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HIV-1 Gag Polymorphisms Determine Treatment Response to Bevirimat (PA-457)

S McCallister[1], J Lalezari[2], G Richmond[3] , M Thompson[4], R Harrigan[5], D Martin[6], K Salzwedel[6], and G Allaway[6].
[1] Panacos Pharmaceuticals, Watertown, MA, USA; [2] Quest Clinical Research, San Francisco, CA, USA; [3] Ft. Lauderdale, FL, USA; [4] AIDS Research Consortium of Atlanta, Atlanta, GA, USA; [4] BC Centre for Excellence in HIV/AIDS, Vancouver BC, Canada; [6] Panacos, Gaithersburg, MD USA

Panacos PHARMACEUTICALS

134 Coolidge Avenue
Watertown, MA 02472
Tel: 617 926-1551
Fax: 617 923-2245
www.info@panacos.com

Background

- Bevirimat is a novel HIV-1 maturation inhibitor in Phase II development that targets the capsid SP-1 cleavage site of Gag. Despite optimal plasma concentrations, not all patients given bevirimat have a robust viral load reduction (VLR). The determinants of treatment response were unknown.

Methods

- In a study to assess the bevirimat trough level associated with an optimal treatment response, 44 heavily treatment-experienced patients were given bevirimat for 14 days as functional monotherapy in escalating dose groups. Baseline clinical and virological variables were assessed to establish the determinants of bevirimat response. Response was also correlated with a standard Gag amino acid sequence.

Results

- 19/20 responder patients (≥0.5 log10 VLR) and 19/24 non-responder patients (<0.5 log10 VLR) had optimal bevirimat trough levels of at least 20ug/mL. In this bi-modal bevirimat treatment response distribution, the mean VLR was -1.26 or -0.05 log10 copies/mL for responder or non-responder patients respectively. Non-responder patients had more frequent baseline Gag polymorphisms near the capsid SP-1 cleavage site than responders (7.3; 5.9; p=NS); Q369H, V370A and T371A/T371deletion were more frequent in non-responders. Patients with any amino acid change at positions 369, 370, 371 had mean VLR of -0.16, -0.24, -0.32 log10 respectively, and patients with consensus amino acid at 369, 370, 371 had mean VLR of -0.69, -0.79, -0.73 log10 respectively; patients without any change at 369, 370 or 371 had mean VLR of -1.08 log10. 12/13 (92%) of patients with bevirimat trough >20ug/mL and with consensus amino acid at 369, 370 or 371 had VLR >0.5 log10. Lower baseline CD4 was the only clinical variable significantly (p=0.01) associated with non-response. Analysis of Gag genotype in a separate database of 567 treatment-naïve HIV+ patients showed that 60.2% had the clade B consensus amino acid at positions 369, 370 or 371.

Conclusion

- Using a genotype assay, treatment response to bevirimat is associated with baseline amino acid polymorphisms at Gag positions 369, 370 or 371 on SP-1; lower baseline CD4 count may be a surrogate for these Gag changes. The Gag data were confirmed by phenotypic assay and a new prospective clinical study to verify these findings is underway.

Background

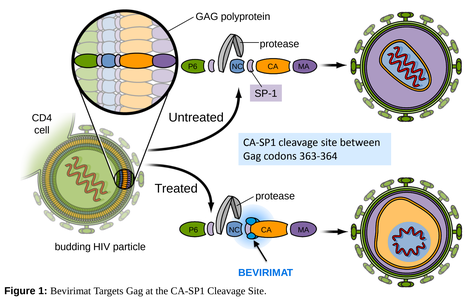

Figure 1: Bevirimat Targets Gag at the CA-SP1 Cleavage Site.

Methods

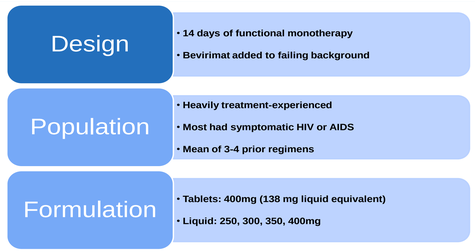

Figure 2: Bevirimat Study 203 Design

	Bevirimat-treated Patients	Placebo-treated Patients
N	46	13
Age	48.0 (27-70)	47.1 (34-63)
Gender	45M, 1F	12M, 1F
Symptomatic HIV or AIDS	74%	67%
Mean Baseline CD4 (cells/mm³)	277 (30-562)	393 (172-859)
Mean Baseline Viral Load (log copies/mL)	4.2 (2.7-5.3)	4.1 (3.7-5.2)

