CROI 2008, BOSTON

15th Conference on Retroviruses and Opportunistic Infections

Poster #789

48-Week Results from BENCHMRK-2, a Phase III Study of Raltegravir (RAL) in Patients Failing Antiretroviral Therapy (ART) with Triple-Class Resistant HIV-1

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Abstract

Background: In 3 studies of HIV-infected patients (pts) with limited treatment options, RAL combined with optimized background therapy (OBT) was generally well tolerated and provided superior viral suppression for ≥24 weeks compared to OBT alone. Here we present the 48-week results from BENCHMRK-2 (Protocol 019), an ongoing double-blind Phase III study being conducted in North and South America.

Methods: Pts failing ART with triple-class resistant HIV were randomized 2:1 to oral BID RAL 400 mg or placebo (PBO). All pts received OBT. Prespecified efficacy endpoints included % pts with HIV RNA levels <400 and <50 copies/mL, and the mean change in CD4 cell counts from baseline.

Results: Baseline characteristics were similar in the RAL and PBO groups. At baseline, median CD4 counts were 102 and 132 cells/mm³, and geometric mean viral loads were 4.7 and 4.7 log_{10} copies/mL in the RAL and PBO groups, respectively. Genotyping demonstrated that OBT contained <1 active drug (sensitivity score = 0) in 20% and 27% of pts in the RAL and PBO groups, respectively. Preplanned 48-week efficacy analyses are shown below, along with the 24-week results:

	% pts (95% CI) with HIV RNA <400 copies/mL[‡]		% pts (95% CI) with HIV RNA <50 copies/mL[‡]		Change from baseline CD4 cells/cu mm[††]	
	Week 24	Week 48	Week 24	Week 48	Week 24	Week 48
RAL (N=230)	75 (69, 81)	71 (65, 77)	65 (59, 71)	60 (53, 66)	81 (69, 94)	98 (84, 113)
PBO (N=119)	41 (32, 51)	38 (29, 47)	35 (26, 44)	35 (26, 44)	37 (23, 51)	40 (24, 56)
RAL - PBO[†]	34 (23, 44)*	33 (22, 43)*	31 (20, 41)*	25 (14, 35)*	44 (25, 63)*	59 (37, 80)*

RAL and PBO were given with OBT
[†] Difference between RAL and PBO; a positive value favors RAL over PBO
[‡] Non-Completer=Failure
[††] Baseline values carried forward for virologic failures
*Nominal P<0.001

RAL was generally well tolerated over 48 weeks.

Conclusions: In this pivotal study of pts failing ART with triple-class resistant HIV, RAL plus OBT maintained superior antiretroviral and immunological responses compared to OBT alone for at least 48 weeks.

Background

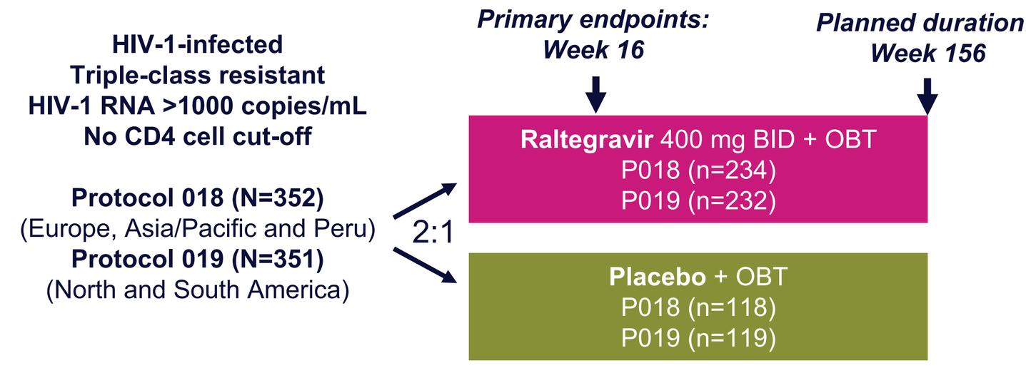
Raltegravir (MK-0518, ISENTRESS™) is an HIV-1 integrase strand-transfer inhibitor (InSTI) with

- Potent *in vitro* activity:
  - IC_{95} = 31 nM ± 20 nM (50% human serum)
  - Active against multi-drug resistant HIV-1, CCR5 and CXCR4 tropic HIV-1
  - HIV resistant to raltegravir remains sensitive to other ARTs
  - Additive/synergistic with NRTIs, NNRTIs, PIs, and enfuvirtide
- Clinical efficacy when used in combination with OBT:
  - in ART-naive patients, 83 – 88% had HIV RNA < 50 copies/mL at Week 48 (Markowitz et al, JAIDS 2007; 46:125-33)
  - In patients failing therapy with triple class resistant virus:
    - 56 – 67% had HIV RNA < 50 copies/mL at Week 24 in the phase II dose-ranging study (Grinsztejn et al, LANCET 2007; 369:1261–69)
    - 63% had HIV RNA < 50 copies/mL at Week 24 in the phase III BENCHMRK-1 and 2 studies combined (Kumar et al, EACS Oct 2007)

