Entecavir Maintains a High Genetic Barrier to HBV Resistance Through 6 Years in Naïve Patients

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Disclosures

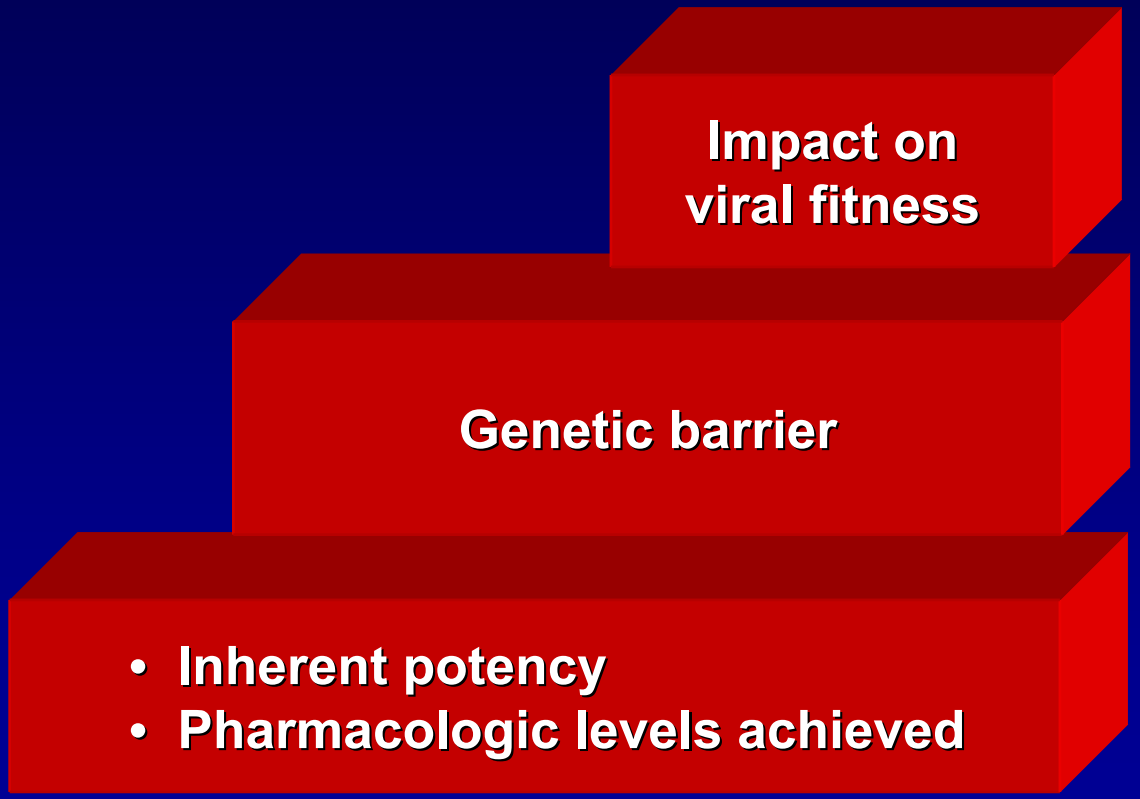
- I am a full-time employee of Bristol-Myers Squibb;
- Data presented are from trials in the entecavir development program

Primary Factors in Antiviral Resistance

Fitness –
replication capacity of viral variants

Genetic Barrier –
number of substitutions required for resistance

Clinical Efficacy –
Reflects intrinsic drug potency and dose administered



ETV Genotypic Resistance: Population Screening

- 2 cohorts: Naïve and LVD-refractory
  - All patients with continuous ETV >12 wks
- Genotype performed:*
  - All baseline specimens
  - If HBV DNA ≥ 300 c/mL (50 IU/mL) at
    - Annual timepoint (Wks 48, 96, 144, 192, 240, 288)
    - End of Dosing
  - If virologic breakthrough while on treatment (confirmed ≥1 log increase in HBV DNA from nadir)

* consistent with monitoring recommendations in Pawlotsky et al, Gastroenterology 2008

ETV Genotypic Resistance: Rate Calculation

- Genotypic resistance to ETV requires both:

