RESIST Program

Randomized **E**valuation of **S**trategic **I**ntervention in Multi-Drug Re**S**istant Patients with **T**ipranavir

Phase 3 comparison of TPV/r and standard-of-care boosted-comparator PI (CPI/r) at 24 weeks

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RESIST Program - Worldwide Enrollment

RESIST 1

US 504
Canada 147
Australia 43

RESIST 2

Brazil 139
Argentina 96
Mexico 30

RESIST 2

France 159
Italy 144
Germany 111
Spain 66
Greece 34
UK 23
Belgium 19
Denmark 16
Netherlands 11
Portugal 7
Switzerland 7
Austria 2
Ireland 2
Sweden 2

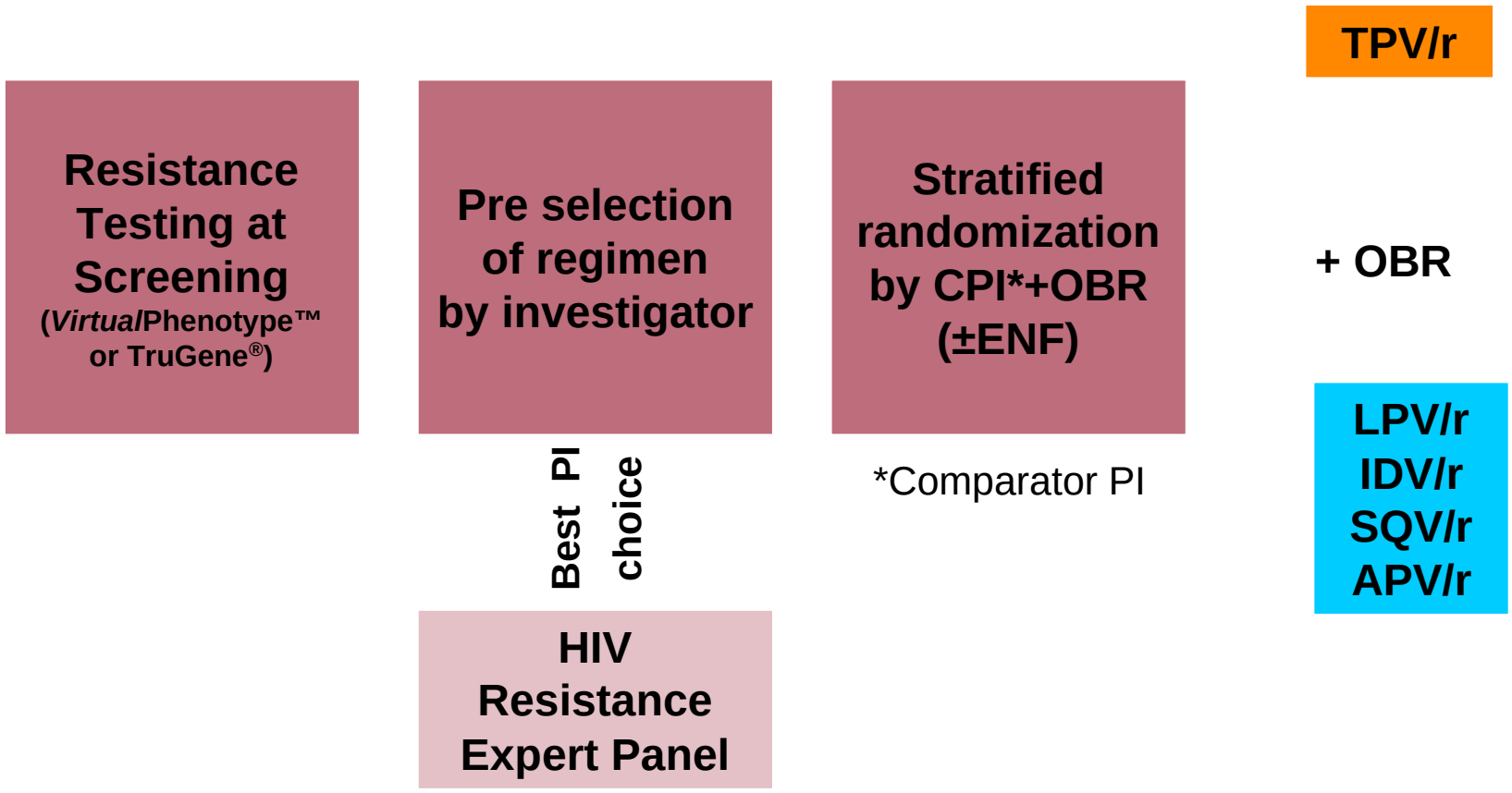
TPV RESIST studies
Key Entry Criteria

- ≥18 years of age
- ≥3 months therapy with NRTI, NNRTI, and PI
  - At least 2 PI regimens for ≥3 consecutive months, one of which must be current regimen
- Viral load ≥1000 copies/mL on therapy
- No CD4+ cell count restrictions
- Genotype indicating
  - **³1 primary PI mutation at codons**
    - 30N, 46I/L, 48V, 50V, 82A/F/L/T, 84V, or 90M and
  - **£2 mutations at codons 33, 82, 84, or 90**

TPV RESIST studies
Endpoints for Planned 24-Week Analysis

- Treatment response defined as
  - Confirmed ≥1 $\log_{10}$ reduction in viral load from baseline at 24 weeks without
    - Viral rebound (confirmed viral load <1 $\log_{10}$ below baseline)
    - Prior treatment change
    - Study discontinuation (including loss to follow-up)
    - Death
- Additional planned analyses included
  - Change in viral load from baseline
  - Proportion <50 and <400 copies/mL
  - Change from baseline in CD4+ cell count

TPV RESIST studies
Screening and Randomization



Failures in CPI arm after week 8 could receive TPV in rollover study

RESIST-2
Baseline Characteristics

		TPV/r (n=435)	CPI/r (n=428)	Total (n=863)
Age (years)	Median	41	42	42
Gender	Male (%)	80.7	85.0	82.9
Race	White (%)	75.9	71.7	73.8
Hepatitis B and/or C	(%)	12.0	18.2	15.1
CD4+ cell count ($cells/mm^3$)	Median	175	196	185
	(Range)	(2-1893)	(2-945)	(2-1893)
HIV RNA (log_{10} copies/mL)	Median	4.78	4.77	4.77
	(Range)	(2.97-6.52)	(2.99-6.76)	(2.97-6.76)