Methods

BENCHMRK-1 and -2 Study Design

- Randomized, double-blind, placebo-controlled with Data and Safety Monitoring Board
- Primary analysis at Week 16; secondary analysis at Week 48



HIV-1-infected
Triple-class resistant
HIV-1 RNA >1000 copies/mL
No CD4 cell cut-off
Protocol 018 (N=352)
(Europe, Asia/Pacific and Peru)
Protocol 019 (N=351)
(North and South America)
Primary endpoints: Week 16
Planned duration: Week 156
2:1
Raltegravir 400 mg BID + OBT
P018 (n=234)
P019 (n=232)
Placebo + OBT
P018 (n=118)
P019 (n=119)

- OBT selected by investigator based on baseline resistance testing and prior treatment history. Selected investigational antiretrovirals, darunavir and tipranavir, were permitted.

Statistical Analysis

- The durability of antiretroviral and immunological activity was assessed by the following predefined endpoints measured at Week 48: HIV RNA <50 copies/mL, HIV RNA <400 copies/mL, change from baseline in plasma HIV RNA (log_{10} copies/mL), and change from baseline in CD4 cell count (cells/mm³).
- For binary endpoints (proportions) over time analysis, Non-Completer = Failure (NC=F) is applied for missing data approach.
- For change from baseline in log_{10} HIV RNA and change from baseline in CD4 cell counts, Observed Failure (OF) approach assumes baseline value was carried forward for virologic failures.
- Data from BENCHMRK-1 & 2 were combined for additional analyses:
  - Efficacy by subgroups — OF approach (virologic failure carried forward) used for missing data.
  - Cancer events — time adjusted analysis based on all treated patients as they were originally randomized.

Results

Table 1. Patient Disposition

	Raltegravir + OBT N	(%)	Placebo + OBT N	(%)
Randomized	232		119	
Treated	230	(99)	119	(100)
Continuing in Double-Blind phase	177	(76)	55	(46)
Entered Open-Label post VF* phase	35	(15)	57	(48)
Discontinued study	18	(8)	7	(6)
Discontinued due to adverse event	7	(3)	3	(3)

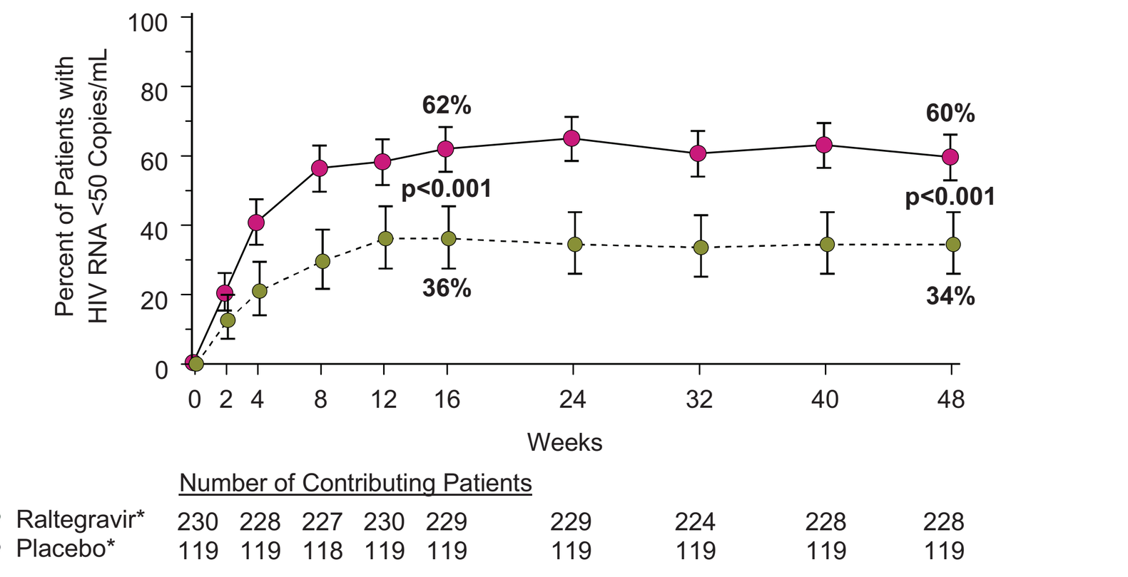
* Definition of virologic failure:
1) <1 log_{10} ↓ HIV RNA from baseline and HIV RNA >400 copies/mL at wk 16, OR
2) virologic relapse: >1 log_{10} ↑ HIV RNA above nadir or >400 copies/mL from nadir after response <400 copies/mL (on 2 consecutive measurements at least 1 week apart).

