GMA Advisory Board

Paroxysmal nocturnal hemoglobinuria (PNH)

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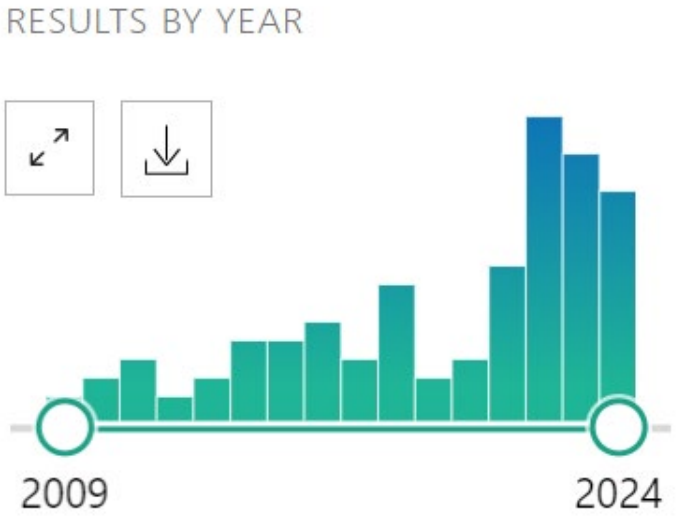
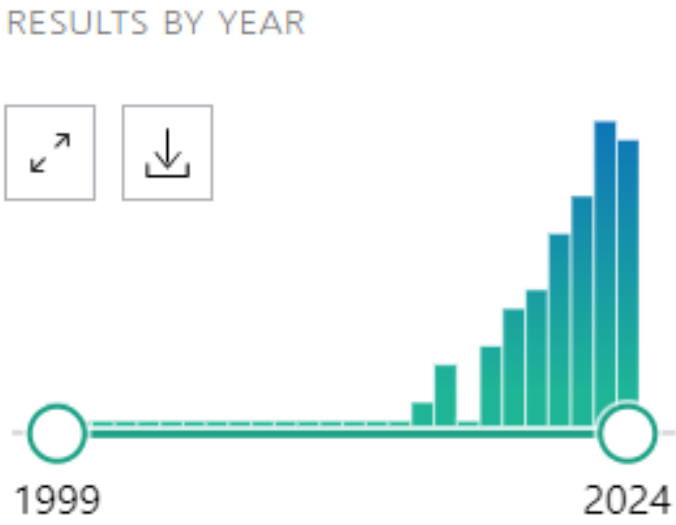
EVH and clincally significant (cs) EVH / intravascular hemolysis

- Overview of EVH and csEVH
  - Definition(s) – compare and contrast across clinical trials
  - Diagnostic criteria + Coombs test
  - German guidelines + overall approach for managing patients who remain anemia / transfusion dependent while on C5i



N=75

search terms: „extravascular hemolysis“ AND „PNH“ and „complement“



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search terms: „intravascular hemolysis“ AND „PNH“

C5i treatment: persistent anemia in a substantial proportion of patients

Reason	timing	Concomitant condition	Mechanism	Intervention
Pharmakokinetic breakthrough	>10 d from ecu dose	None required May be aggravated by coincident infection	Free C5 > 0.5 µg/l	decrease dosing interval or increase dose (1.200 mg) or switch to **ravulizumab**
Pharmakodynamic breakthrough	any time	Complement activating condition (infection, surgery, pregnancy)	Usually free C5 <0.5 µg/l Massive complement activation → dense C3b deposits, C5 conformational change („priming“) which can bypass C5i	**Treat underlying condition** Combination of C5 inhibitors (in-vitro) switch to an **inhibitor of the alternative pathway**
Shift to extravascular hemolysis (EVH)	any time	None required, Inherent problem of single-agent C5i, interindividual variability	PNH cell lack CD55 as regulator of C3, AP activation insufficently controlled at the level of C3 C5i do not block at this level, → C3b coating of red blood cells → EVH	Alternative pathway inhibitors: **C3 inhibitor** (**Pegcetacoplan**; approved for this indication); **Factor D inhibitor**: **Danicopan** (in combination with C5i) **Factor B inhibitior**: **Iptacopan** (single agent)
Resistance to ecu/ ravu	Tx start	C5-Polymorphism p.Arg885His	Eculizumab / ravulizumab can not bind to C5 (3.5% in Japan, very rare in Europe)	Other inhibitors.
Bone marrow failure	any time	Aplastic anemia	Insufficient reticulocyte production	Treatment of aplastic anemia: IS or SCT