  LVD resistance (M204I/V ± L180M), and

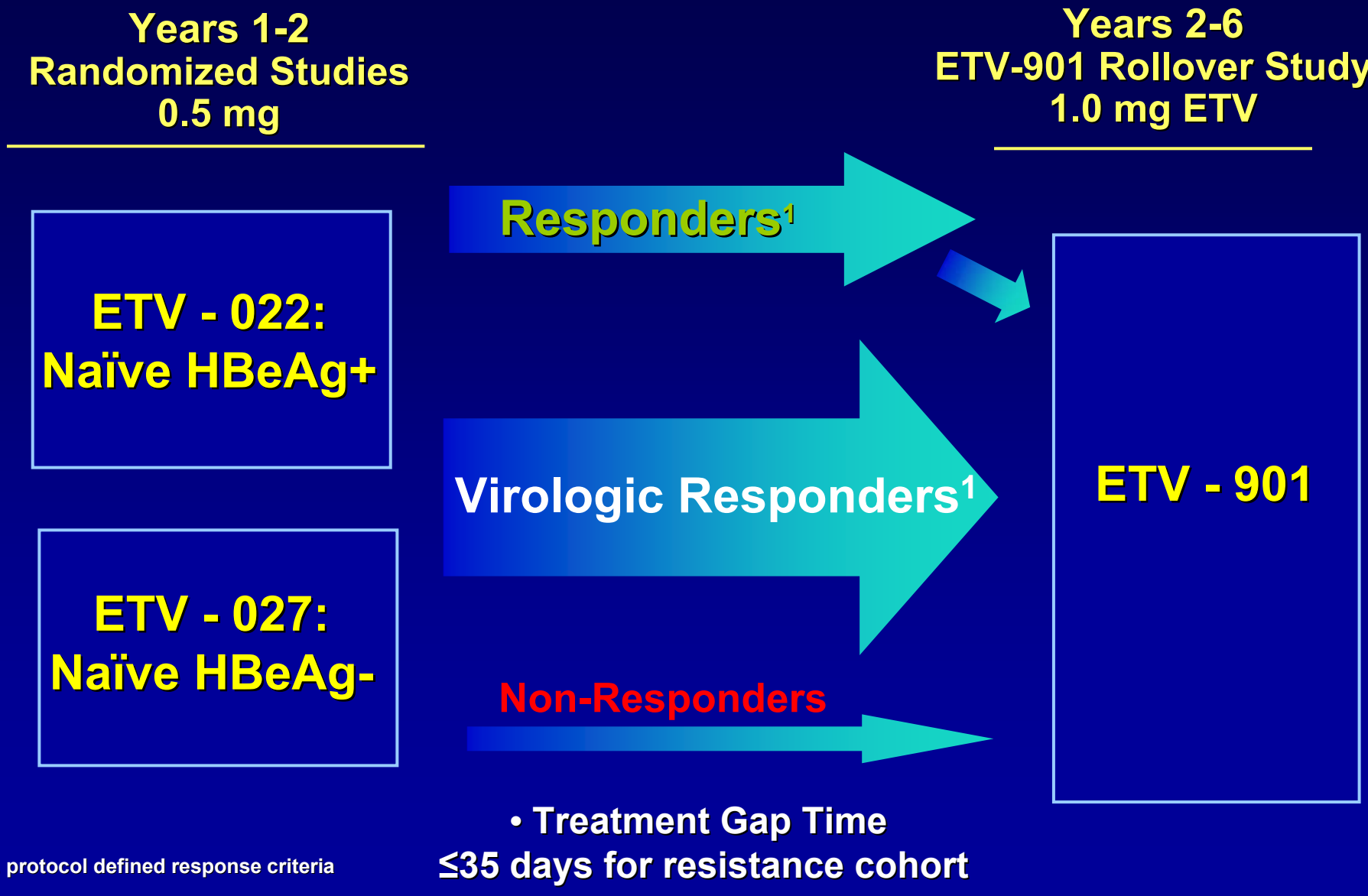
  ETV-specific change (T184, S202 or M250)