Table 2. Patient Characteristics

	Raltegravir + OBT N = 230	Placebo + OBT N = 119
Mean Age, yrs (SD)	45 (9)	47 (8)
% Male	91	90
% Caucasian	55	65
Median CD4 Count, cells/mm³	102	132
GM Viral Load, copies/mL (log_{10} HIV RNA)	48366 (4.7)	47850 (4.7)
% with AIDS	91	92
Median yrs of prior ARTs (Mean # ART)	10 (12)	10 (12)
% Hepatitis B+ / % Hepatitis C+ / both	10 / 3 / 0	3 / 4 / 0
% GSS[†] 0 / 1	20 / 44	27 / 40
% PSS[†] 0 / 1	10 / 34	19 / 28
% new enfuvirtide in OBT	19	20
% new darunavir in OBT	45	50

[†] GSS/PSS = total ART in OBT to which patient's virus showed geno/phenotypic sensitivity by Phenosense GT assay. Enfuvirtide and darunavir use in naïve patients were each counted at +1 active agent and added to GSS/PSS.

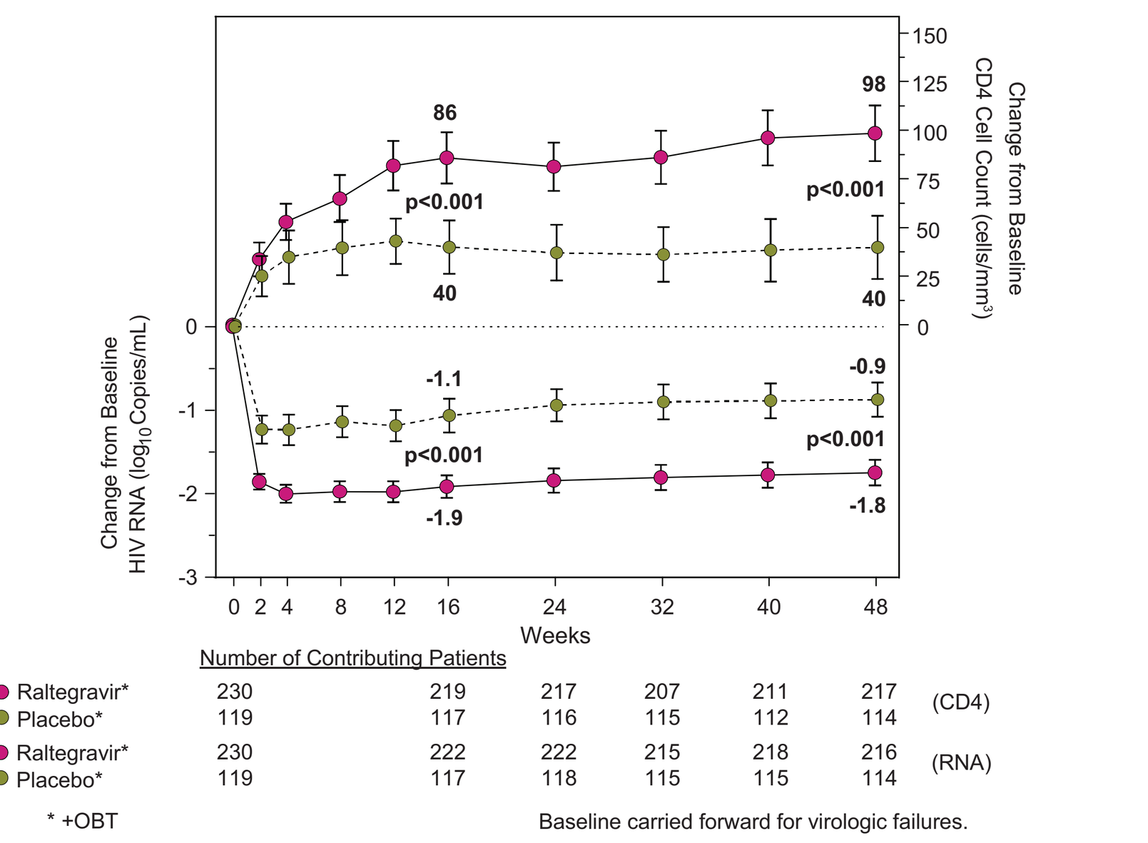
Figure 1. Percent of Patients Achieving HIV RNA <50 Copies/mL (95% CI) (BENCHMRK-2, Non-Completer=Failure Approach)



* + OBT; p-value derived from logistic regression model adjusted for baseline HIV RNA level (log_{10}), first enfuvirtide use in OBT, first darunavir use in OBT, and active PI in OBT.

At week 48, HIV RNA <400 copies/mL was achieved in 71% of the raltegravir group vs 38% of the placebo group (p<0.001).

Figure 2. Change From Baseline in CD4 Cell Count (cells/mm³) and Log_{10} HIV RNA (BENCHMRK-2, Observed Failure Approach)



Change from Baseline CD4 Cell Count (cells/mm³)
Change from Baseline HIV RNA (log10 Copies/mL)
86
98
p<0.001
p<0.001
40
40
-1.1
-0.9
p<0.001
p<0.001
-1.9
-1.8
Weeks
Number of Contributing Patients
Raltegravir* 230 219 217 207 211 217 (CD4)
Placebo* 119 117 116 115 112 114
Raltegravir* 230 222 222 215 218 216 (RNA)
Placebo* 119 117 118 115 115 114
* +OBT
Baseline carried forward for virologic failures.

