




- ACY-1215 is rapidly absorbed
- Drug half-life ~3 hr
- Background levels of drug reached at 8-12 hr post-dose
- No evidence of drug accumulation (Day 1 vs Day 11)
- Dose proportional increase in exposure from 40 to 160 mg
- Exposures similar at ≥160 mg

➢ **Twice daily dosing is feasible to increase drug exposure**

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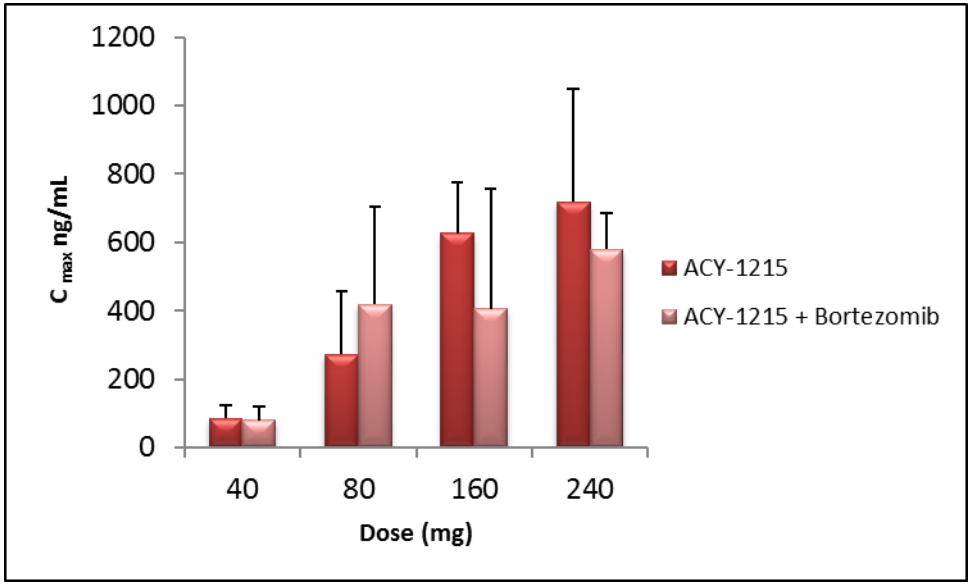
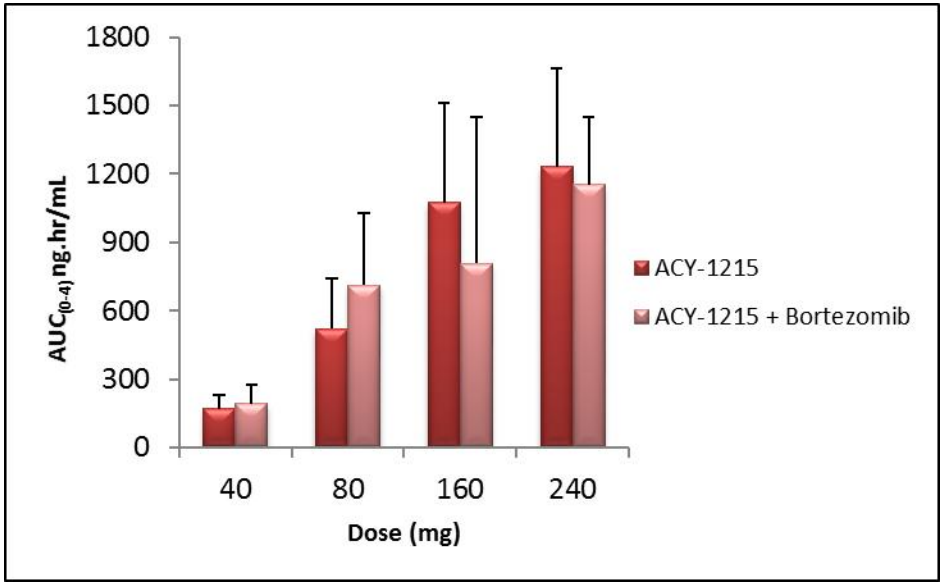
# Pharmacokinetics of ACY-1215, Bortezomib and Dexamethasone




- Pharmacokinetics of ACY-1215 -/+ Bortezomib (1.3 mg/m$^2$) are similar (left: $C_{max}$ and right: $AUC_{0-4}$)
- Exposure increases with dose to ≥ 160 mg