Table 1: Bevirimat Study 203 Demographics

Results

- 46 treatment-experienced patients received bevirimat
- 44/46 patients correctly received the assigned dose of bevirimat
- RESPONDERS (definition: ≥ 0.5 log viral load reduction)
  - N=20/44 (45%)
  - 19/20 (95%) had bevirimat trough ≥ 20ug/mL
  - Mean viral load reduction=1.26 log copies/mL
- NON-RESPONDERS (definition: < 0.5 log viral load reduction)
  - N=24/44 (55%)
  - 19/24 (79%) had bevirimat trough ≥ 20ug/mL
  - Mean viral load reduction=0.05 log copies/mL

	Non-Responders	Responders	Sig.
N	24	20	--
Mean Baseline VL	4.23	3.99	NS
Mean Day 15 VL	-0.05	-1.26	<0.0001
Mean Baseline CD4	233	342	<0.01
Mean No. IAS-USA primary PR mutations	3.7	2.8	NS
Mean No. Gag polymorphisms (positions 320-400)	7.3	5.9	NS

Table 2: Bevirimat Study 203 Responder Non-Responder Comparison

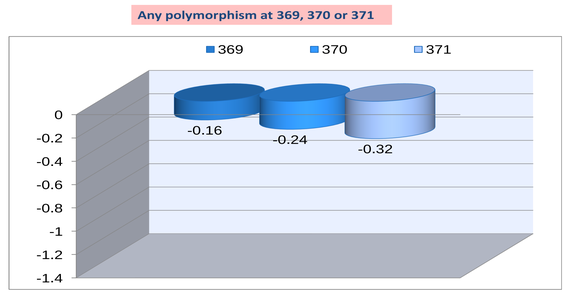

Figure 3: Bevirimat Study 203 VL Reduction by Gag Polymorphisms.

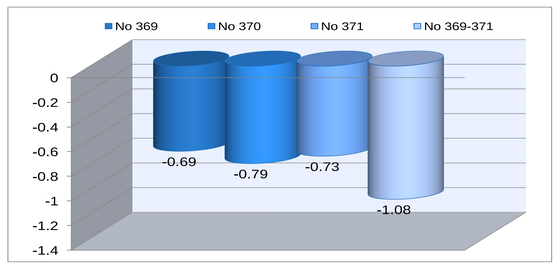

Figure 4: Bevirimat Study 203 VL Reduction by Gag Polymorphisms.

Frequency of baseline Gag polymorphisms seen in all study patients (n=59)

Gag Residue Number	Polymorphism	Number (%)
Q369	Q369H	9 (15.3%)
V370	V370A V370M V370deletion	15 (25.4%) 4 (6.8%) 3 (5.1%)
T371	T371A T371S T371N T371deletion	4 (6.8%) 2 (3.4%) 1 (1.7%) 4 (6.8%)

Table 3: Bevirimat Study 203 Specific Gag Amino Acid Changes at 369-371

RED: locations of *in vitro* resistance mutations*

ORANGE: locations of key polymorphisms

Figure 5: Bevirimat Gag Polymorphisms - Different than in vitro Mutations.

Gag Polymorphisms at 369, 370 or 371 Prevalence

- Univ. British Columbia (Harrigan)
  - 567 ARV-naïve patients (2008)
  - (mean CD4: 280; mean VL: 5.0 log)
  - 60.2% had no polymorphisms at positions 369, 370 or 371
  - Nearly all clade B

Clade B Consensus Amino Acid Position	Poly-morphism	Proportion (of 567 patients)
V370	A V/A Deletion M I L	18.6% 3.2% 2.1% 1.4% 1.2% 1.2%
T371	Deletion A N	5.2% 1.6% 1.2%
Q369	H Q/H	2.3% 2.3%

Table 4: Univ. British Columbia Prevalence in ARV-Naïve Patient Data Base

- Proportion without baseline polymorphisms:
  - V370: 72.3%
  - T371: 92.0%
  - Q369: 95.4%
- Other more commonly occurring polymorphisms:
  - R380K: 37.1%
  - G357S: 20.4%
  - S373P: 19.9%

Conclusions

- Mean viral load reduction of 44 heavily treatment-experienced patients
  - Responders: -1.26 log copies/mL
  - Non-Responders: -0.05 log copies/mL
- Optimal bevirimat treatment response requires plasma trough >20 ug/mL and lack of Gag polymorphisms at positions 369, 370 or 371
- Relative impact of specific amino acid shifts at positions 369-371 and impact in non-Clade B isolates not yet established
- Phenotype confirmation of genotype data made at Panacos and at 2 independent labs
- Free of Gag polymorphisms at positions 369, 370 or 371 in external data bases
  - 60.2% in 567 treatment-naïve patients (Harrigan, UBC)
  - 68.3% in isolates from 82 PI-experienced patients (Malet, Paris)