For change from baseline in CD4 cell counts, p-value was derived from a mixed-effects model adjusted for baseline CD4 cell count, stratum, treatment, visit, interactions between visit and previous variables. For change from baseline in log_{10} HIV RNA level, p-value was derived from a parametric regression model adjusted for baseline HIV RNA level(log_{10}), first enfuvirtide use in OBT, first darunavir use in OBT and active PI in OBT.

Table 3. Number (%) of Patients Treated with Raltegravir with Virologic Failure[†] by Week 48 with HIV Integrase Mutations at Amino Acids 148 and/or 155 (BENCHMRK-2)

	Virologic Failure[§] (n=48) Patients with Baseline and Follow-up sequence[¥] (n=45)
With Mutation at Amino Acid 148 or 155	29 (64)
With Mutation at Amino Acid 148	14 (31)
With Mutation Q148H	4 (9)
With Mutation Q148K	2 (4)
With Mutation Q148R	9 (20)
With Mutation at Amino Acid 155	19 (42)
With No Mutation at either 148 or 155	16 (36)
With Other Known RAL Resistance Mutations[‡]	2 (4)
With Changes from Baseline, Unknown Phenotype[††]	1 (2)
With No Significant AA Changes from Baseline	13 (29)

Virologic failure is generally associated with mutations at one of two primary residues, Q148 or N155, in combination with at least one other mutation.

[†] Virologic failure with integrase tests.
[§] Includes only patients with virologic failure (as defined in Table 1) for whom integrase genotypic data were available.
[¥] 3 patients had only baseline sequence available.
[‡] Included 1 patient with Y143C, L74M, S230R, and 1 patient with Y143R
[††] Included 1 patient with G163R.

Table 4. Summary of Clinical Adverse Events (AEs) in BENCHMRK-2

	Raltegravir + OBT (N=230)	Placebo + OBT (N=119)	Difference from Placebo[†] % (95% CI)	p-Value
Mean follow-up (weeks)	51.7	40.2		
% patients with:				
Any AE	89.6	91.6	-2.03 (-8.1, 5.2)	0.704
Drug-related[‡] AE	60.9	56.3	4.57 (-6.2, 15.5)	0.423
Serious AE	15.7	20.2	-4.52 (-13.7, 3.7)	0.298
Serious drug-related AE	1.7	5.0	-3.30 (-9.0, 0.4)	0.096
Deaths	3.0	2.5	0.52 (-4.4, 4.1)	1.000
Discontinued due to AE	3.0	2.5	0.52 (-4.4, 4.1)	nps[§]

[†] Tests of significance were performed on the percentage of patients with at least one adverse experience in the category. The 95% CIs were calculated using Miettinen and Nurminen's method. p-Values were generated using the Fisher exact test.
[‡] Determined by the investigator to be possibly, probably, or definitely drug related.
[§] nps=not pre-specified for statistical analysis.

Table 5. Percent of Patients with Drug Related[‡] Clinical Adverse Events (≥ 2%, any intensity, BENCHMRK-2)

	Raltegravir + OBT (N = 230)	Placebo + OBT (N = 119)
Mean follow-up (weeks)	51.7	40.2
% patients with:		
Abdominal Distension	4.3	0.8
Abdominal Pain	4.3	0.8
Constipation	2.2	0
Diarrhea	13.9	10.1
Flatulence	4.8	1.7
Nausea	9.6	9.2
Vomiting	3.0	2.5
Fatigue	5.2	2.5
Injection Site Reaction	13.0	9.2
Pyrexia	1.3	3.4
Anorexia	0.4	2.5
Decreased Appetite	1.7	2.5
Dizziness	2.6	1.7
Headache	8.7	5.0
Rash	1.7	2.5
Hematoma	0.9	2.5

[‡] Determined by the investigator to be possibly, probably, or definitely related to any drug in the treatment regimen.

Table 6. Percent of Patients with Grade 3 or 4 Laboratory Abnormalities (BENCHMRK-2)

Laboratory Test (Unit)	Toxicity Criteria*		Raltegravir (N=230)	Placebo (N=119)
ANC (10³/µL)	Grade 3	0.50 - 0.749	3.5	4.2
	Grade 4	<0.50	1.3	1.7
Hemoglobin (gm/dL)	Grade 3	6.5 - 7.4	0.4	0
	Grade 4	< 6.5	0	0
Platelet count (10³/µL)	Grade 3	25 - 49.999	0.4	0
	Grade 4	<25	0	0
Fasting LDL-C (mg/dL)	Grade 3	≥190	2.8	1.9
Fasting cholesterol (mg/dL)	Grade 3	>300	4.3	5.0
Fasting triglyceride (mg/dL)	Grade 3	751 - 1200	6.1	4.2
	Grade 4	>1200	3.5	3.4
Fasting glucose (mg/dL)	Grade 3	251 - 500	1.7	1.7
	Grade 4	>500	0	0
Total bilirubin (mg/dL)	Grade 3	2.6 - 5.0 x ULN	3.0	4.2
	Grade 4	>5.0 x ULN	0	0
Serum creatinine (mg/dL)	Grade 3	1.9 - 3.4 x ULN	2.2	2.5
	Grade 4	≥3.5 x ULN	0.4	0
AST (IU/L)	Grade 3	5.1 - 10.0 x ULN	3.5	3.4
	Grade 4	>10.0 x ULN	0.4	1.7
ALT (IU/L)	Grade 3	5.1 - 10.0 x ULN	1.7	0.8
	Grade 4	>10.0 x ULN	0.4	1.7
Alkaline phosphatase (IU/L)	Grade 3	5.1 - 10.0 x ULN	0.4	0.8
	Grade 4	>10.0 x ULN	0	0
Pancreatic amylase (IU/L)[§]	Grade 3	2.1 - 5.0 x ULN	4.3	2.5
	Grade 4	>5.0 x ULN	0.4	0
Lipase (IU/L)	Grade 3	3.1 - 5.0 x ULN	0.4	0.8
	Grade 4	>5.0 x ULN	0	0
Creatine kinase (IU/L)	Grade 3	10.0 - 19.9 x ULN	3.0	2.5
	Grade 4	≥20.0 x ULN	3.0	1.7

