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Will the latest genetic discoveries have an impact on clinical management in ET and PMF?

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Phenotypic driver mutations in MPNs

Gene/hotspot	PV	ET	PMF
JAK2 V617F	93-95%	53-64%	58-65%
JAK2 exon12	2-4%	0	0
MPL W515	0	3-5%	4-8%
CALR	0	16-33%	21-25%
"Triple negative"	3-5%	12-16%	9-11%

Tefferi A, *et al. Am J Hematol.* 2014;E121-4;epub; Andrikovics H, *et al. Haematologica.* 2014;99:1184 -1190; Gangat N, *et al. Eur J Haematol.* 2014;epub; Chen CC, *et al. Ann Hematol.* 2014;epub; Rotunno G, *et al.Blood.* 2014;123:1552-5; Rumi E, *et al. Blood.* 2014;123:1544-51; Rumi E, *et al. Blood.* 2014;epub; Klampfl T *et al. N Engl J Med*. 2013; 369:2379 – 90.

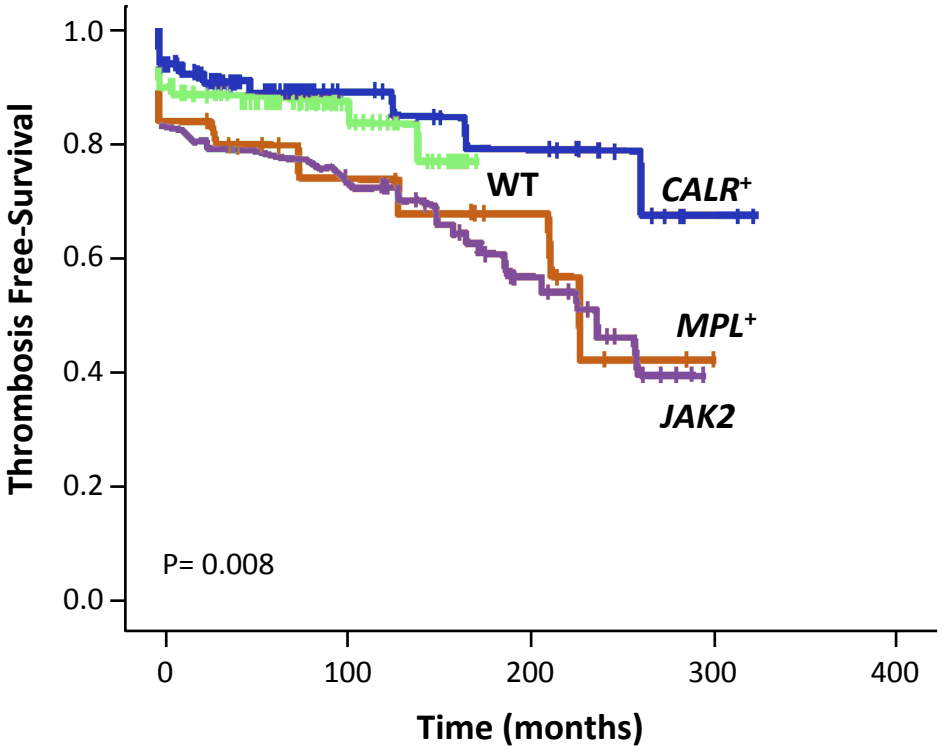
Clinical correlates of the *CALR* mutation in ET

- ***CALR* mutated subjects (compared with *JAK2* V617F mutated)*:**
  - Are younger [1- 4]
  - Are male in prevalence [5,6]
  - Have higher platelet count [2-9]
  - Have lower leukocyte count [1 - 5, 8, 9,]
  - Have lower haemoglobin [2, 4, 5, 7, 8, 9]
  - Have lower rate of transformation to PV [5]
  - Have similar rate of evolution to PET-MF [3, 5]
  - Have similar rate of transformation to AML[10]
  - Have similar overall survival [10]

