#1008

DISEASE SEVERITY IMPACT ON LONG-TERM VIROLOGIC RESPONSE TO IBALIZUMAB IN EXPANDED ACCESS PROTOCOL (TMB-311)

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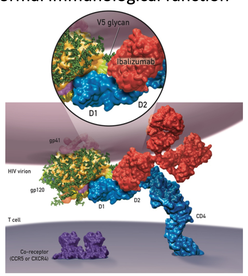
THERA technologies

Introduction

- Ibalizumab (IBA) is a long-acting humanized immunoglobulin G4 monoclonal antibody that blocks entry of HIV into CD4+ T cells and is the first post-attachment inhibitor approved for MDR HIV-1 treatment
- Unlike other antiretroviral agents, IBA binds to a conformational epitope on the 2nd extracellular domain of the CD4 receptor, away from MHC II binding sites
- It prevents HIV from infecting CD4+ immune cells while preserving normal immunological function



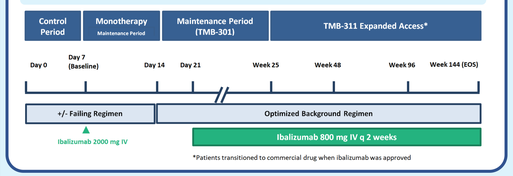
- IBA was approved by the FDA in March 2018 for treatment of HIV-1 infection in heavily treatment-experienced (TE) adults with multidrug resistant (MDR) HIV-1 infection failing their current antiretroviral (ARV) regimen
- Ongoing viremia can lead to further accumulation of drug resistance, increased morbidity and mortality in TE patients
- ART efficacy often depends on HIV disease severity;
  - Therefore we assessed the impact of disease severity on long-term virologic suppression in patients treated with IBA

Methods

- TMB-301 was a single arm, 25-week study of IBA plus optimized background regimen (OBR) in TE patients infected with MDR HIV-1
- Subjects receiving their current failing ARV therapy, or no therapy, were monitored for 7 days
  - A single loading dose of 2,000 mg of intravenous (IV) IBA was then added to their regimen for 7 days
  - Thereafter an OBR was started with ≥ one additional sensitive agent
  - IBA continued at doses of 800 mg IV every 2 weeks (Q2W) through 25 weeks on study treatment
- Subjects who completed the 25-week TMB-301 study in the US and Puerto Rico were eligible to receive IBA at 800 mg Q2W in study TMB-311 (Expanded Access) for up to 144 weeks
- To determine the impact of baseline disease on long-term virologic response, we conducted an on-treatment (OT) analysis stratified by baseline viral load and CD4 count up to week 96
- Patient populations were:
  - "OT population"*
  - "OT censored population" – that is the OT population from which patients with Stanford level 1 and 2 resistance to all OBR ARVs at baseline had been removed (protocol violators)
- Differences in the proportion of suppressed (<50 c/mL) individuals among the strata were assessed by Fisher's exact test
- Overall susceptibility score (OSS) was calculated for each patient as the number of fully active ARVs (Stanford levels 1 and 2) in the OBR at baseline determined by viral genotype and phenotype (Monogram, San Francisco, CA) and historical results
- Genotypic Susceptibility score (GSS) is defined as the cumulative resistance of a treatment regimen including intermediate and low level resistance and was calculated for each patient as the sum on all the drugs in the regimen: (5-drug resistance level) × 0.25

* Two additional patients were on treatment at W96 but were not part of the analysis as their study visits were offset by 2 weeks due to late enrollment into TMB-311

STUDY DESIGN



Results

BASELINE CHARACTERISTICS

Characteristic	Value
Number of patients in OT analysis	40
Mean viral load	102,141 c/mL
Median viral load	35,350 c/mL
Subjects with viral load <10,000 copies/mL	11
Subjects with viral load 10,000 –70,000 copies/mL	17
Subjects with viral load ≥70,000 copies/mL	12
Mean CD4+ cell count	150 cells/µL
Median CD4+ cell count	73 cells/µL
Subjects with <10 cells/µL	12
Subjects with <10–100 cells/µL	10
Subjects with 100–200 cells/µL	5
Subjects with >200 cells/µL	13
Median duration of HIV infection	20.3 years
Deaths during study*	4
Baseline OSS	
0	5
1	12
2	18
3	5
Baseline GSS	
0	13
1	13
2	10
≥3	4

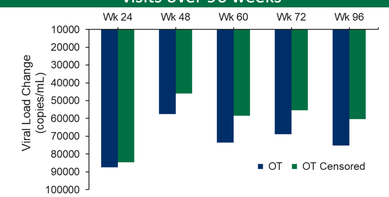
*unrelated to study drug

Results (cont'd)

VIRAL LOAD – BASELINE TO WEEK 96

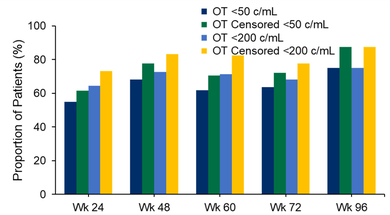
- After 24 weeks of treatment the mean and median decreases in viral load from baseline in the OT population (n=31) were 87,428 copies/mL (c/mL) and 15,081 c/mL respectively
- Mean decrease in viral load from baseline was sustained over 96 weeks (75,207 c/mL; n=20) and was statistically significant (p=0.027)