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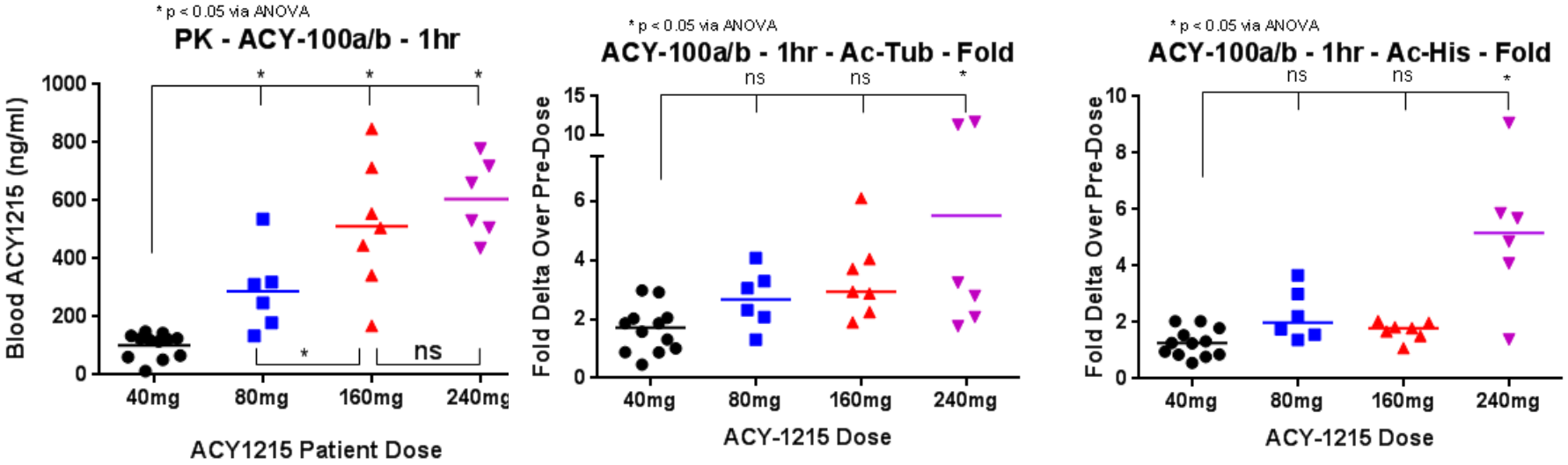
# Pharmacodynamics : ACY-1215 +/- Bortezomib and Dexamethasone




- Increase in Ac-tubulin (center panel) correlates with increase in plasma levels of ACY-1215
- Change in Ac-histone levels ~background until 240 mg dose level is reached

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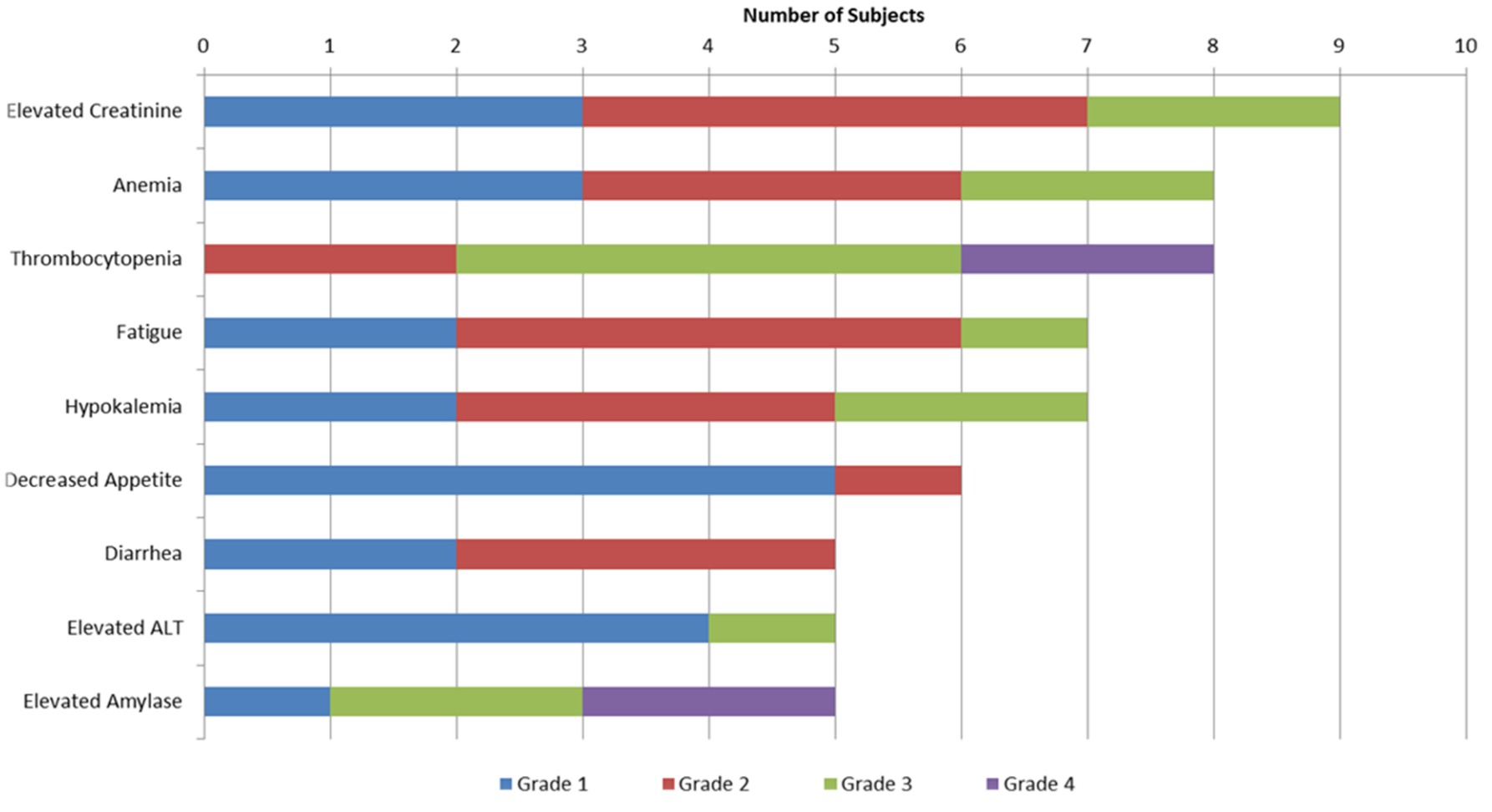
# Most Common Treatment Emergent AEs (>20%) by Severity