Median prior 12 ARVs (6 NRTIs, 1 NNRTI, and 4 PIs)

TPV RESIST Studies
Prior Treatments

	TPV/r		CPI/r	
N	582		577	
Total ARVs, median	12		12	
PIs, median	4		4	
N (%)				
1	5	(0.9)	10	(1.7)
2	51	(8.8)	52	(9.0)
3	104	(17.9)	106	(18.4)
4	163	(28.0)	143	(24.8)
≥5	259	(44.5)	266	(46.1)
NRTIs, median	6		6	
NNRTIs, median	1		1	
Enfuvirtide, N (%)	69	(11.9)	68	(11.9)

TPV RESIST Studies
Baseline Genotype

	TPV/r (n=582)	CPI/r (n=577)
Number of protease gene mutations		
≤12	117 (20.1)	121 (21.0)
13–15	160 (27.5)	160 (27.7)
16–18	181 (31.1)	154 (26.7)
≥19	123 (21.1)	142 (24.6)
Primary mutations*		
0	4 (0.7)	3 (0.5)
1–2	220 (37.8)	214 (37.1)
3–4	348 (59.8)	354 (61.4)
5–6	9 (1.5)	6 (1.0)
Total PRAMs§		
0	23 (4.0)	20 (3.5)
1	165 (28.4)	160 (27.7)
≥2	393 (67.5)	397 (68.8)

*30N, 46I/L, 48V, 50V, 82A/F/L/T, 84V, or 90M
§PRAMs are mutations at codons 33, 82, 84, and 90

RESIST-2
Study Regimens

		RESIST-1
● Preselected PI		
– Lopinavir (LPV)	38.0%	(61,0%)
– Indinavir (IDV)	2.6%	(4,4%)
– Saquinavir (SQV)	19.9%	(20,6%)
– Amprenavir (APV)	39.5%	(14,0%)
● Enfuvirtide (ENF) included in regimen	11.5%	(36,1%)
● Ongoing PI selected in	29.7%	

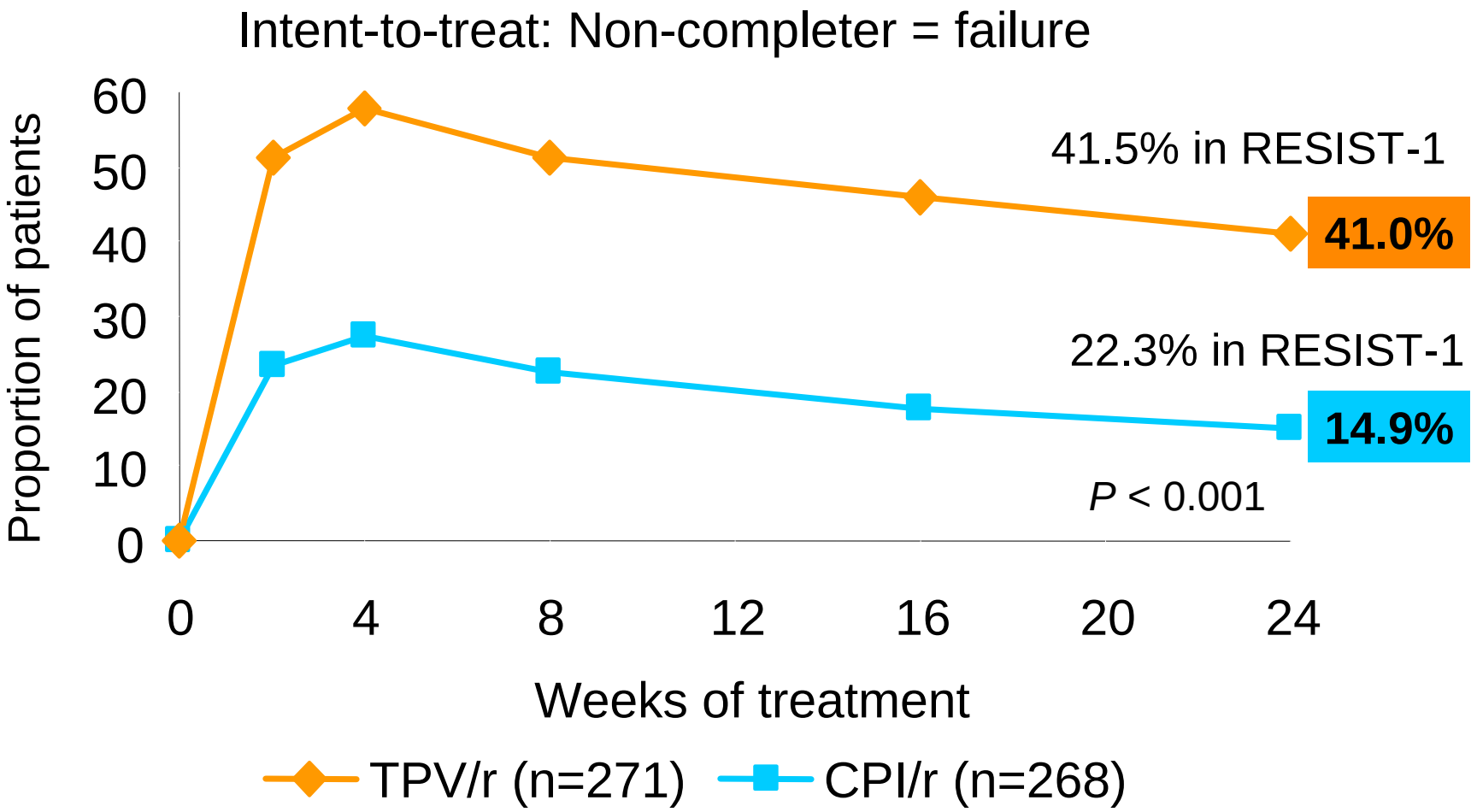
RESIST-2
Patient Disposition (n=863)

	TPV/r	CPI/r
Total treated	435	428
24-week analysis dataset (analysis performed when last patient reached 16 weeks)	271	268
Disposition through week 8*		
On treatment	254	239
Discontinued	17	29
Disposition through week 24		
On treatment	212	96
Discontinued	50	125
Virologic failure	5	71
Adverse events	25	14