- Cumulative probability*

  $P = 1-(1-n1/N1)(1-n2/N2)\ldots(1-nx/Nx)$

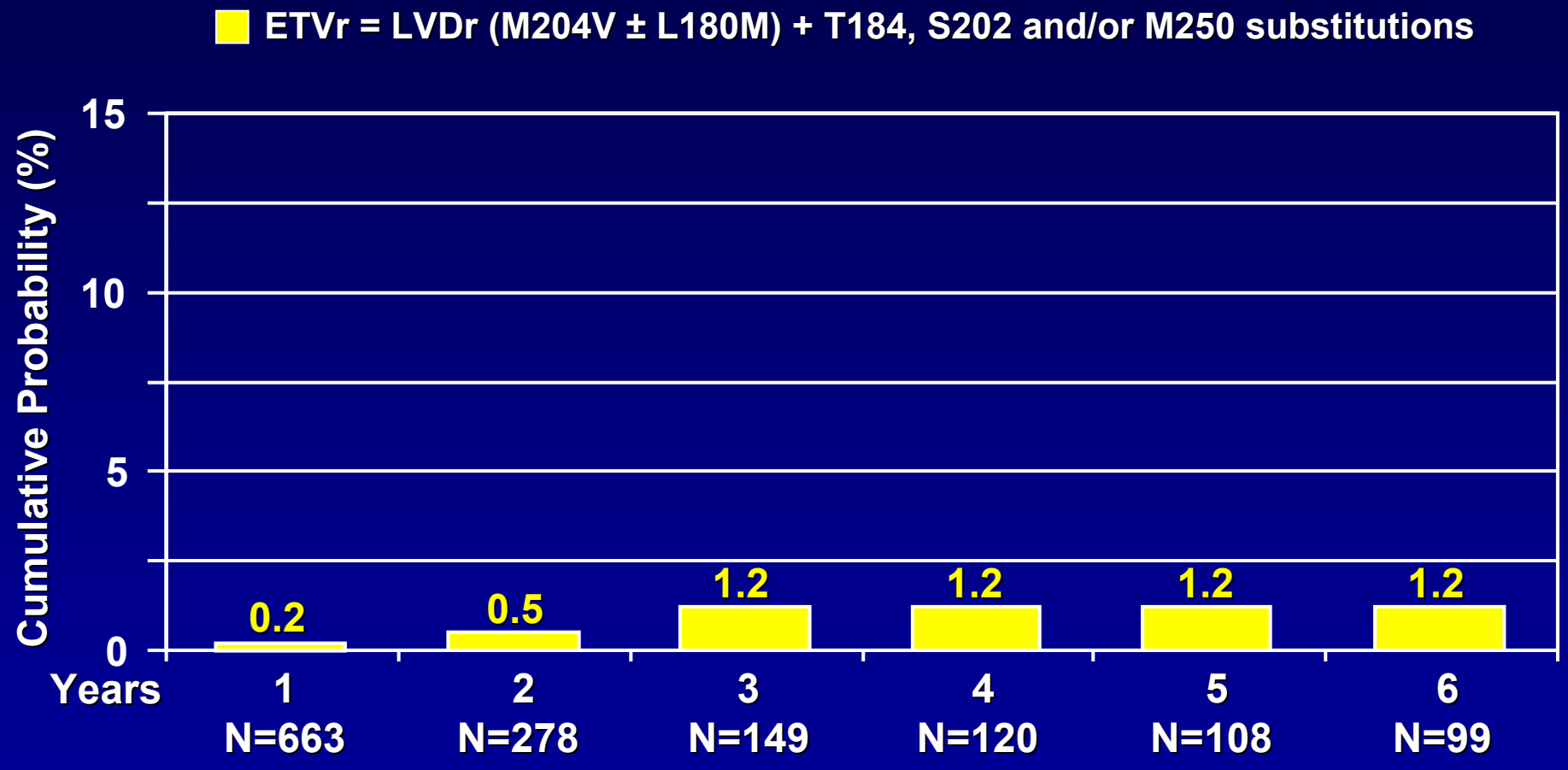
* consistent with monitoring recommendations in Pawlotsky et al, Gastroenterology 2008