***Some variability was found in a large majority of studies reported**

1.Rumi E, *et al. Blood.* 2014; 123:1544-51;2. Tefferi A, *Leukemia.* 2014;28:1494-1500; 3. Chen CC, *et al. Ann Hematol* 2014;epub; 4. Qiao C, *et al. Haematologica.* 2014; epub; 5. Rotunno G, *et al. Blood.* 2014; 123:1552-5; 6. Gangat N, *et al. Eur J Haemtol* 2014; epub; 7. Nangalia J, *et al. N Engl J Med*. 2013; 369:2391-405; 8. Klampfl T *et al. N Engl J Med*. 2013; 369:2379 – 90; 9. Tefferi A, *et al. Am J Hematol.* 2014;E121-4; epub; 10. Andrikovics H, *et al. Haematologica.* 2014; 99:1184 -1190;

CALR mutated ET patients have lower rate of thrombosis



Adapted from Rotunno G, *et al. Blood.* 2014; 123:1552-5

	HR	95% CI
JAK2 mut	1.78	1.06-3.18
MPL mut	1.65	1.70-3.92
CALR mut	0.74	0.33-1.00

N.B. Wild type patients were taken as a reference population

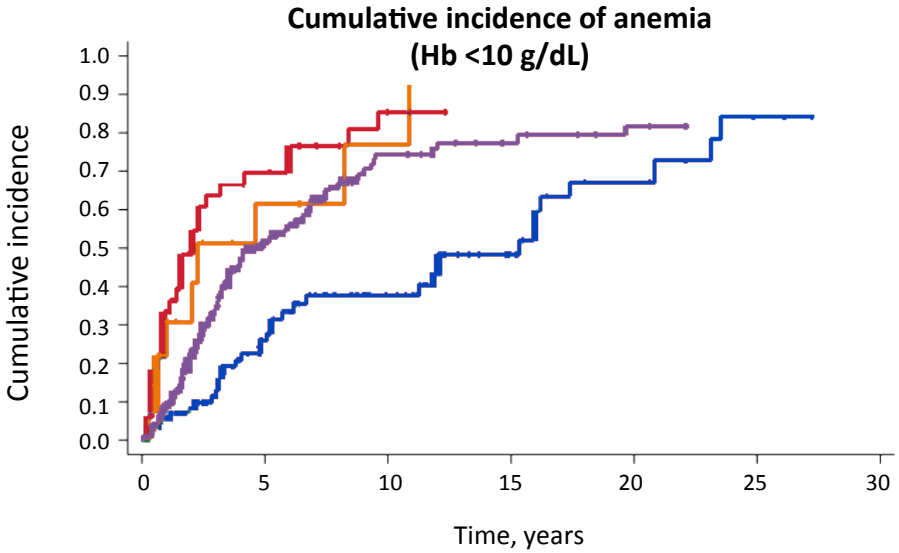
HR-Hazard ratio

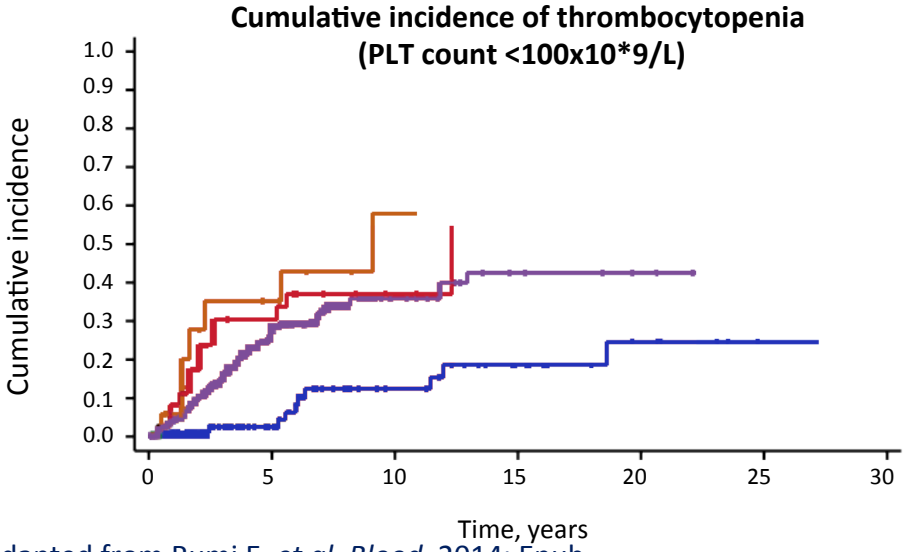
Adapted from Rotunno G, *et al. Blood.* 2014; 123:1552-5