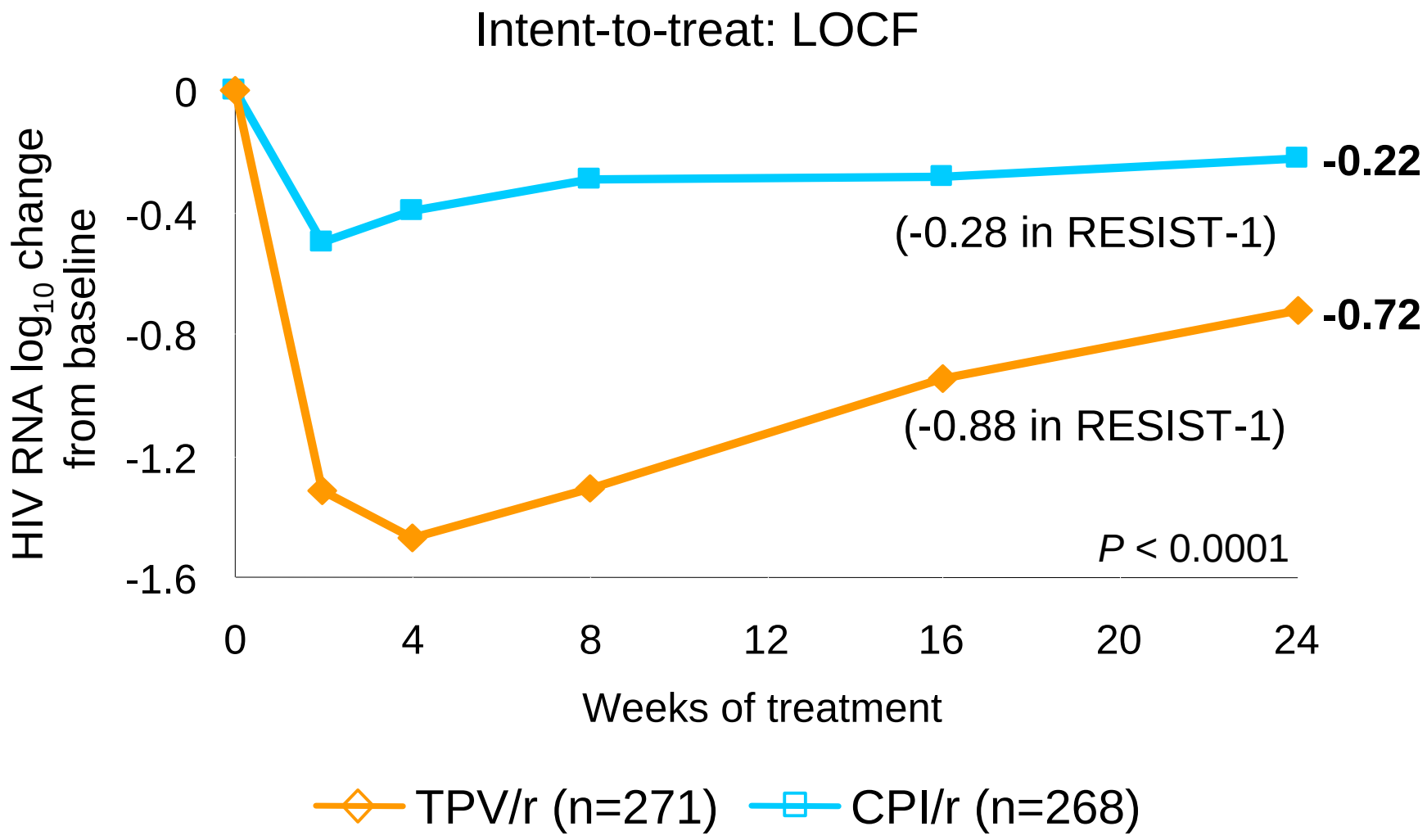
* Failures in CPI/r arm after week 8 could receive TPV/r in a rollover study: failure defined as VL drop ≤0.5 $\log_{10}$, VL >100,000 copies/mL, or rebound to <1 $\log_{10}$ decrease in VL.

RESIST-2

Proportion with Treatment Response (=1 log_{10} VL reduction)