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# Grade 3 & 4 Treatment Emergent AEs Possibly Related to ACY-1215 in Combination with Bortezomib and Dexamethasone

| Term [1,] | 40 QD + 1.0 + dex (n=7) | 40 QD + 1.3 + dex (n=3) | 80 QD + 1.3 + dex (n=3) | 160 QD + 1.3 + dex (n=3) | 240 QD + 1.3 + dex (n=3) | 160 BID + 1.3 + dex (n=3) | Total N = 22 n (%) |
|---|---|---|---|---|---|---|---|
| Thrombocytopenia | 3 | 1 | 0 | 0 | 0 | 0 | 4 (19) |
| Elevated Amylase | 2 | 0 | 0 | 0 | 0 | 0 | 2 (9) |
| Elevated lipase | 1 | 0 | 0 | 0 | 0 | 0 | 1 (5) |
| Anemia | 0 | 1 | 0 | 0 | 0 | 0 | 1 (5) |
| Hyponatremia | 1 | 0 | 0 | 0 | 0 | 0 | 1 (5) |
| Hypophosphatemia | 1 | 0 | 0 | 0 | 0 | 0 | 1 (5) |
| Stomach cramps | 1 | 0 | 0 | 0 | 0 | 0 | 1 (5) |
| Diarrhea | 0 | 0 | 0 | 0 | 1 | 0 | 1 (5) |

1 If a patient experienced more than one episode of an adverse event, the patient is counted once for that term at highest grade