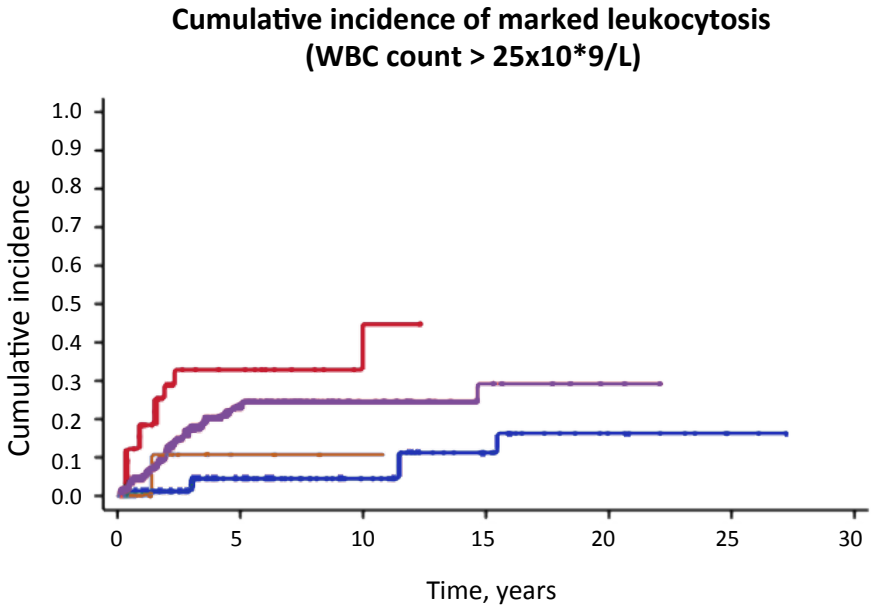
- Triple-negative patients may be at a very low risk of thrombosis, and the effect of the *CALR* mutation may be particularly evident in younger patients

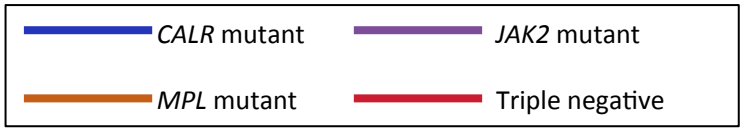
Gangat N, *et al. Eur J Haemtol* 2014; epub;

CALR mutated PMF is a milder disease than *JAK2* V617F or *MPL* W515 mutated or Triple Negative