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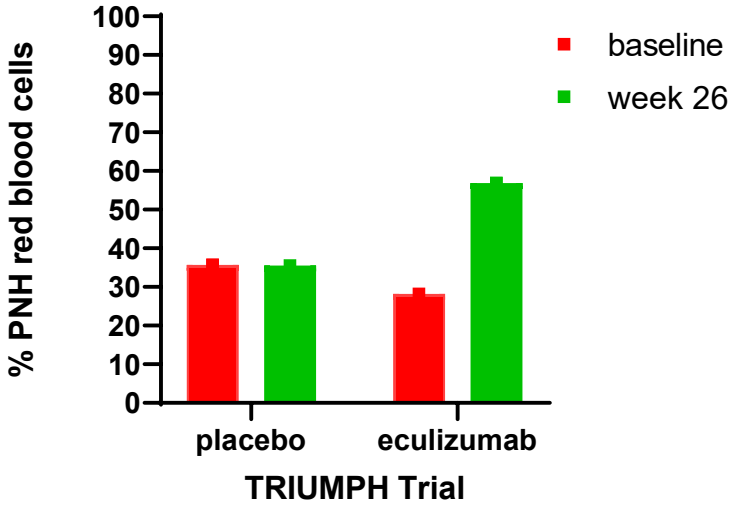
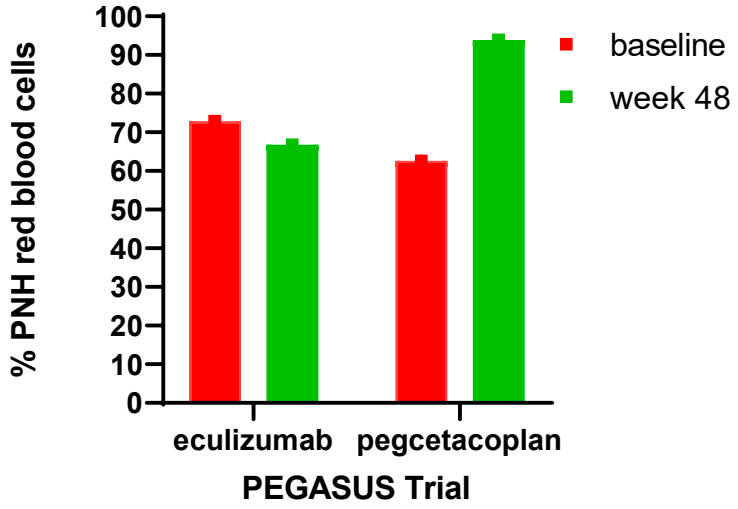
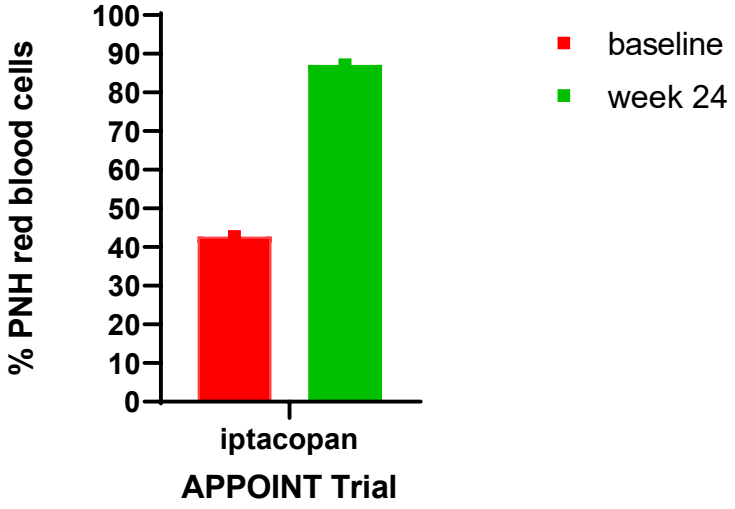
Definition of breakthrough

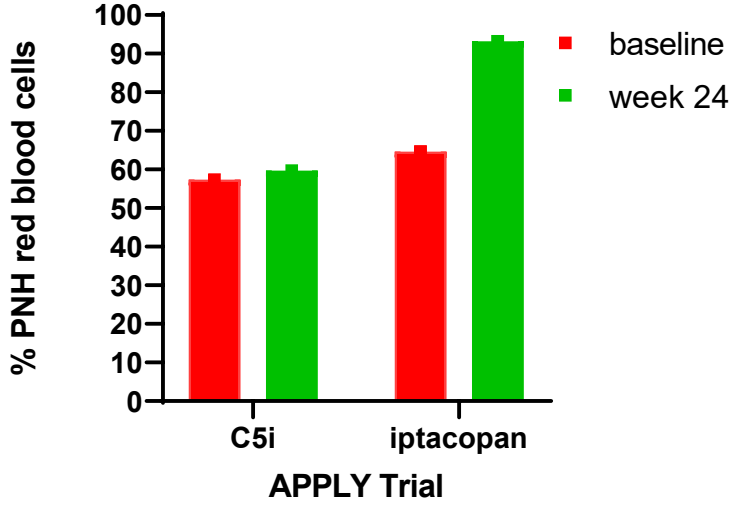
Definition of extravascular hemolysis in PNH?

PNH Clone Size in untreated and complement inhibitor treated patients









ALPHA Trial:

C5i vs. C5i + placebo: RBC clone size 27.6 mean difference

Increase of RBC red clone size

- by C5i treatment (blockade of IVH) to about 60%
- by proximal inhibition (i.e. additional blockade of EVH) to about 90%

→ Risk of massive breakthrough hemolysis in case of loss of control of complement activation in patients under proximal inhibitors

  - large clone size
  - C3 amplification loop

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Definition of breakthrough

-→ see presentation Bruno Fattizzo.

Paroxysmal nocturnal hemoglobinuria (PNH)
Definition of breakthrough hemolysis (BTH)

- There is a **common understanding of breakthrough hemolysis**

BUT

- there are differences in the definitions of BTH which were used in studies so far.
- need for a common definition of breakthrough hemolysis
  (note: a) should include also description whether it is BTH during proximal/terminal/combined complement inhibition.
  b) the baseline values (before BTH) should be considered (in addition to the absolute increase of LDH or drop in Hb).
  c) the cause of BTH should be included (complement amplifying condition; dosing problems / compliance regarding intake of oral proximal inhibitors); BTH without identifiable cause.

- BTH definition (yes /no) is not sufficient:
  In addition, a classification of severity is required – both
  - to guide management
  - to better compare outcome after different management

  The severity classification should take into account:
  - clinical symptoms of BTH
  - complications of BTH (e.g. breakthrough thrombosis)
  - Intervention required to control BTH (dose escalation, rescue doses of another drug or switch to another drug)
  - Duration of BTH