ETV 6-Year Program: Naïve Patient Flow



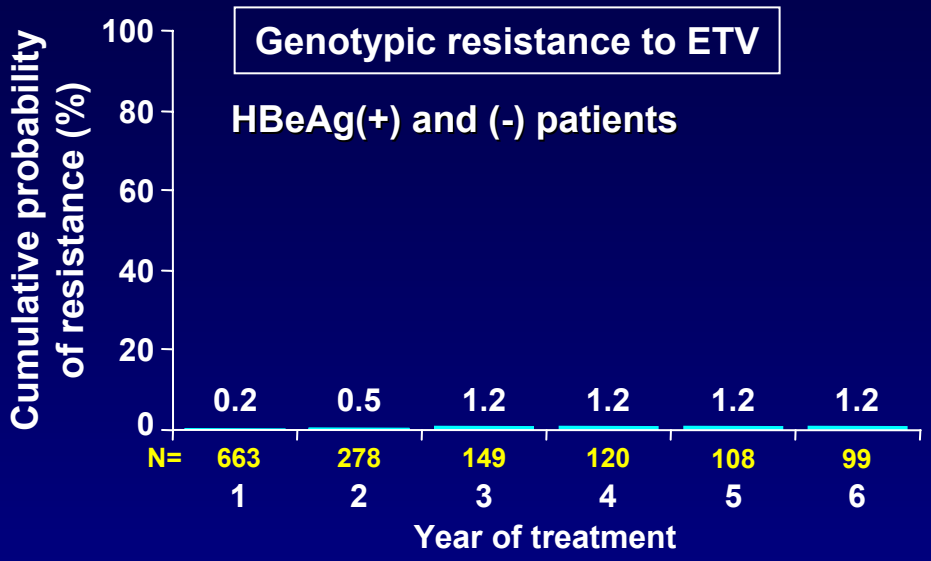
1. protocol defined response criteria

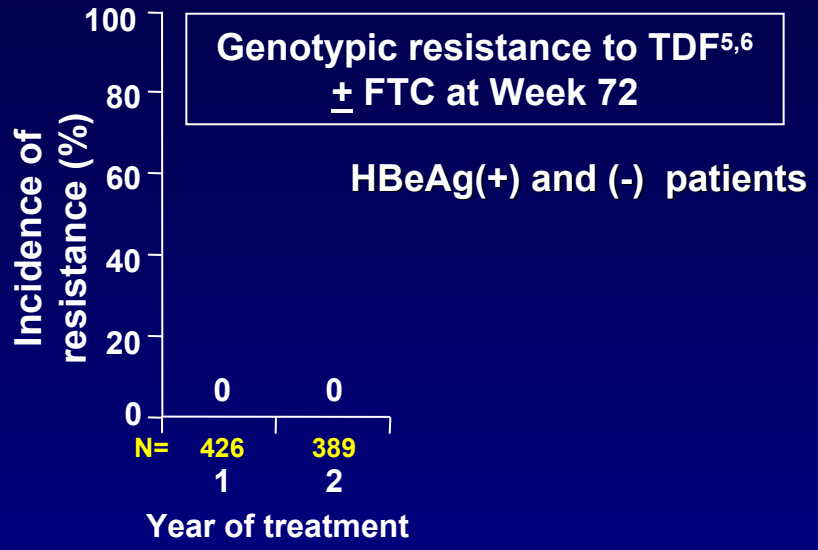
Nucleoside-Naïve Cohort (HBeAg+ & HBeAg-): Cumulative Probability of ETV Resistance Through 6 Years