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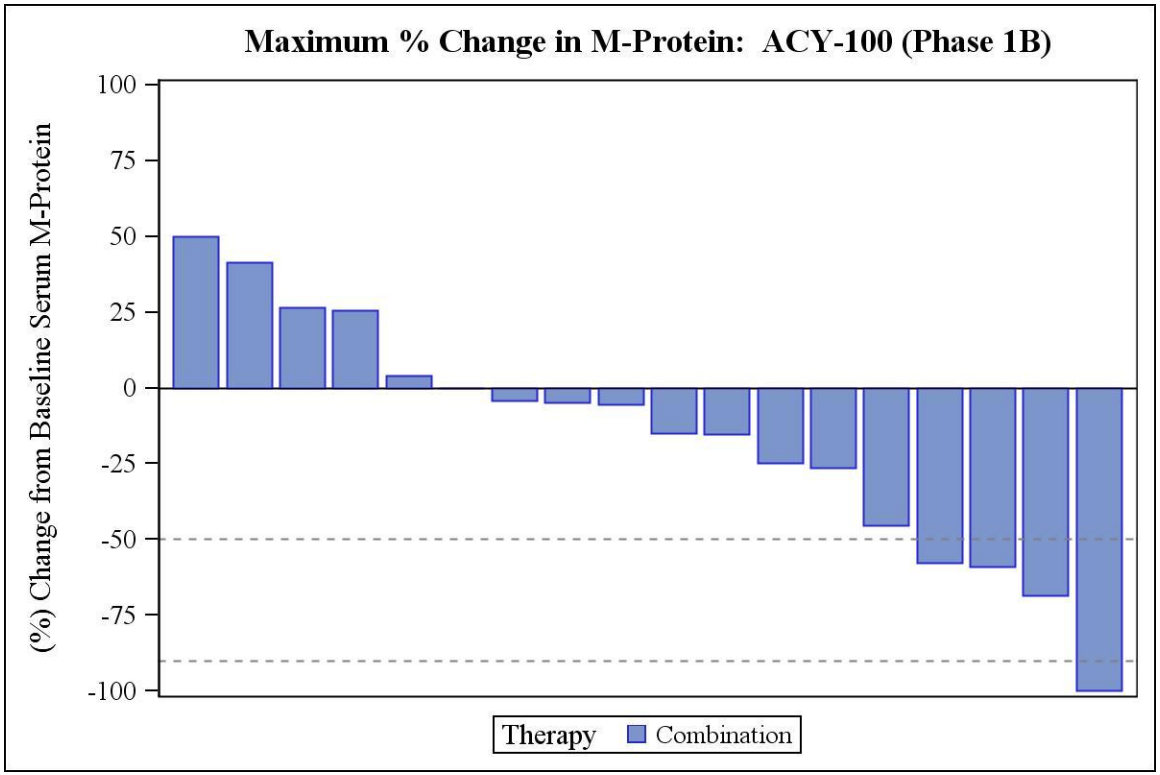
# Maximum % Change in M-Protein




[1]One patient with response of VGPR not noted as light chain only

Data cut Nov 8, 2013 from ongoing study

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# Patient Outcomes

- **Monotherapy**
  - 6/15 patients had stable disease (SD) as their best response.
- **Combination with bortezomib and dexamethasone**
  - 20/22 were evaluable for response assessment in six combination cohorts

    - Overall response rate (≥PR): 25% in heavily pretreated patients
    - 5 patients withdrew after one cycle and 3 had progressive disease after 2 cycles
    - Clinical benefit rate (≥SD): 60%
    - 6/10 patients refractory to bortezomib had ≥SD (1 VGPR, 1 MR, 4 SD)
    - Responding patients have been on study 2 to 16 cycles

| | |
|---|---|
| **VGPR** | **2** |
| **PR** | **3** |
| **MR[1]** | **2** |
| **SD** | **5** |

Monotherapy response data from Final CSR. Combination response data pulled from live database Nov 8, 2013

[1] One patient had a 26% decrease in M Protein after Cycle 2 and withdrew after two subsequent cycles with SD

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# Conclusions

- Combination therapy with ACY-1215, bortezomib and dexamethasone was well tolerated up to 240 mg QD (days 1-5, 8-12) and 160 mg BID
- Grade 3 or 4 GI adverse effects were rare and hematologic adverse events were manageable
- PD markers show effects on HDAC6 targets (tubulin) before class 1 HDAC effects (histone acetylation), demonstrating selectivity in the clinic
- 60% clinical benefit rate and 25% response rate were observed including in patients refractory to bortezomib

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# Ongoing Studies and Future Directions

- Preclinical studies with Carfilzomib (Mishima et al, Poster # 4431)
- Preclinical studies with IMiDs (Quayle et al, Poster # 1952)
- Ongoing clinical trial in combination with lenalidomide and dexamethasone (Yee, et al, Poster #3190, ASH 2013)
- Trials of ACY-1215 in combination with pomalidomide and dexamethasone, and with carfilzomib and dexamethasone will open imminently
- Pivotal trials in combination with immunomodulatory agents are in development

