

Tipranavir/r (TPV/r) maintains long term virological suppression – Three year follow-up of RESIST

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Abstract

RESIST 1 and 2 are ongoing, randomized Phase III studies of TPV/r (500/200 mg BID) or CPI/r, plus OBR in HTE patients. At Week 156, 218/1483 patients were still taking assigned study medication: 155 TPV/r; 63 CPI/r. Greater treatment discontinuation occurred in CPI/r arm: TPV/r patient exposure years (PEY) was 2X CPI/r (1315.3 vs. 688.5 PEY). Discontinuation was predominantly due to virologic failure (TPV/r: 201/746 (26.9%); CPI/r: 352/737 (47.8%)). Previous analyses demonstrated that patients who had added a new class of ARV (ENF) with TPV/r or CPI/r had improved responses. At >3 years, the patients adding new ARV class achieved four-fold greater treatment response rates for TPV/r vs. CPI/r (37.9% vs. 8.2%). Their proportions <50 cp/mL were 21.8% versus 9.3%. For the overall study population at >3 year, the percentages of TPV/r patients <50 cp/mL, <400 cp/mL and treatment response were twice that of CPI/r. Median VL decreases from baseline were -0.57 log₁₀ copies/mL in TPV/r; -0.21 in CPI/r. The PEY-adjusted AE profile was similar between TPV/r and CPI/r groups, respectively: any grade 3/4 AE: 25.9 vs. 28.9/100 PEY; serious: 20.0 vs. 22.2; AEs resulting in discontinuation: 9.4 vs. 6.8. GI AEs were most common in TPV/r and CPI/r, respectively: diarrhoea: 28.0 vs. 35.1; nausea: 15.7 vs. 19.3; vomiting 9.4 vs. 10.5. Grade 3/4 ALT/AST elevations and hyperlipidemia were more frequent in TPV/r patients. HTE patients who responded to TPV/r experienced durable responses lasting more than 3 years. TPV/r response rates were approximately twice those of CPI/r and were markedly higher for those patients who also started a new class of ARV (ENF). The safety profile of TPV/r was similar to previously observed, suggesting long term tolerability among those with initial treatment success.

Introduction

Tipranavir (TPV, Aptivus[®]) is a second generation protease inhibitor (PI) that exhibits potent activity against multiple PI-resistant HIV-1. TPV/r is effective and well tolerated in patients who have taken more than one PI-based regimen and are infected with HIV-1 that exhibits reduced susceptibility to more than one PI [1–4]. RESIST 1 and 2 are randomized Phase III studies of tipranavir/r (TPV/r) at a dose of 500/200 mg BID or a comparator ritonavir-boosted protease inhibitor (CPI/r), plus optimized background regimen (OBR) in highly treatment experienced (HTE) patients [1,5,6]. Week 24, 48 and 96 efficacy and safety data from RESIST have been presented: at all of these timepoints, treatment with TPV/r was associated with superior virological and immunological responses when compared to CPI/r [1,5–9].

The RESIST study is ongoing and this poster reports three year (Week 156) data.

Study design

RESIST 1 and 2 enrolled adult patients with HIV infection who fulfilled the following criteria. Full details of the entry criteria are provided in reference [1]:

- ≥3 consecutive months' experience with 3 classes of antiretroviral (ARV) drugs (NRTIs, NNRTIs, PIs)
- ≥2 PI-based regimens for ≥3 months; one of which was the current treatment regimen
- Viral isolate carrying ≥1 primary protease mutation at 30N, 46I/L, 48V, 50V, 82A/F/L/T, 84V, 90M
- Viral isolate carrying ≤2 mutations at codons 33, 82, 84, 90.

The investigators selected the CPI/r (lopinavir/r, indinavir/r, saquinavir/r or amprenavir/r) and the OBR prior to randomization based on genotypic resistance testing (Figure 1). The use of enfuvirtide (ENF) was allowed; patients were stratified by the planned use of ENF, as well as by the pre-selected CPI/r.

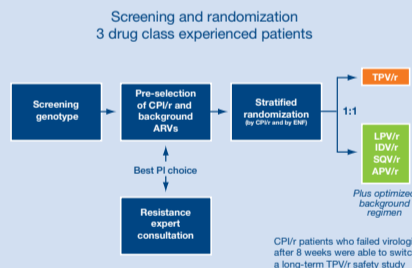


Figure 1: Study design of RESIST 1 and 2

Patients received 500/200 mg BID TPV/r or standard doses of the CPI/r plus approved doses of the components of the OBR.

After Week 8, patients who failed virologically in the CPI/r arm were able to receive TPV/r prior to its regulatory approval via a long term parallel safety study, provided that there was documented evidence that they had been adherent to their study medication.

Treatment response (TR) rates (confirmed VL reduction ≥1 log₁₀ copies/mL at Week 156 without viral rebound [confirmed VL <1 log₁₀ copies/mL below baseline], death or treatment changes), time to treatment failure (TTF), and the proportions of patients with viral loads (VL) <400 and <50 copies/mL at Week 156 were determined. The TTF was analyzed using Cox proportional hazards models or log-rank tests. Analyses were Intent to Treat, Non-Completer equals Failure (ITT NCF) unless otherwise stated.

Results

At Week 156, 218/1483 patients (15.7%) were still taking assigned study medication: 155 were taking TPV/r; and 63 were taking CPI/r. The rate of treatment discontinuation was higher in the CPI/r arm than in the TPV/r arm due to an inferior virologic response rate. Discontinuation was predominantly due to virologic failure: in the TPV/r arm, approximately one quarter (201/746; 26.9%) of patients failed virologically compared to nearly half (352/737; 47.8%) of the CPI/r patients. Overall, the number of TPV/r patient exposure years (PEY) was twice that of the CPI/r patients: 1315.3 vs. 688.5 PEY.