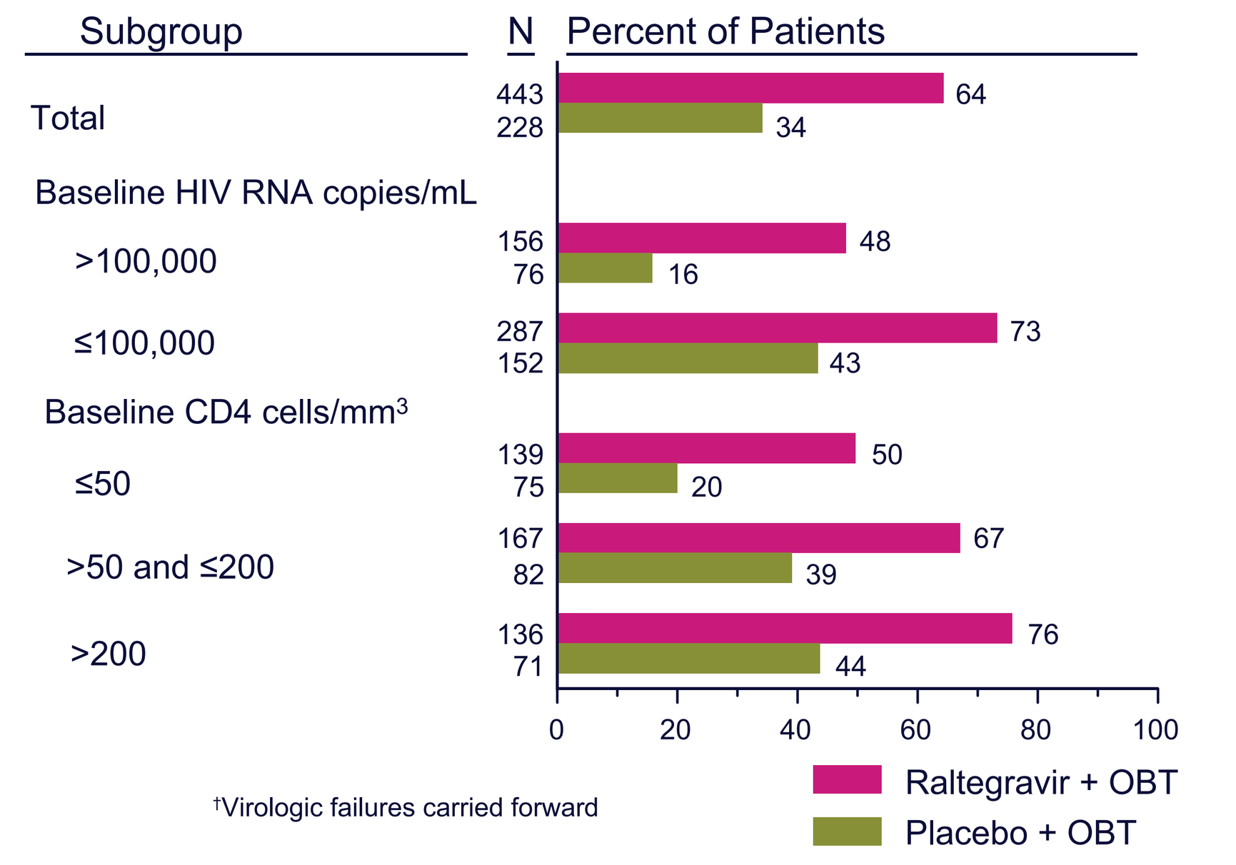
*Grades 3 and 4 per DAIDS toxicity criteria.
[§] Defined as (number of patients meeting the specific serum pancreatic amylase criteria) / (number of patients with serum amylase test result).