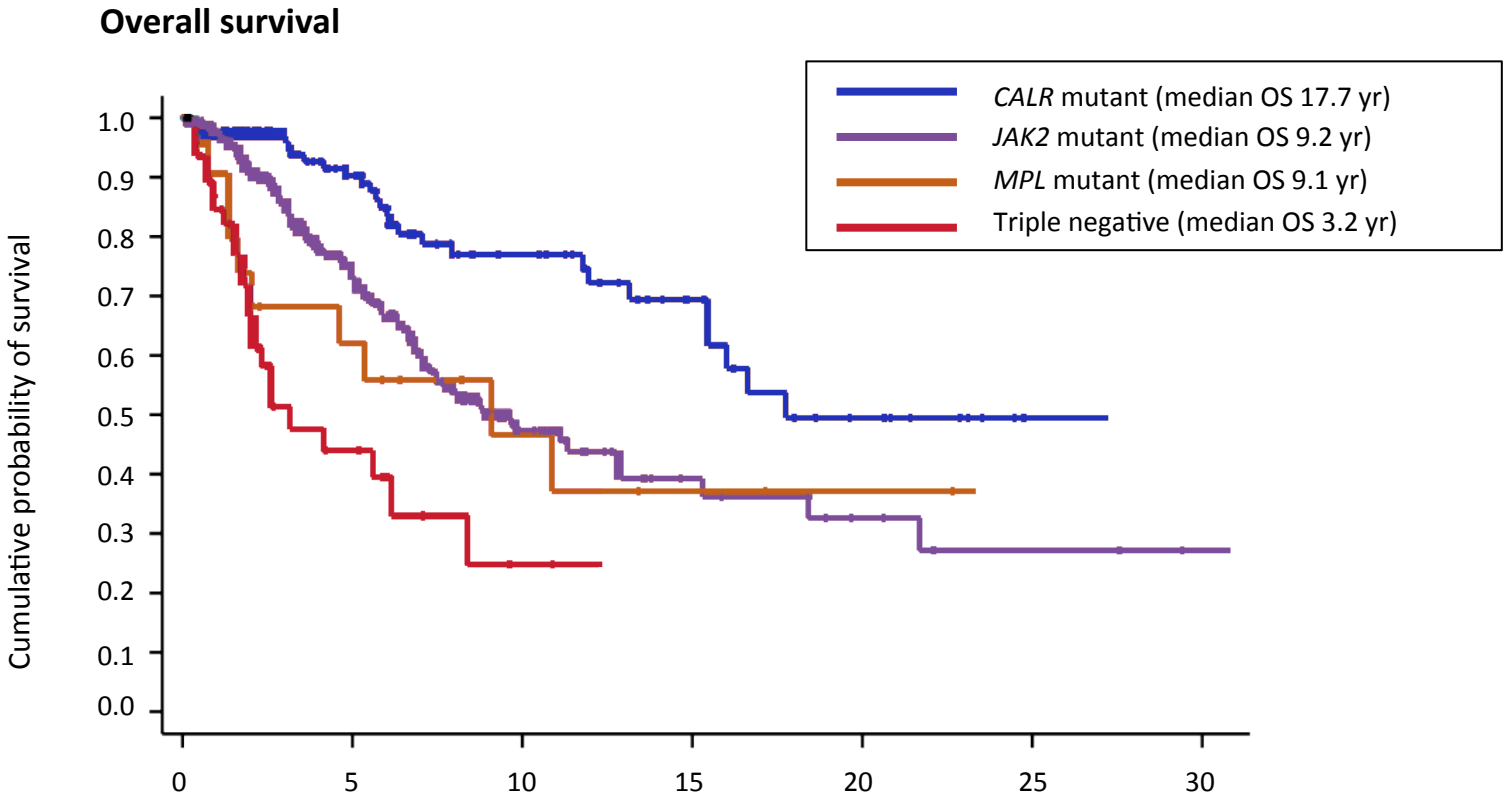






Adapted from Rumi E, *et al. Blood.* 2014; Epub

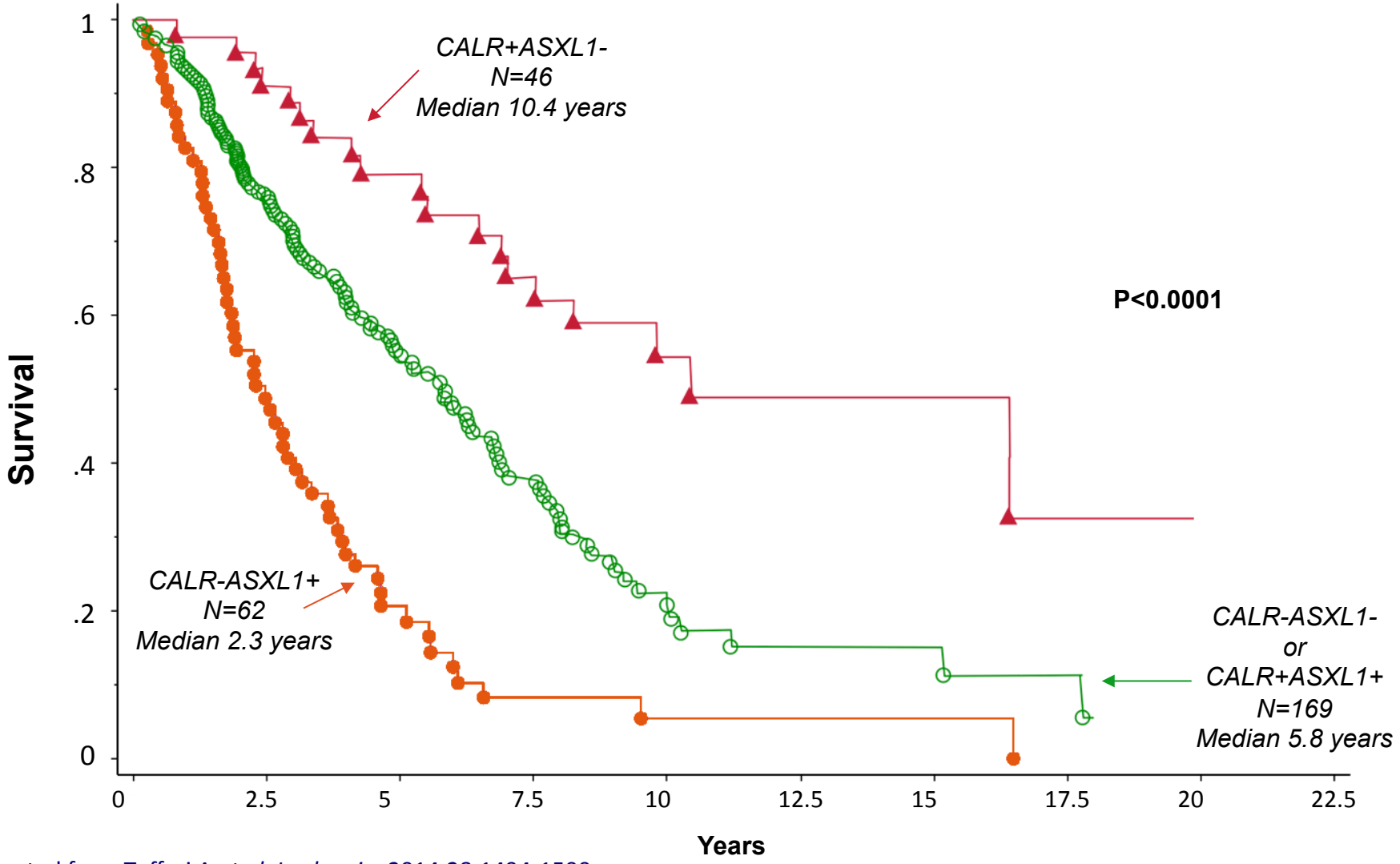
Phenotype driver mutations have a strong prognostic impact in PMF