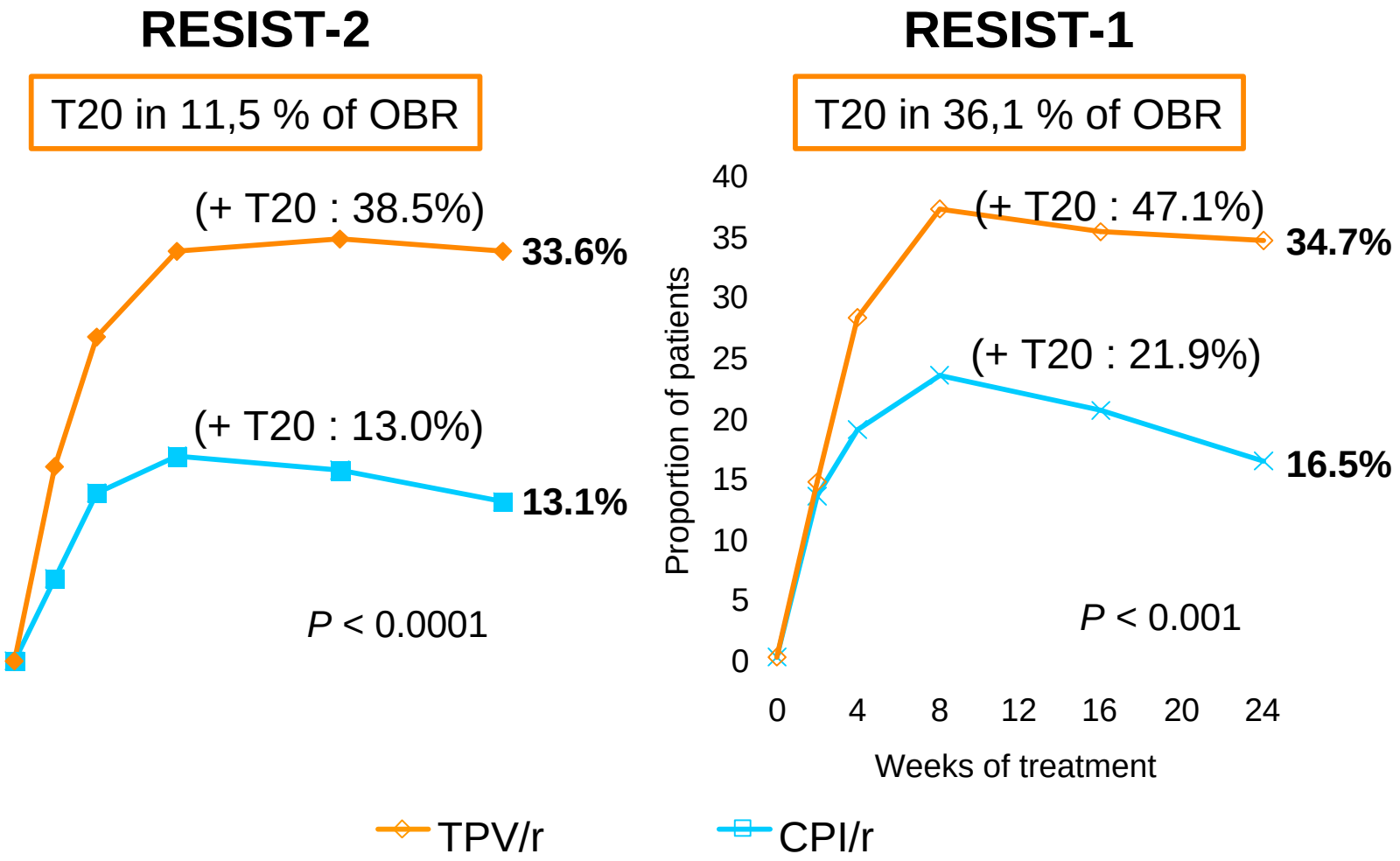


RESIST-2
HIV RNA Median Change From Baseline



RESIST-1 and -2
Proportion With Undetectable VL (< 400 cpi/mL)

Intent-to-treat: non-completer = failure



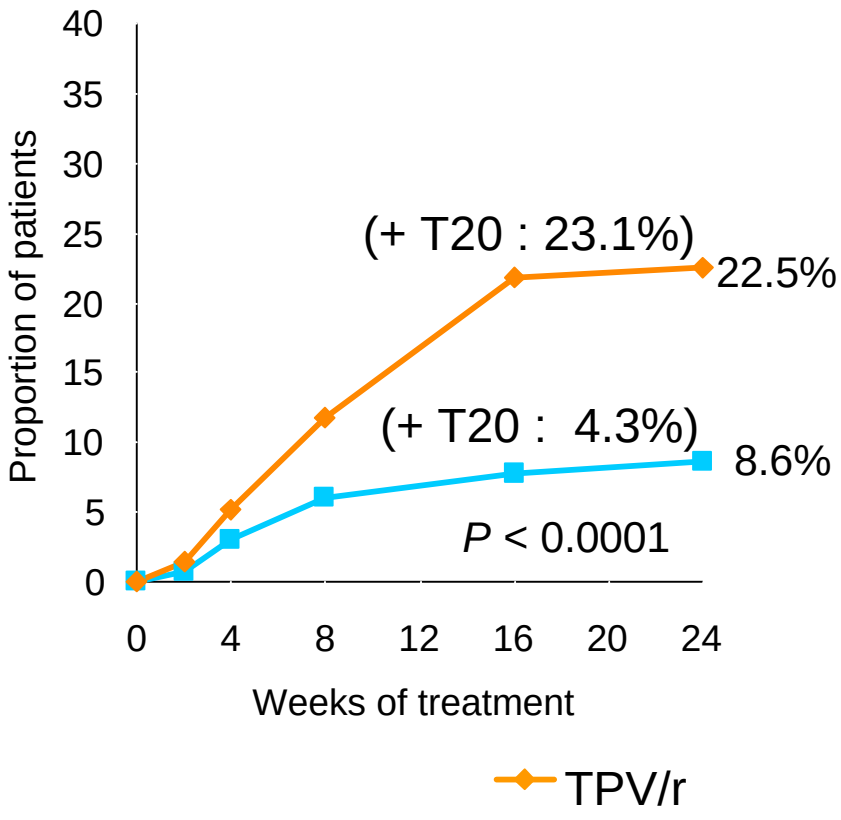
RESIST-1 and -2

Proportion With Undetectable VL (< 50 copies/mL)