Combined Analyses

- Data from BENCHMRK-1 & -2 combined
- Also displayed in poster #788 (BENCHMRK-1)

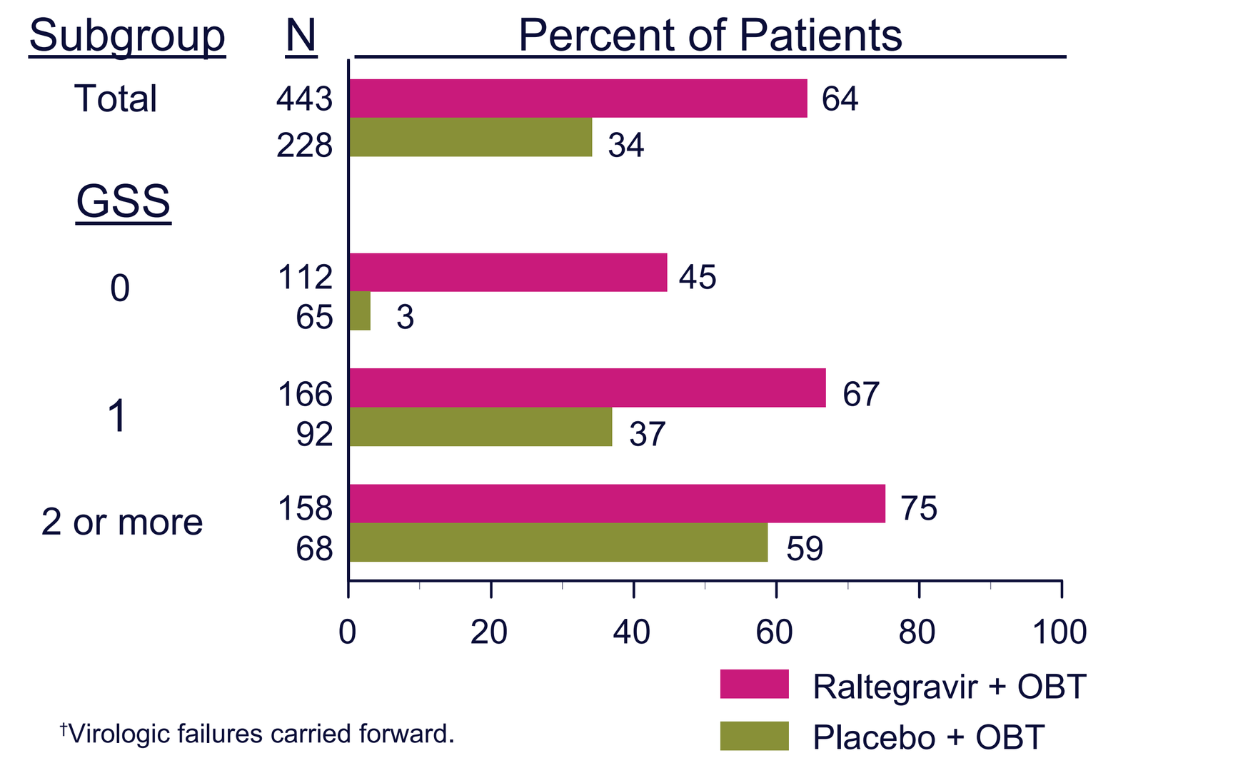
Efficacy by Subgroups

Figure 3. BENCHMRK-1 & -2 Combined Efficacy[†] Percent of Patients with HIV RNA <50 copies/mL at Week 48 by Baseline HIV RNA and CD4 Cell Count



[†]Virologic failures carried forward

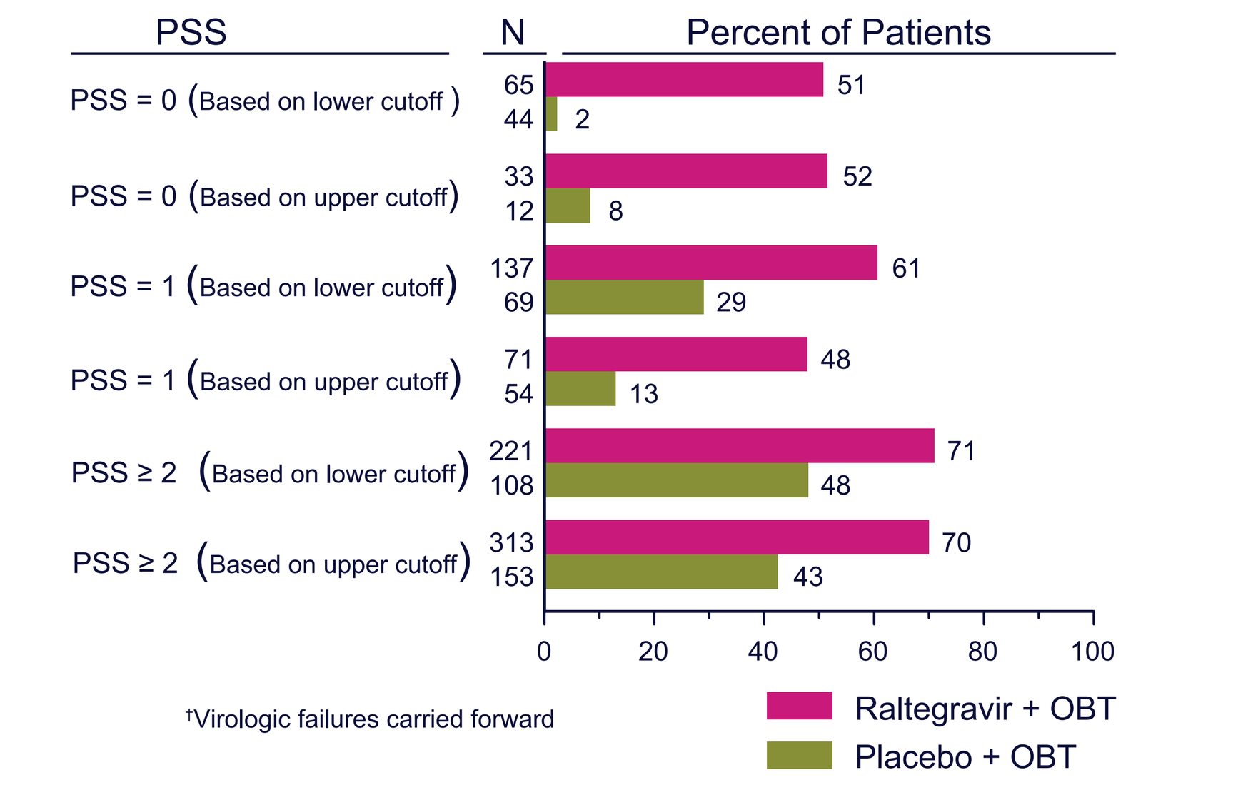
Figure 4. BENCHMRK-1 & -2 Combined Efficacy[†] Percent of Patients With HIV RNA <50 copies/mL at Week 48 by Genotypic Sensitivity Score (GSS)