No. of patients at risk:						
CALR mutant	140	72	37	19	9	1
JAK2 mutant	396	135	39	13	7	3
MPL mutant	25	10	5	3	2	0
Triple negative	53	11	2	0	0	0

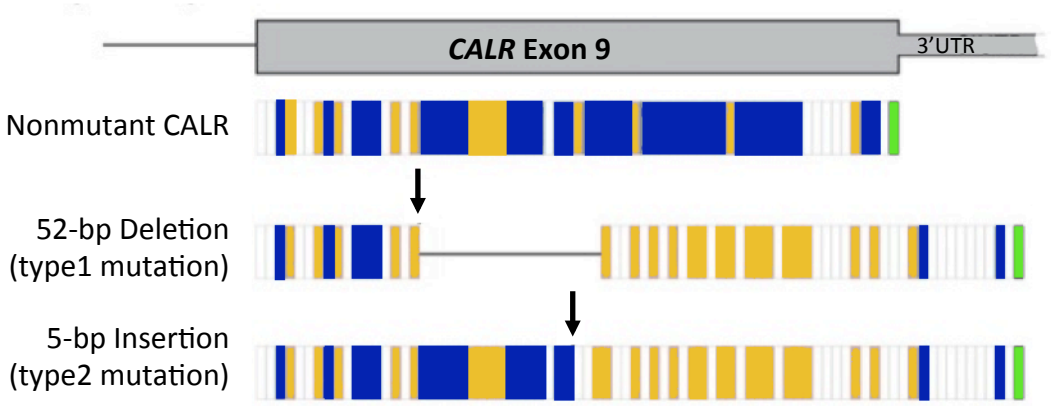
Adapted from Rumi E, *et al. Blood.* 2014; Epub