Intent-to-treat: non-completer = failure

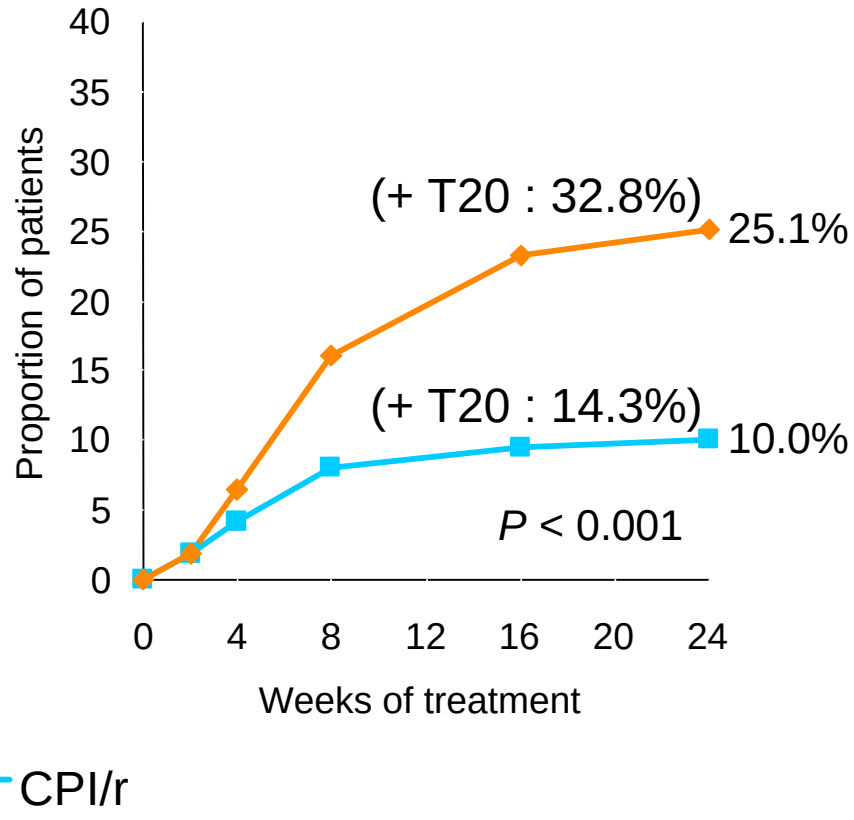
RESIST-2

T20 in 11,5 % of OBR



RESIST-1

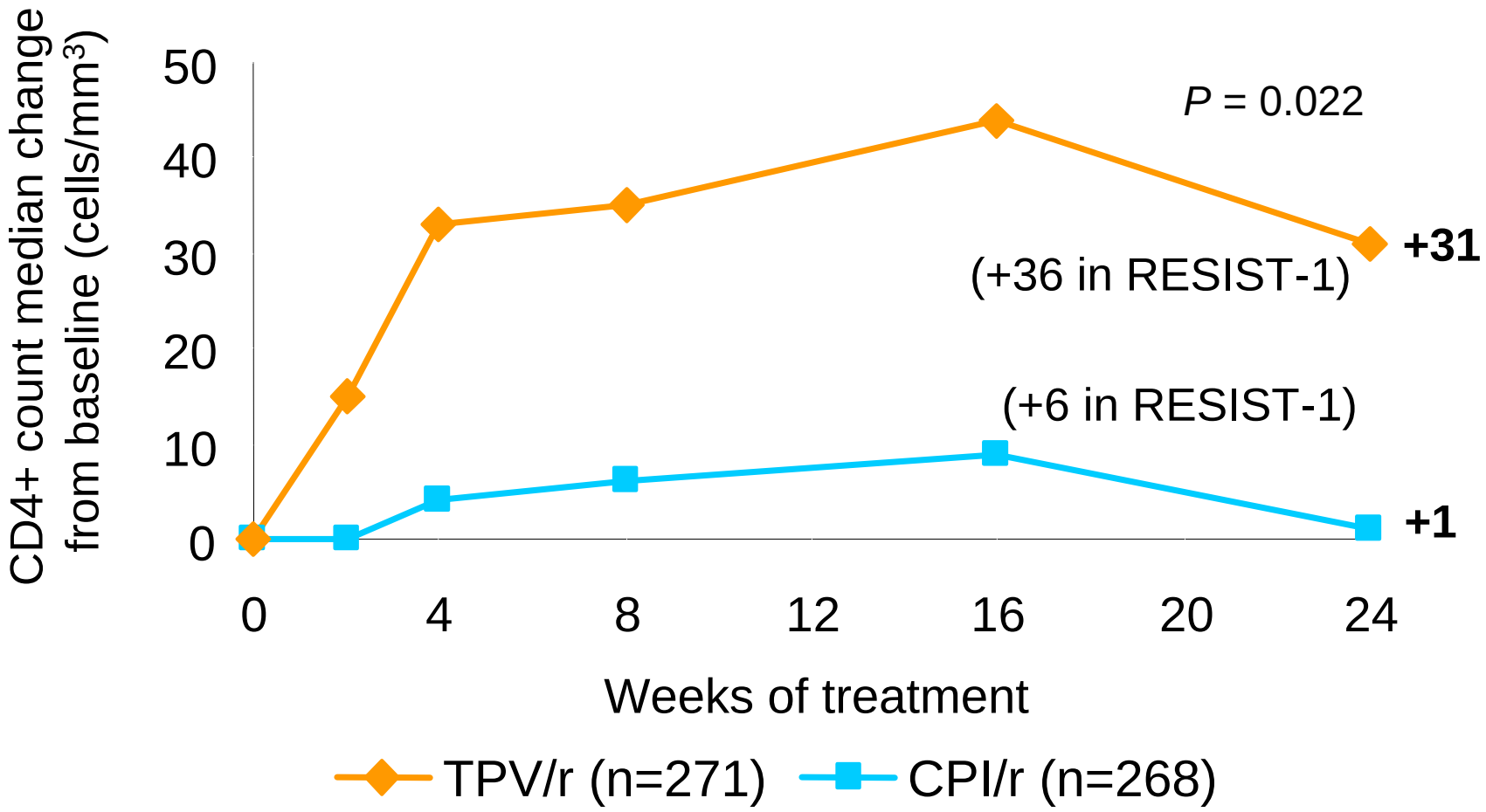
T20 in 36,1 % of OBR



TPV/r CPI/r