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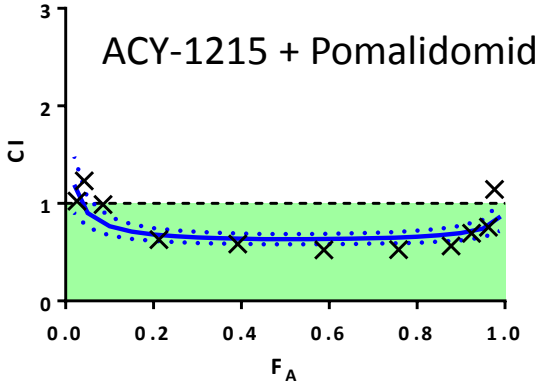
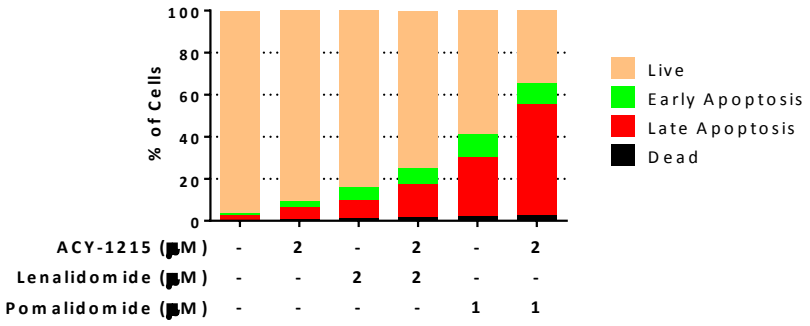
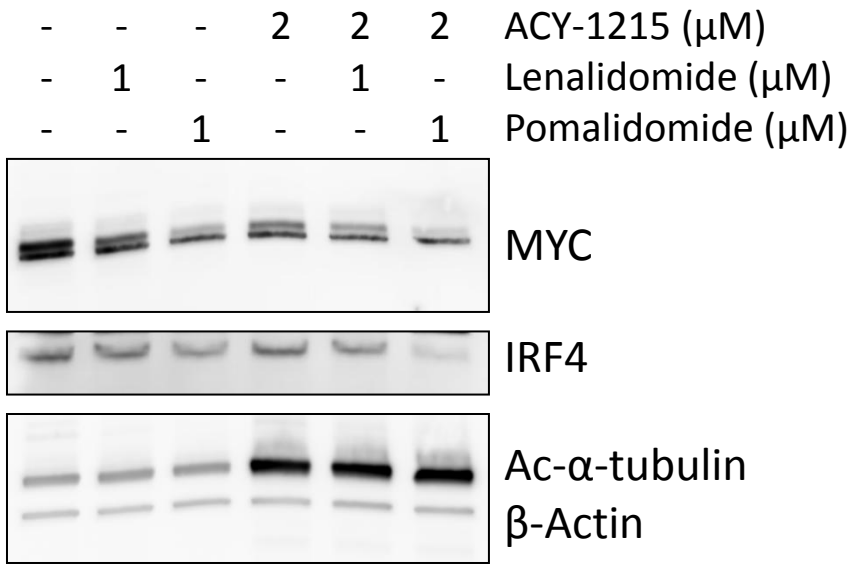
# Preclinical Synergy of ACY-1215 with IMiDs




ACY-1215 and IMiDs show significant synergy on multiple myeloma cells (H929 and MM.1s) increasing apoptosis and downregulating Myc and IRF4

(ASH 2013 #1952)

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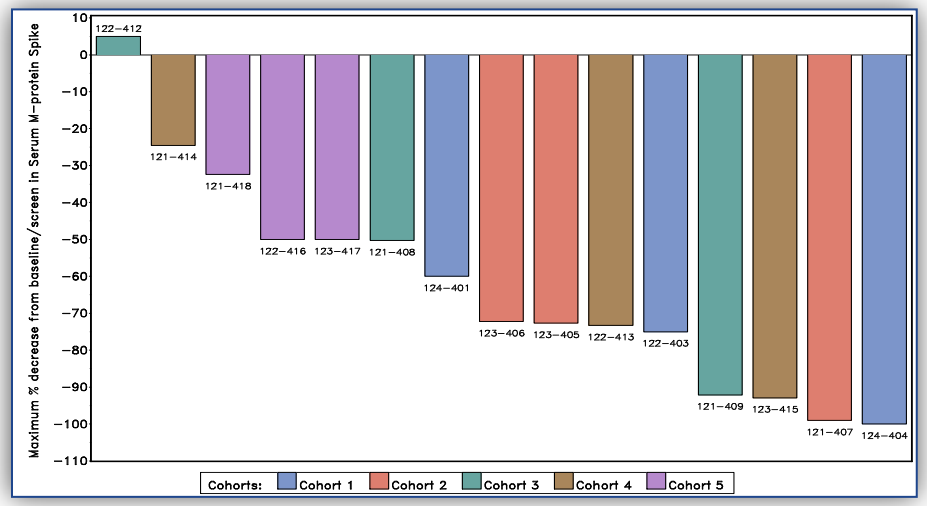
# Ongoing ACY-1215 in Combination with Lenalidomide and Dexamethasone

M protein % change




| | |
|---|---|
| CR | 1 |
| VGPR | 3 |
| PR[1] | 7 |
| MR | 2 |
| SD | 3 |

- 11/16 pts (69%) had PR or better
- 16/16 pts (100%) had clinical benefit (including MR and SD)

*Yee, et al, Poster #3190, ASH 2013*

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