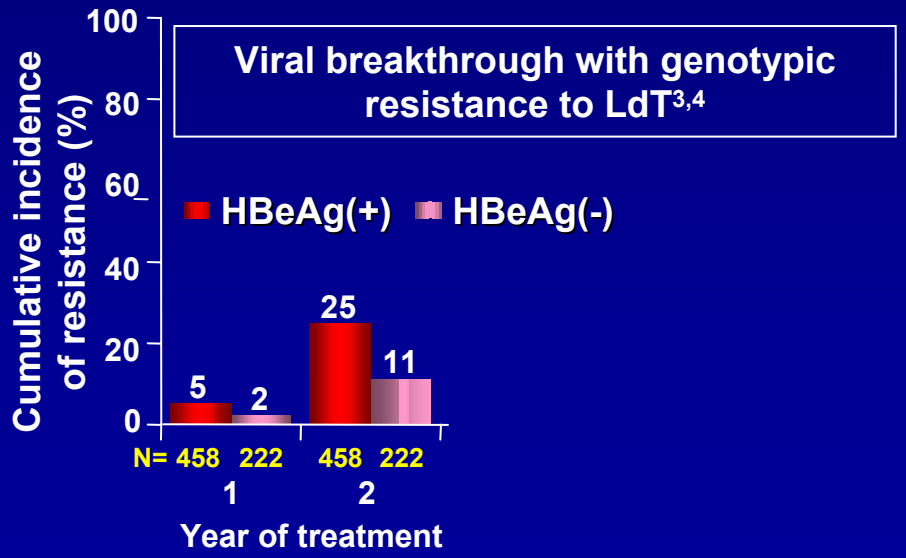


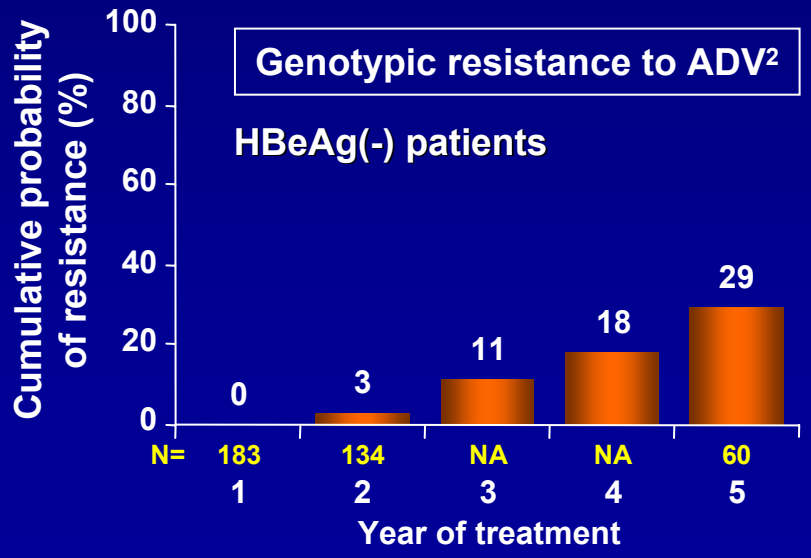
- HBV DNA <300 c/mL in 94% of patients in Year-6 (N = 99)
- HBV DNA <300 c/mL at last on-treatment visit in 89% of those discontinuing