Mean viral load decrease from baseline at follow-up visits over 96 weeks



- In the OT population 55% of patients achieved viral load <50 c/mL and 65% achieved <200 c/mL at Week 24. The proportion of patients who were undetectable (<50 c/mL) increased from 55% at week 24 (n=31) to 75% for patients remaining on treatment for 96 weeks (n=20)
- Excluding patients with baseline resistance to all their OBR, the proportion of patients on treatment with a viral load <50 c/mL at Week 24 was 61.5% (n=26) and at Week 96 was 87.5% (n=16), and with a viral load <200 c/mL at Week 24 was 73.1% (n=26) and at Week 96 was 87.5% (n=16)
- There was a higher proportion of patients with viral suppression through to Week 96 when patients with baseline resistance were excluded

Proportion of patients with viral loads <50 and <200 copies/mL over 96 weeks



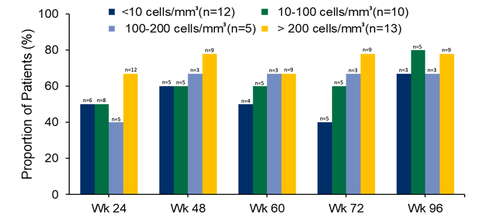
VIRAL SUPPRESSION – BY BASELINE CHARACTERISTICS

- Amongst patients remaining on treatment at Week 96, viral loads were <50 c/mL in:
  - 66.7% of patients who had baseline CD4 counts <10 cell/µL
  - 80% of patients who had baseline CD4 counts 10-100 cell/µL
  - 66.7% of patients who had baseline CD4 counts 100-200 cell/µL, and
  - 77.8% of patients who had baseline CD4 counts >200 cells/µL

Results (cont'd)

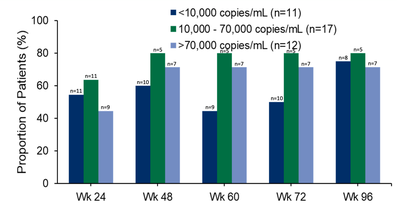
- The percentage of patients achieving an undetectable viral load was numerically higher in patients with a CD4 baseline >200 cells/µL. Due to the small sample size it was not possible to assess a statistical difference between the other strata

Proportion of patients with viral loads <50 copies/mL stratified by baseline CD4 (OT Population)



- In this OT analysis 71.4% patients on treatment after 96 weeks ,who had a viral load >70,000 c/mL at baseline, were fully suppressed
- For those on treatment at Week 96, no statistically significant differences were found across groups: baseline viral load did not have an effect on suppression of viral load, as viral loads were <50 c/mL in:
  - 75% of patients with baseline viral load of <10,000
  - 80% of patients with baseline viral load 10,000 – 70,000 and
  - 71% of patients with baseline viral load >70,000 c/mL

Proportion of patients with viral loads <50 copies/mL stratified by baseline viral load (OT Population)



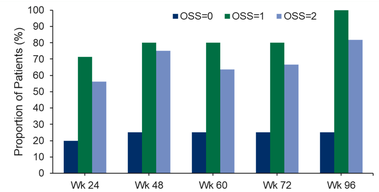
ACTIVITY OF ARVs IN OBR

- The proportion of patients with viral loads suppressed <50 c/mL over time were stratified according to the number of fully active ARVs (0, 1 or 2) by overall susceptibility score (OSS) and by genotypic susceptibility score (GSS)
- At Week 24 the proportion of patients with viral loads <50 c/mL for OSS=0 was 20%, OSS=1 was 71.4% and OSS=2 was 56.3%. By Week 96 the proportion of patients with viral loads <50 c/mL for OSS=0 was 25%, OSS=1 was 100% and OSS=2 was 81.8%
- GSS analysis showed a similar pattern where the proportion of patients with viral loads <50 c/mL for GSS=0 was 30%, GSS=1 was 80% and GSS=2 was 55.6% at Week 24. At Week 96 the proportion of patients with viral loads <50 c/mL for GSS=0 was 62.5%, and GSS=1 and GSS=2 were both 83.3%

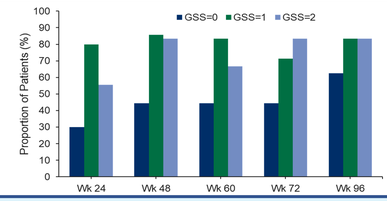
Results (cont'd)

- Both OSS and GSS scores demonstrate the necessity to include 1 or 2 fully active ARVs in combination with IBA for optimal suppression of viral load, which concurs with guidelines

Proportion of patients with viral loads <50 copies/mL stratified by OSS (OT Population)



Proportion of patients with viral loads <50 copies/mL stratified by GSS (OT Population)



Conclusions

- The current study assessed IBA efficacy in highly treatment experienced patients representing the most severely advanced HIV-1 infected population in a registrational clinical trial to date
- Treatment with IBA resulted in significant and sustained large decreases in mean viral loads over 96 weeks in this advanced patient population with MDR HIV
- When patients with baseline resistance to all components of OBR, besides IBA, were censored, the proportion of patients achieving suppression was higher at every time point, highlighting the importance of resistance testing for ARVs being considered for combination
- Baseline viral load >70,000 copies may reduce viral load suppression by Week 24. However by Week 96 viral load suppression did not appear to be affected by baseline viremia
- Notable differences in achievement and maintenance of viral suppression were seen in patients between OSS=0 and OSS=1, emphasizing the importance of not leaving patients on failing regimens
- Together these data show that TE patients from across the clinical spectrum of HIV disease can achieve viral suppression with a treatment regimen that includes a post-attachment inhibitor that blocks entry of HIV into CD4+ T cells, regardless of baseline CD4 count or viral load strata