CALR mutation contributes to risk stratification in PMF with subclonal mutations (*ASXL1*)

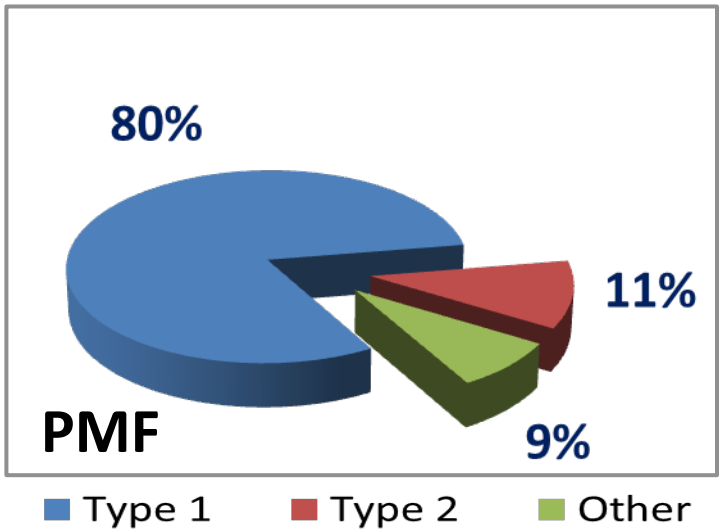


Adapted from Tefferi A *et al*. *Leukemia.* 2014;28:1494-1500

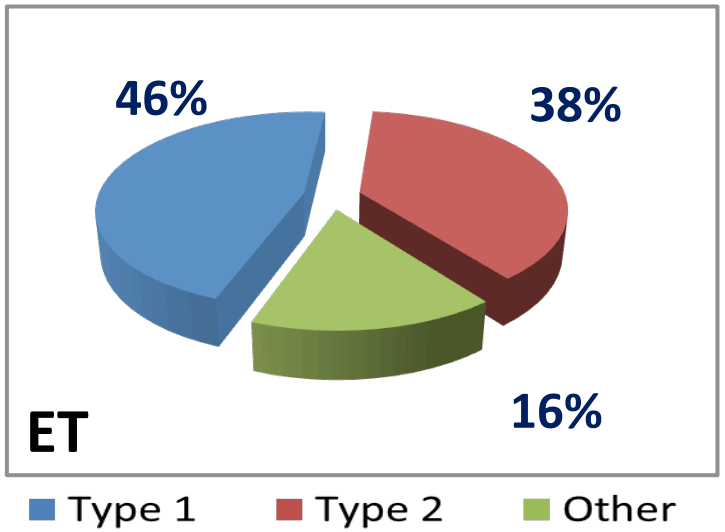
CALR mutation Type 1 & Type 2: differences between ET and PMF