RESIST-2

Median Change in CD4+ Cell Count

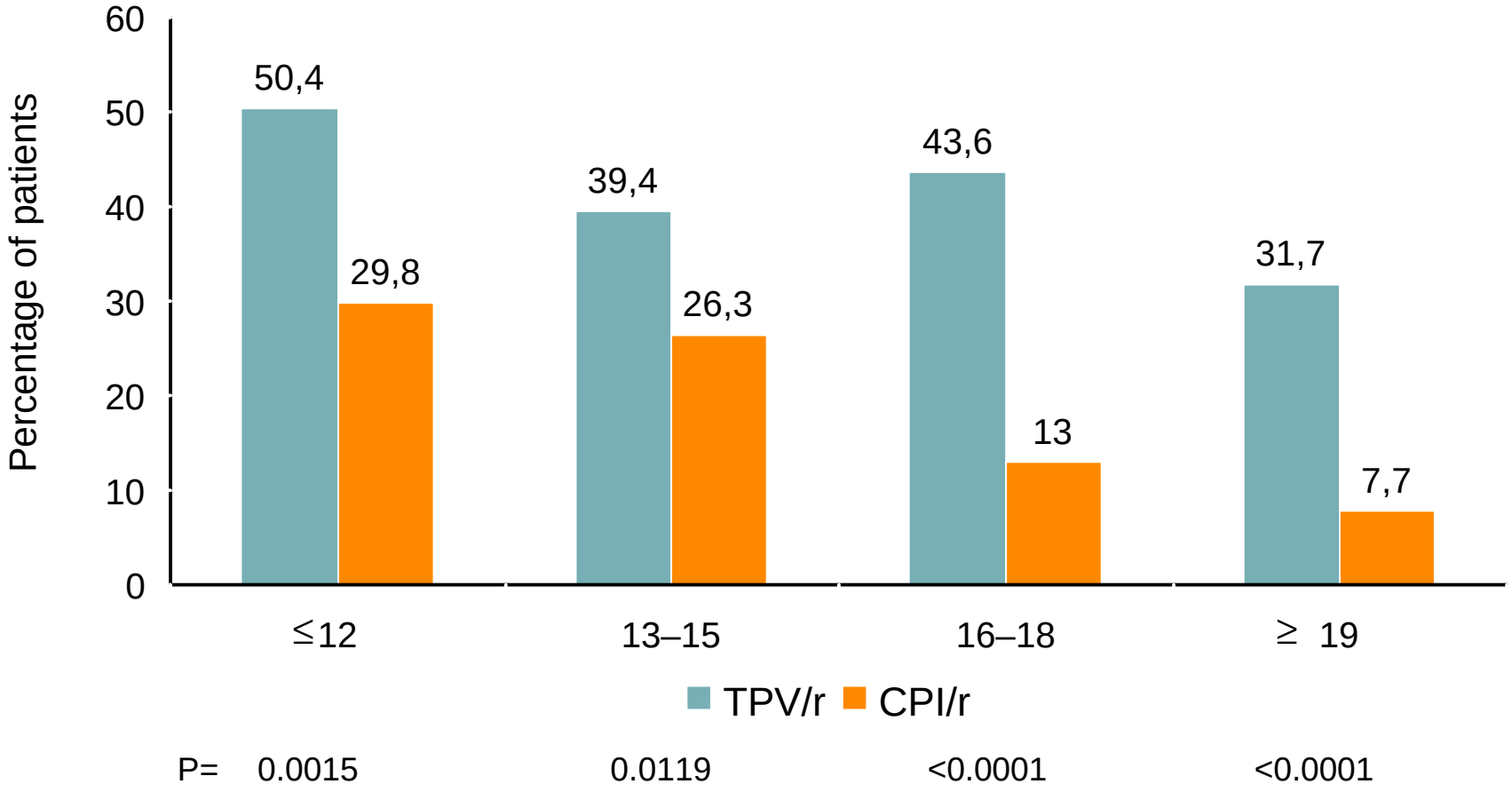


TPV RESIST Studies

Evaluation of baseline genotypic resistance of TPV/r and CPI/r, relative to response