Resistance Rates Across Studies in Nucleoside-Naïve Patients





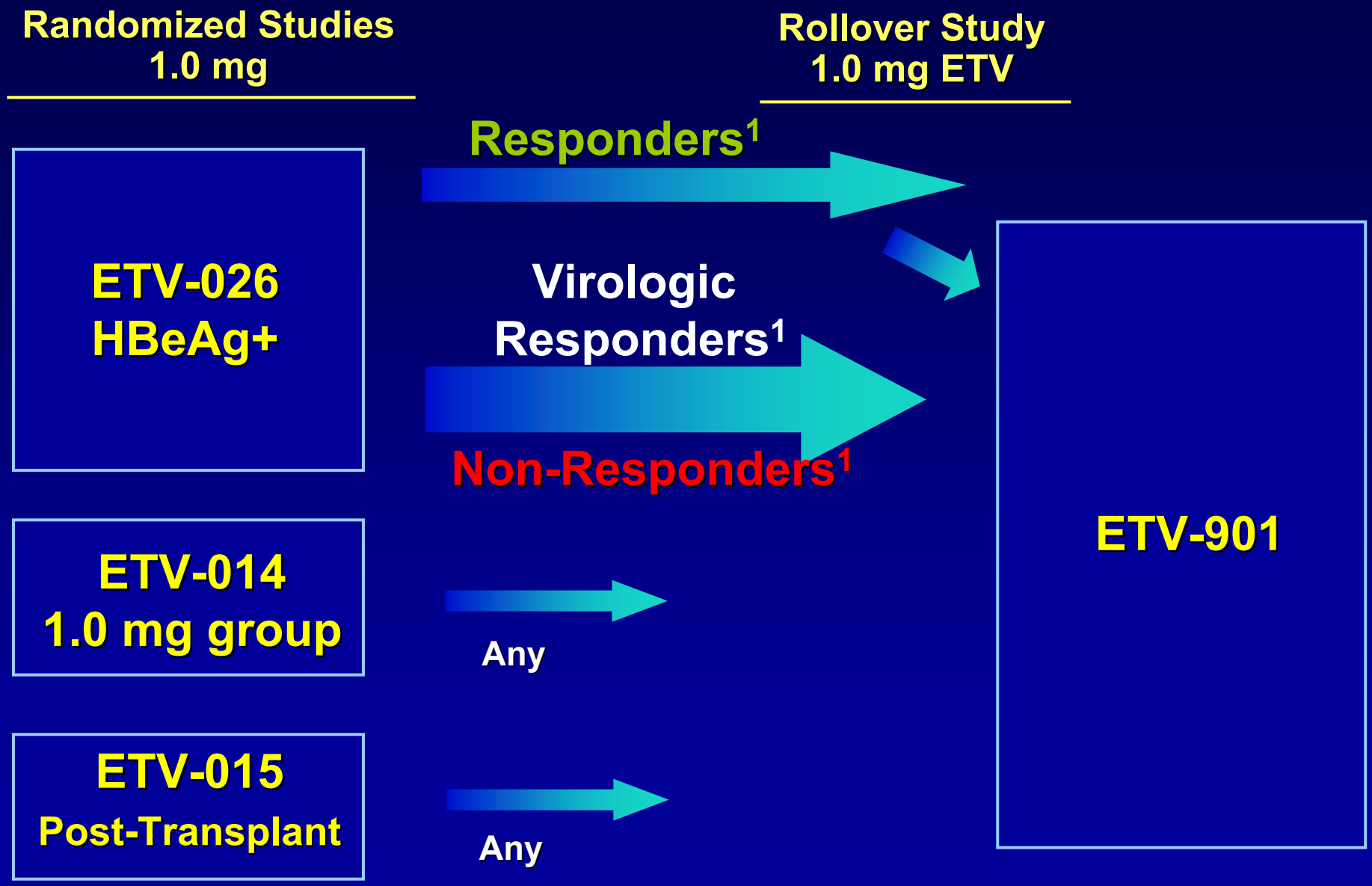




1. Chang TT, et al. *J Gastroenterol Hepatol* 2004;19:1276-1282; 2. Hadziyannis S, et al. *Gastroenterology* 2006;131:1743-1751; 3. Lai CL, et al. *N Engl J Med,* 2007;357:2576-2578; 4. Liaw YF, et al. Gastroenterology 2009;136:486-495. 5. Marcellin P, et al. *N Engl J Med* 2008;359:2442-2455; 6. Snow-Lampart A, et al. *Hepatology* 2008;48(suppl.): 745A.