Adapted from Klampf T *et al. N Engl J Med.* 2013;2379-90

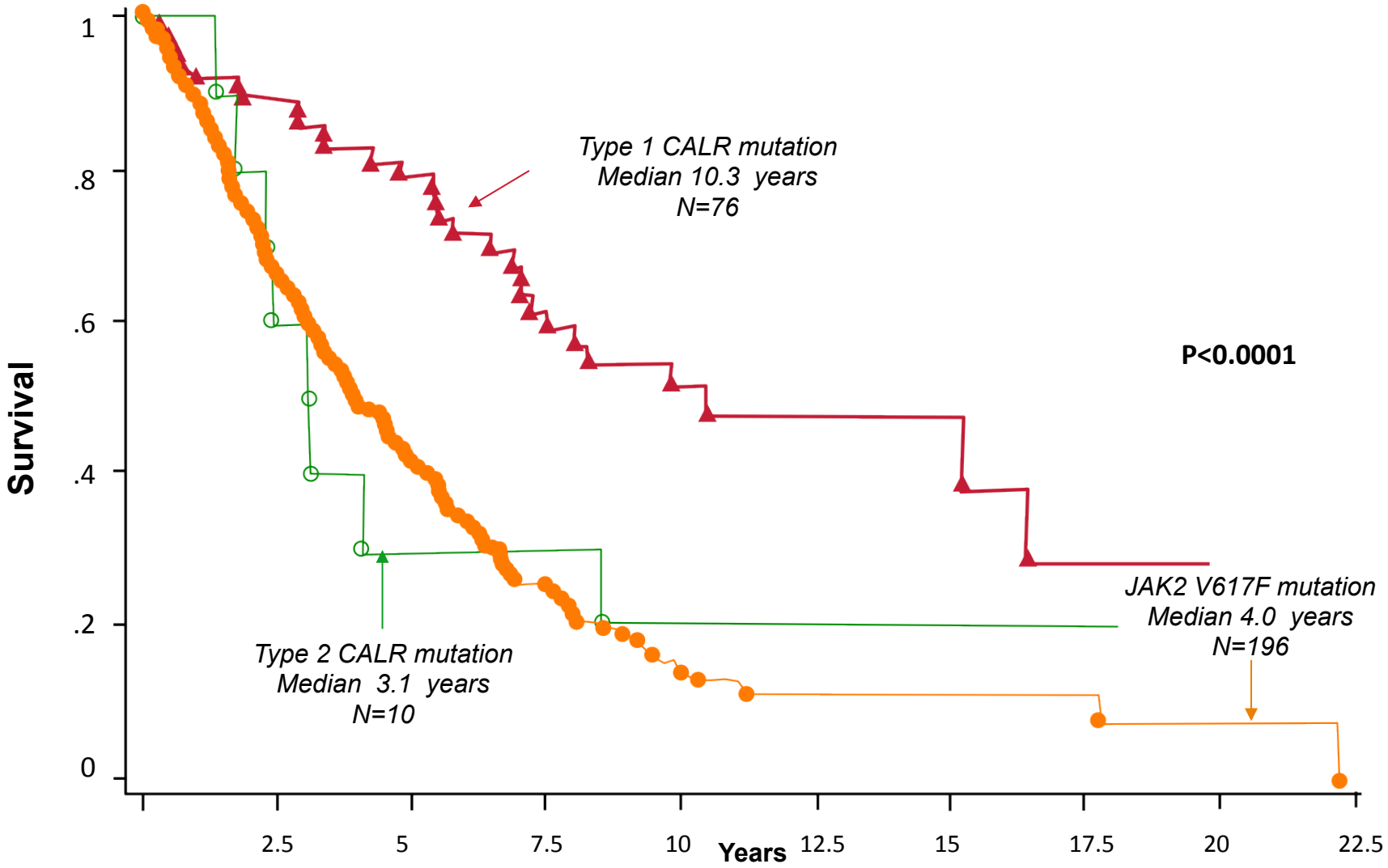


Adapted from Tefferi A *et al. Leukemia.* 2014;28:1568-70



Adapted from Rumi E, *et al. Blood.* 2014; 123:1544-51

CALR Type 1 vs Type 2 Mutations in PMF



Adapted from Tefferi A *et al. Leukemia.* 2014; 28:1568-70

- In ET, no difference between Type 1 and Type 2 for thrombosis-free and overall survival

Tefferi A *et al. Am J Hematol.* 2014; epub

In summary:

- Grouping of patients with ET and PMF based on their mutation asset is highlighting intriguing prognostic correlations
- Patients with *CALR* mutated ET constitute a group at lower risk of thrombosis, but triple negative do even better
- In PMF, *CALR* mutation points to patients with lower propensity to disease progression
- *CALR* mutated PMF patients have better overall survival compared to mutated *JAK2* or *MPL*, while triple negative have the worst outcome
- However, how to translate this information into patient management strategies requires further studies