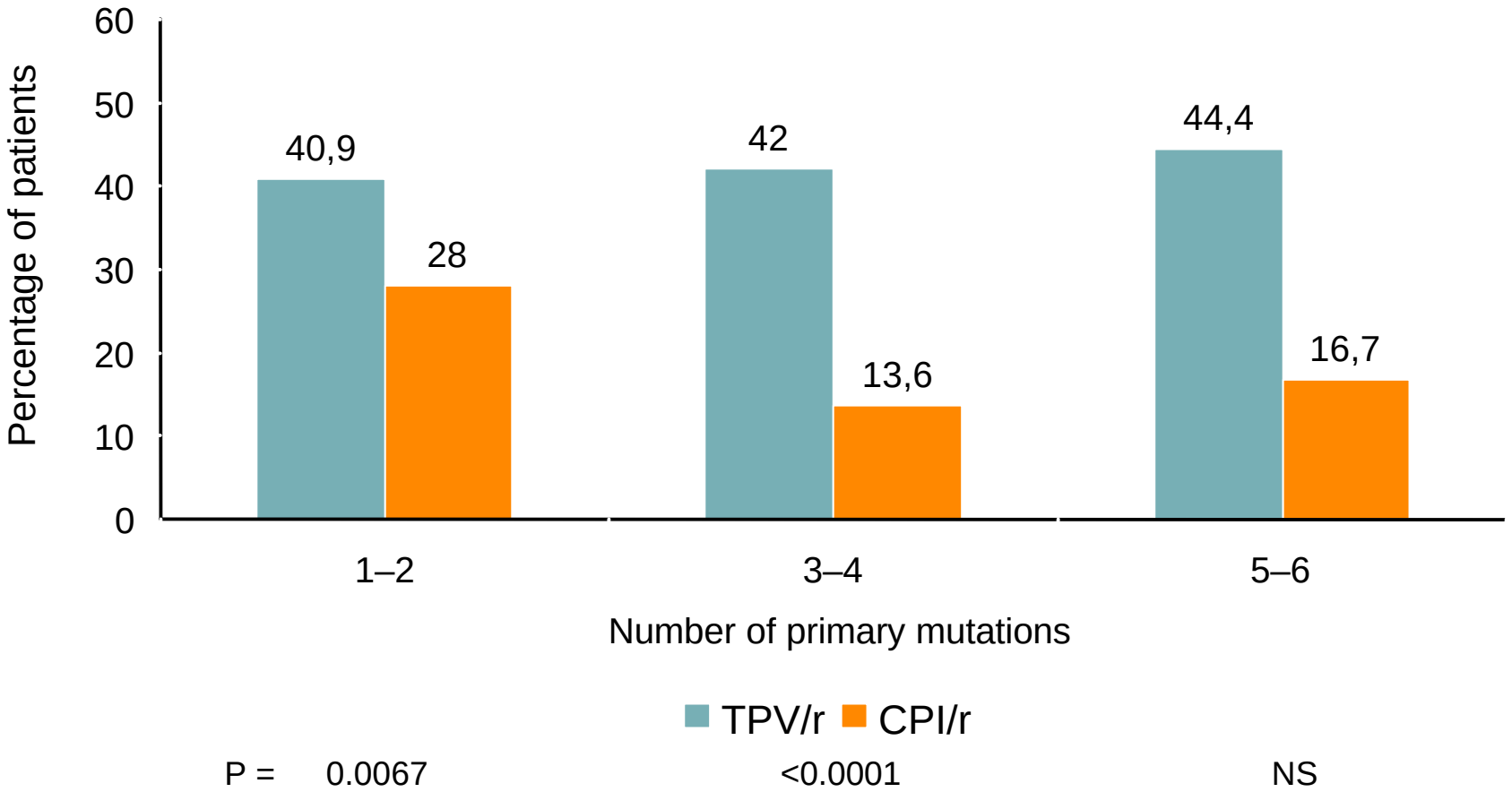
TPV RESIST Studies

Treatment Response at Week 24 According to Baseline Protease Gene Mutations

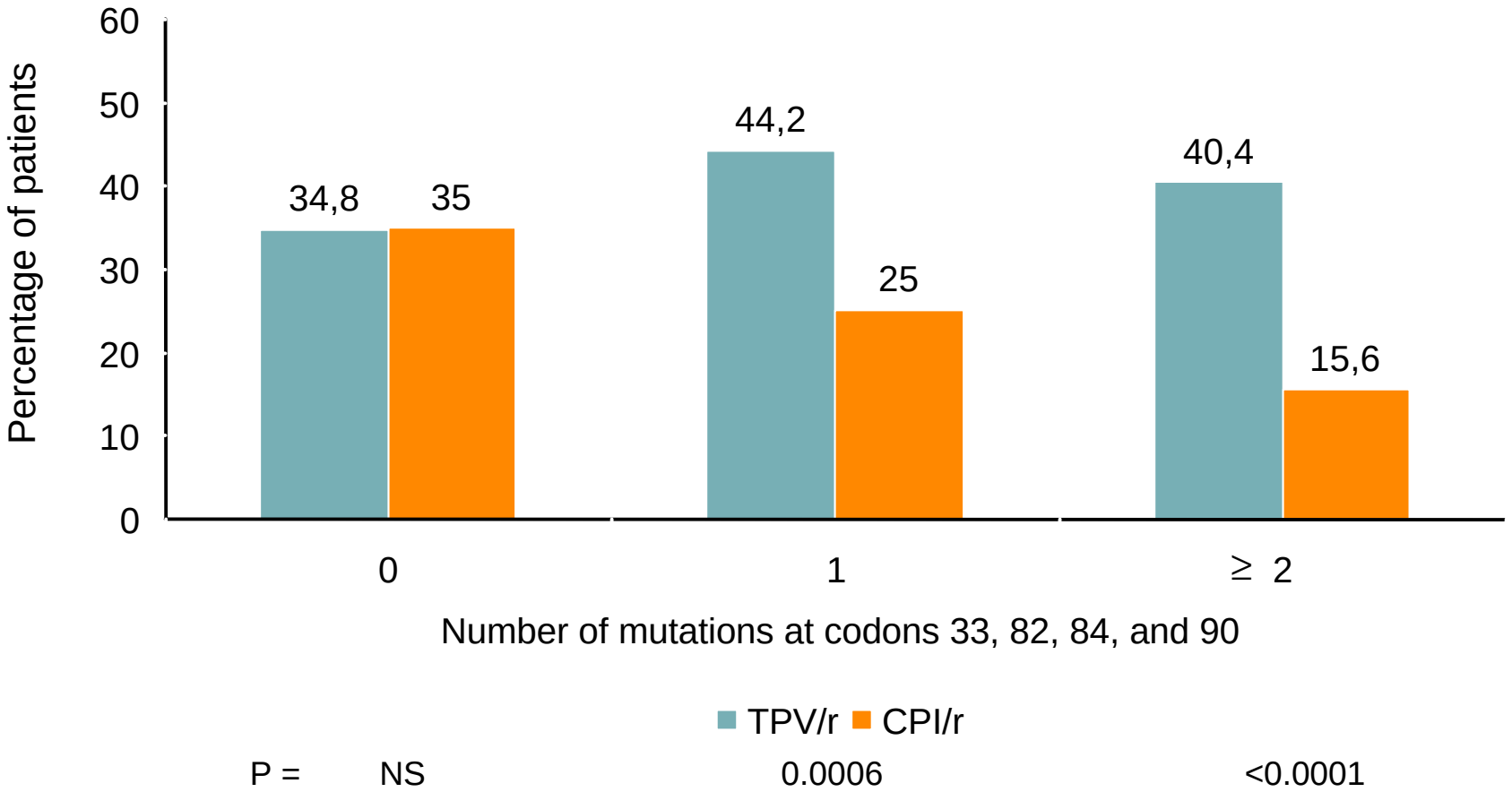


TPV RESIST Studies

Treatment Response at Week 24 According to Baseline Primary Mutations



TPV RESIST Studies
Treatment Response at Week 24 According to Baseline PRAMs



TPV RESIST Studies

Safety

TPV RESIST Studies

Adverse Events in ³5% of Patients

	Treatment groups/No. (%) of patients	
	TPV/r	CPI/r
Total treated	746 (100.0)	737 (100.0)
Total with any AE	615 (82.4)	569 (77.2)
Diarrhea	173 (23.2)	148 (20.1)
Nausea	123 (16.5)	99 (13.4)
Vomiting	61 (8.2)	53 (7.2)
Abdominal pain	44 (5.9)	39 (5.3)
Nasopharyngitis	40 (5.4)	28 (3.8)
Fatigue	70 (9.4)	66 (9.0)
Pyrexia	68 (9.1)	54 (7.3)
Headache	78 (10.5)	54 (7.3)
Rash	40 (5.4)	39 (5.3)
Insomnia	26 (3.5)	37 (5.0)

TPV RESIST Studies
Grade 2–4 Adverse Events

N (%)	TPV/r	CPI/r
Total treated	746 (100.0)	737 (100.0)
Total with any moderate or severe AE	423 (56.7)	374 (50.7)
Diarrhea	81 (10.9)	69 (9.4)
Nausea	50 (6.7)	34 (4.6)
Vomiting	25 (3.4)	22 (3.0)
Abdominal pain	18 (2.4)	14 (1.9)
Bronchitis	22 (2.9)	8 (1.1)
Fatigue	30 (4.0)	29 (3.9)
Asthenia	11 (1.5)	17 (2.3)
Pyrexia	34 (4.6)	32 (4.3)
Headache	23 (3.1)	23 (3.1)
Depression	15 (2.0)	22 (3.0)
Insomnia	9 (1.2)	19 (2.6)
Cough	6 (0.8)	16 (2.2)