For the overall study population at three years, the proportions of TPV/r patients with VLs <50 copies/mL or <400 copies/mL or with treatment response were approximately twice those achieved by patients taking CPI/r. Treatment response rates at Week 156 were 20.9% (156/746) in the TPV/r arm versus 7.5% (55/737) in the CPI/r arm (ITT NCF) (Figure 2). The proportions of patients who had VLs <400 copies/mL at Week 156 were 17.3% (129/746) and 7.6% (56/737) in the TPV/r and CPI/r arms, respectively (ITT NCF) (Figure 3). Using the <50 copies/mL assay, 13.9% of TPV/r patients had undetectable VLs at Week 156 as compared to 6.5% of CPI/r patients (ITT NCF) (Figure 4). Median VL decreases from baseline were -0.57 log₁₀ copies/mL in the TPV/r arm and -0.21 log₁₀ copies/mL in the CPI/r arm (Figure 5).

The results of previous analyses demonstrated that patients who added a new class of antiretroviral drug (e.g. enfuvirtide) to their OBR plus TPV/r or CPI/r had improved virological and immunological responses [1,5,6]. At >3 years, TPV/r patients who took enfuvirtide for the first time in their OBR achieved four-fold greater treatment response rates than CPI/r patients: 37.9% vs. 8.2%. In this group of patients, the proportions with VLs <50 copies/mL were 21.8% versus 9.3%, respectively (Figure 6) (ITT NCF).

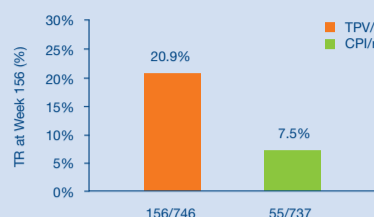


Figure 2: Week 156 treatment response rates in TPV/r and CPI/r arms of RESIST studies (ITT NCF)

TR = confirmed VL reduction ≥1 log₁₀ copies/mL at Week 156 without viral rebound [confirmed VL <1 log₁₀ copies/mL below baseline], death or treatment changes

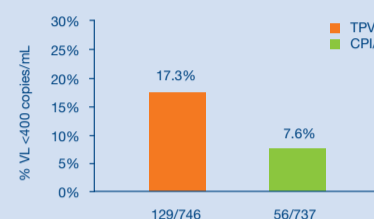


Figure 3: Proportion of patients in the RESIST studies with VL <400 copies/mL at Week 156 (ITT NCF)

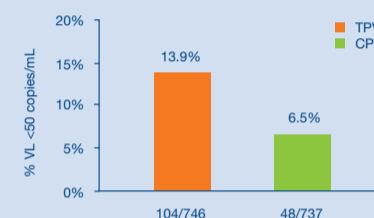


Figure 4: Proportion of patients in the RESIST studies with VL <50 copies/mL at Week 156 (ITT NCF)

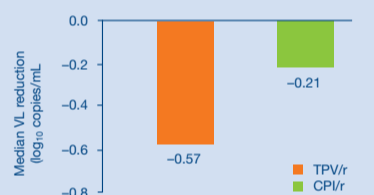


Figure 5: Median viral load reduction from baseline at Week 156 in TPV/r and CPI/r patients

The PEY-adjusted adverse event (AE) profile was similar between the TPV/r and CPI/r groups. Any Grade 3/4 AE occurred in 25.9/100 PEY in the TPV/r arm versus 28.9/100 PEY in the CPI/r arm. Serious AEs occurred at a rate of 20.0/100 PEY in the TPV/r arm versus 22.2/100 PEY in the CPI/r arm. The rate of AEs that resulted in discontinuation of study medication was: 9.4/100 PEY in the TPV/r arm and 6.8/100 PEY in the CPI/r arm. Gastro intestinal (GI) AEs were less common in the TPV/r arm than the CPI/r arm: diarrhea: 28.0/100 PEY in the TPV/r arm vs. 35.1/100 PEY in the CPI/r arm; nausea: 15.7/100 PEY vs. 19.3/100 PEY, respectively; and vomiting 9.4/100 PEY vs. 10.5/100 PEY, respectively. Grade 3/4 ALT/AST elevations (100/737 [13.6%] vs. 22/727 [3%]) and hyperlipidemia (triglycerides: 197/737 [26.7%] vs. 100/727 [7.7%]) were more frequent in TPV/r patients than in those taking a CPI/r.

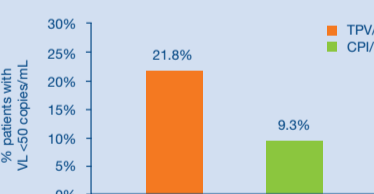


Figure 6: Proportion of patients in the RESIST studies who took enfuvirtide for their first time in their OBR and who achieved a VL <50 copies/mL at Week 156 (ITT NCF)

Conclusions

- In this highly treatment experienced population, patients who responded to TPV/r experienced durable responses lasting more than 3 years.
- TPV/r treatment response rates were approximately twice those of CPI/r and were four-fold greater for those patients who took enfuvirtide for the first time.
- The PEY-adjusted adverse event profile was similar between the TPV/r and CPI/r groups. Gastro intestinal AEs were less common in the TPV/r arm than the CPI/r arm.
- There were no new safety findings that emerged with TPV/r administration for ≥3 years. In general, emergence of safety events was lower after Week 48, than prior to Week 48.

References

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