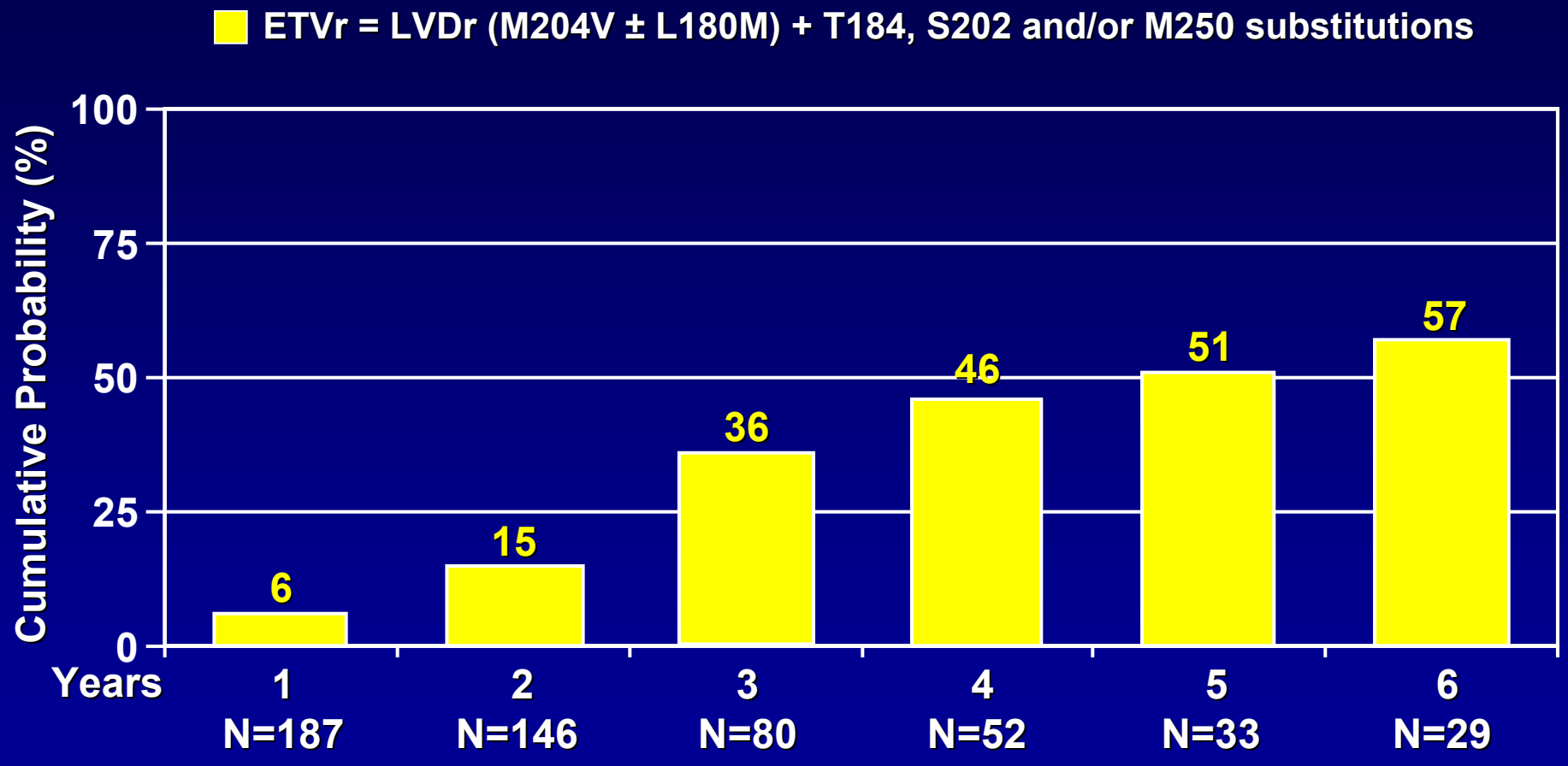
Lamivudine-Refractory Patients

Lamivudine Refractory – Patient Flow



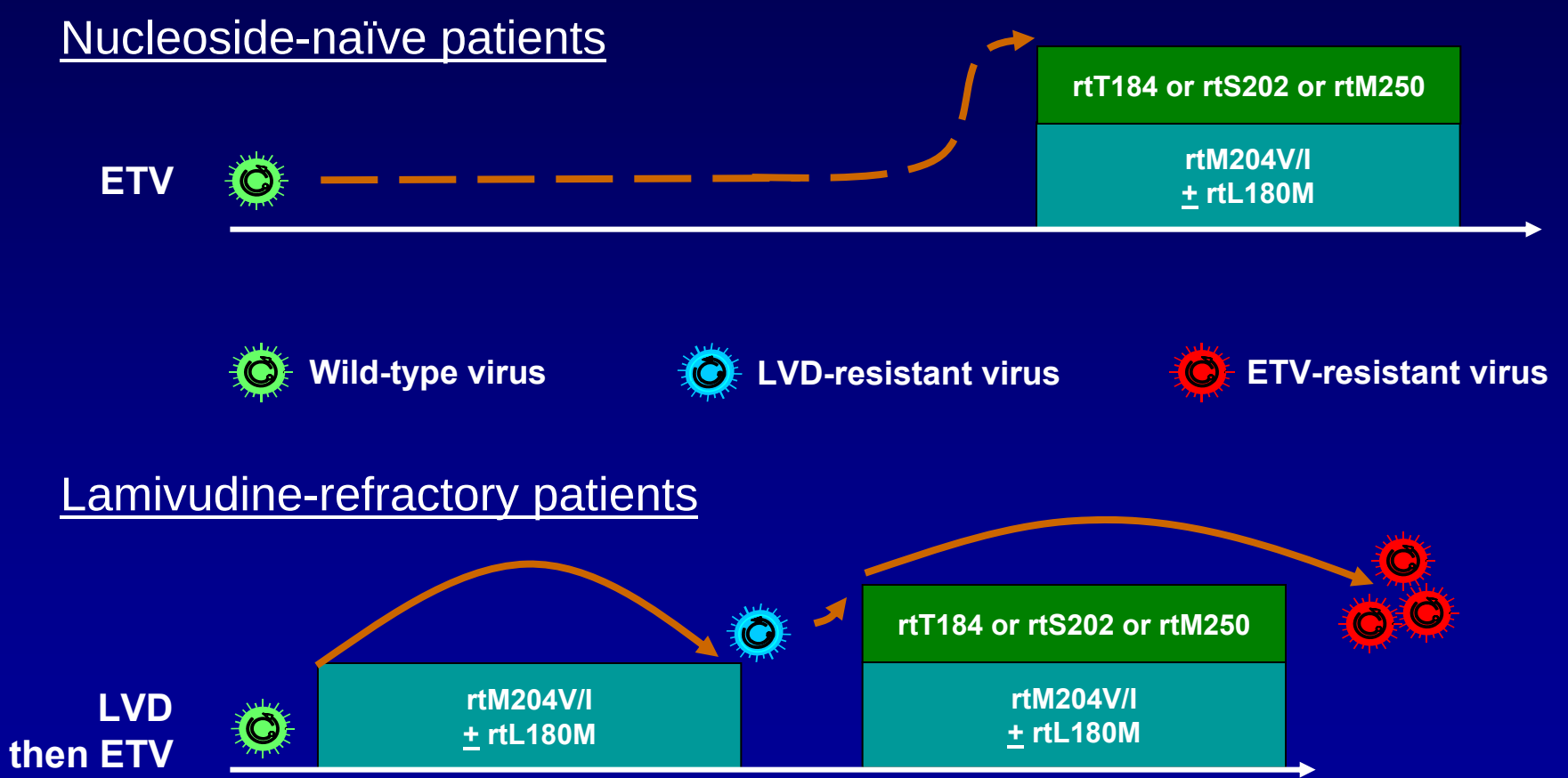
1. protocol defined response criteria

Lamivudine-Refractory Cohort (HBeAg+): Cumulative Probability of ETV Resistance Through 6 Years



- 74/187 (40%) achieved HBV DNA <300 copies/mL
- 5/74 (7%) with HBV DNA < 300 c/mL had subsequent genotypic ETV resistance

Genetic Barrier to Entecavir Resistance



Baraclude® (entecavir) Summary of Product Characteristics. Bristol-Myers Squibb Pharma EEIG. January 2008

Entecavir Resistance Through 6 Years

Nucleoside-Naïve:

- ETV has high potency and high genetic barrier
- Resistance is rare through 6 years
  - 1.2% genotypic resistance

LVD-refractory:

- ETV potency and genetic barrier are reduced
- Incremental increase in resistance over time
- Favorable prognostic subgroups can be identified by early response to treatment and lower baseline HBV DNA (< 10^7 copies/mL)

Acknowledgements

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- >850 patients and
- >340 investigators from
- 30 countries

Participating in studies:

  - ETV-014, ETV-015, ETV-022, ETV-026, ETV-027 and ETV-901