TPV RESIST Studies
Grade 3/4 Laboratory Abnormalities

N (%)	TPV/r	CPI/r
Patients with available data	732 (100.0)	726 (100.0)
Hemoglobin	2 (0.3)	2 (0.3)
WBC count (decrease)	26 (3.6)	38 (5.2)
Platelets	6 (0.8)	7 (1.0)
Prothrombin time	6 (0.8)	7 (1.0)
ALT	43 (5.9)	13 (1.8)
AST	29 (4.0)	10 (1.4)
Bilirubin, total	3 (0.4)	4 (0.6)
Alkaline phosphatase	1 (0.1)	1 (0.1)
Amylase	33 (4.5)	42 (5.8)
Lipase	13 (1.8)	14 (1.9)
Total cholesterol	24 (3.3)	2 (0.3)
Triglycerides	152 (20.8)	81 (11.2)
Glucose (increase)	10 (1.4)	6 (0.8)
Creatinine	2 (0.3)	1 (0.1)

TPV RESIST Studies
Conclusions

- For the combined RESIST analyses at 24 weeks, 41.2% TPV/r patients achieved a treatment response compared with 18.9% CPI/r patients (*P*<0.0001)

- TPV/r-based therapy was consistently superior to CPI/r for this patient population regardless of
  - Total baseline protease mutations
  - Number of primary PI mutations
  - Number of PRAMs

- TPV has a high genetic barrier to resistance
  - TPV Maintains activity despite a large number of mutations

RESIST-2
Acknowledgments

Argentina: C Zala, P Patterson, I Cassetti, G Reboredo, J Benetucci, A Casiro, M Losso **Belgium:** N Clumeck, M Moutschen, JC Legrand, B Vandercam, JP Van Vooren, JC Schmit, R Colebunders, E Van Wijngaerden, P Lacor, B Van Der Gucht **Brazil:** B Grinsztejn, M Schechter, O Leite, M Della Nega, A Castello, P Rogerio, V Madruga, RA Sautini, J Mendouca, A Timerman, R Badaró, C Rosenthal, JLA Neto **Denmark:** J Gerstoft, L Mathiesen, CS Larsen, N Obel, AL Laursen **France:** H Gallais, JA Gastaut, P Dellamonica, T May, P Morlat, B Hoen, JM Lang, P Yeni, C Katlama, M Kazatchkine, JM Molina, JF Delfraissy, F Raffi, PM Girard, R Verdon, F Boue, L Cotte, D Vittecoq, W Rozenbaum, M Dupon, C Michelet **Germany:** K Arasteh, F Bergmann, N Brockmeyer, S Esser, G Faetkenheuer, FD Goebel, T Harrer, M Hartmann, E Jägel-Guedes, H Knechten, B Kuhlmann, S Mauss, A Mutz, A Kroidl, A Plettenberg, D Reichelt, J Rockstroh, B Salzberger, RE Schmidt, E Schnaitmann, L Schneider, B Schuster, S Staszewski, A Ulmer, J Rump, J van Lunzen, U Walker, L Weitner **Greece:** N Stavrianeas, M Lazanas, E Giamarellou, A Karafoulidou, V Kiosses, V Papastamopoulos, P Gargalianos, G Panos, G Chryssos, C Bassaris **Ireland:** F Mulcahy, M Horgan **Italy:** F Aiuti,A Antinori, M Arlotti, D Bassetti, P Caramello, A Cargnel, G Carosi, R Cauda, A Chiodera, F Chiodo, A Chirianni, E Concia, G Di Perri, R Esposito, G Filice, F Ghinelli, PA Grossi, A Lazzarin, F Leoncini, F Mazzotta, F Meneghetti, L Minoli, F Montella, M Moroni, AM Orani, G Pastore, N Piersantelli, E Raise, G Rizzardini, G Scalise, ML Soranzo, F Suter, A Vaglia, G Vigevani, V Vullo **Mexico:** C Cano, M Jauregui, P Lopez, L Nieto, C Rivera, E Zapata **Netherlands:** ME van der Ende, K Brinkman, JH ten Veen, PL Meenhors, SA Danner, R Vriesendorp, A van Eeden, G Schreij, HG Sprenger, PP Koopmans **Portugal:** F Antunes, A Melico-Silvestre, M Miranda, K Mansinho, J Vera **Spain:** B Clotet, JC López, Bernaldo de Quirós, D Podzamczer, J González Lahoz, E Ribera, M Gurguí, P Viciana, E Ortega, J Portilla, H Knobel, JA Iribarren, A Rivero, J López Aldeguer, M Márquez, J Vergas, A Ocampo, JM Peña, R Rubio, S Moreno, JM Gatell **Sweden:** A Blaxhult, M Gisslén, L Flamholc **Switzerland:** M Battegay, M Opravil, P Vernazza, B Hirschel **United Kingdom:** I Alexander, C Bignall, H Birley, P Easterbrook, M Fisher, B Gazzard, V Harindra, P Hay, M Johnson, S Khoo, GR Kinghorn, R Kulasegaram, C Leen, M Murphy, M Snow, J Weber, D White, E Wilkins, M Wiselka, C Wood **Expert Resistance Panel:** J Baxter, C Boucher, J Schapiro **Boehringer Ingelheim:** J Villacian, R Chaves, I Fleming, V Kohlbrenner, D Mayers, S McCallister, D Neubacher, MA Quinson

TPV RESIST Studies
Conclusions—Safety

- Types of adverse events reported with TPV/r and CPI/r arms were similar
- TPV/r arms had a higher rate of overall and Grade 2–4 adverse events
- Grade 3 or 4 ALT or AST elevations more common in patients on the TPV/r arms
  - Mostly asymptomatic: most patients able to continue without permanent discontinuation
- Grade 3 or 4 plasma lipid elevations more common in patients on the TPV/r arms

RESIST-2
Conclusions—Efficacy

- After 24 weeks, TPV/r was superior to CPI/r:

Treatment response	41.0% vs 14.9%	$P < 0.001$
Change in VL	-0.72 $\log_{10}$ vs -0.22 $\log_{10}$	$P < 0.0001$
% <400 copies/mL	33.6% vs 13.1%	$P < 0.0001$
% <50 copies/mL	22.5% vs 8.6%	$P < 0.0001$
Change in CD4+ cell count	+31 cells/mm^3 vs +1 cells/mm^3	$P < 0.022$

- TPV/r treatment response was improved with use of other active ARV drugs in the OBR
  - ENF
  - NRTIs/NNRTIs