[†]Virologic failures carried forward.

For patients with GSS=1, 4 ART agents represented at least 80% of the active agents in OBT: darunavir (52%, 52% in raltegravir and placebo groups, respectively), enfuvirtide (8%, 16%), tenofovir (12%, 6%), and tipranavir (11%, 11%).

Figure 5. BENCHMRK-1 & -2 Combined Efficacy[†] Percent of Patients with HIV RNA <50 copies/mL at Week 48 by PSS Based on Upper and Lower cutoffs



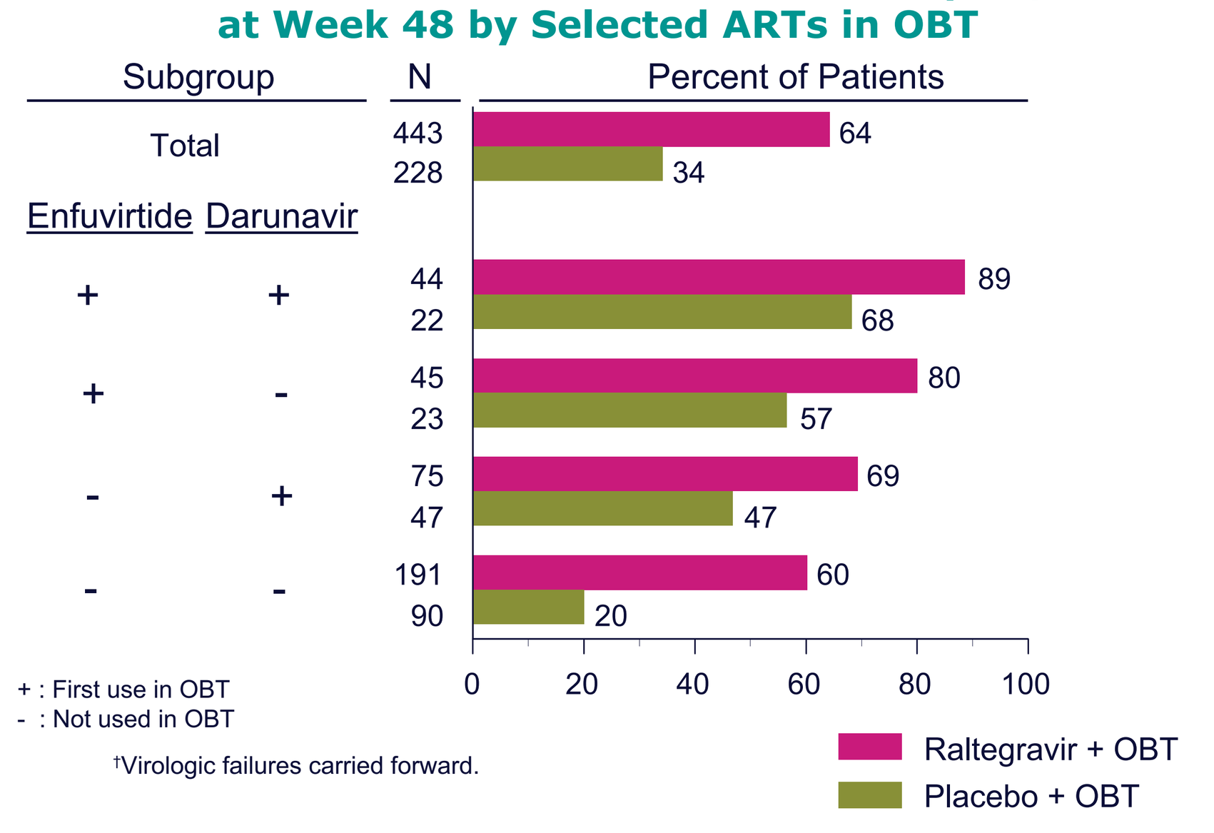
PSS
N
Percent of Patients
PSS = 0 (Based on lower cutoff) 65 51
44 2
PSS = 0 (Based on upper cutoff) 33 52
12 8
PSS = 1 (Based on lower cutoff) 137 61
69 29
PSS = 1 (Based on upper cutoff) 71 48
54 13
PSS ≥ 2 (Based on lower cutoff) 221 71
108 48
PSS ≥ 2 (Based on upper cutoff) 313 70
153 43
Raltegravir + OBT
Placebo + OBT

[†]Virologic failures carried forward

- The analysis by PSS score has been reanalyzed using the upper cutoff to better account for the impact of partial ART activity.
- Isolates with fold-change IC_{50} above the lower but below the upper cutoff are now reported as "partially sensitive". The upper cutoff was developed because the lower cutoff may underestimate partial ART activity in a regimen.
- At the time the BENCHMRK studies were initiated, only the lower cutoff was reported. The efficacy by PSS has been reanalyzed using the upper cutoffs, where available, to better account for the impact of partial ART activity.

Conclusion: At all levels of PSS, the results using the upper and lower cutoffs are similar, confirming the contribution of raltegravir in the treatment regimen.

Figure 6. BENCHMRK-1 & -2 Combined Efficacy[†] Percent of Patients With HIV RNA <50 copies/mL at Week 48 by Selected ARTs in OBT



+ : First use in OBT
- : Not used in OBT

[†]Virologic failures carried forward.

Table 7. Cancer Events – Relative Risk and Associated 95% CI (BENCHMRK-1 and -2)

	Raltegravir Group N	Raltegravir Group Cases/PYR[†] (Rate[‡])	Control Group N	Control Group Cases/PYR[†] (Rate[‡])	Relative Risk (95% CI)
Total	462	16/460 (3.5)	237	4/178 (2.3)	1.5 (0.5, 6.3)
BENCHMRK-1	232	8/237 (3.4)	118	1/87 (1.2)	
BENCHMRK-2	230	8/224 (3.6)	119	3/91 (3.3)	

[†] Patients-years at risk.
[‡] Per 100 person-years (PYR).

For a comprehensive assessment of risk, a similar analysis was done including all double blind data from Phase II and Phase III studies (Protocols 004, 005, and BENCHMRK-1 and -2), which provides a malignancy rate of 2.2/100 PYR for raltegravir and 1.8/100 PYR for the comparator group, resulting in a relative risk (95% CI) of 1.2 (0.4, 4.1).

Conclusions

In HIV-infected, treatment-experienced patients failing antiretroviral therapy with triple-class resistant HIV:

- Raltegravir 400 mg b.i.d. plus OBT has potent and superior antiretroviral and immunological efficacy compared to placebo plus OBT, which is sustained through Week 48.
  - In patients receiving new, active antiretroviral therapies in OBT, up to 89% achieved HIV RNA < 50 copies/mL at Week 48.
- Virologic failure is generally associated with mutations at one of two primary residues, Q148 or N155, in combination with at least one other mutation.
- Raltegravir 400 mg b.i.d. plus OBT is generally well tolerated, as compared to placebo in combination with OBT.
  - Few adverse events leading to discontinuation.
  - Risk of developing malignancy is comparable between raltegravir and comparator groups, whether only the Phase III data are examined, or all Phase II and Phase III data are included.

Acknowledgements

All patients who participated in BENCHMRK-2.

BENCHMRK-2 Investigators: *Brazil:* Grinsztejn B, Madruga JV, Schechter M; *Canada:* Baril J-G, Loutfy MR, Montaner JS, Tremblay C, Tsoukas CM, Vezina S; *Colombia:* Cortes JA, Mendoza H, Velez J; *Mexico:* Quintero Perez N, Ramos J, Rodriguez E; *Puerto Rico:* Morales-Ramirez JO, Sepulveda-Arzola GE; *USA:* Aberg J, Beatty GW, Benson P, Bolan RK, Bredeek UF, Bruno C, Campbell T, Campo R, Coodley GO, Corales RB, DeJesus E, Eron JJ, Fessel WJ, Fetchick RJ, Gonzalez CJ, Hicks C, Horberg MA, Klein DB, Kozal MJ, Kumar PN, LaMarca A, Lennox JL, Luetkemeyer A, Lichtenstein KA, Liporace R, Little SJ, Mariuz P, Markowitz M, McMahon DK, Perez G, Pierone G, Reichman RC, Rhame F, Shalit P, Short W, Skolnik PR, Steigbigel RT, Tedaldi EM, Ward DJ, Wiznia AA, Wright DP.

Merck Research Laboratories: M. Nessly, J. Chen, A. Rodgers, J. Zhao, X. Xu, D. Hazuda, R. Isaacs, M. Miller, R. Danovich, R. Rhodes, B. Jackson, K. Strohmaier, P. Sklar, R. Leavitt, H. Teppler, B-Y. Nguyen.

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