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Myeloproliferative disorders

# NEXT GENERATION SEQUENCING IN TRIPLE NEGATIVE ESSENTIAL THROMBOCYTHEMIA: IMPACT OF ADDITIONAL MUTATIONS IN RISK ASSESSMENT

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**Introduction:** Triple Negative Essential Thrombocythemia (TN ET) represents 10% of ET cases and is known for its indolent course, with limited thrombotic and disease progression risk. Next Generation Sequencing (NGS) analysis is not routinary applied in ET, despite prognostic significance of additional myeloid mutation has been explored in indolent myeloproliferative neoplasms and new molecular tools were introduced. Aim of the study was to analyze incidence and prognostic significance of additional mutations in TN ET.
**Methods:** We retrospectively analyzed 28 consecutive WHO-defined TN ET diagnosed between 1994 and 2024 at the Divisions of Hematology of Udine. Molecular status was defined as soon as analysis were available. NGS analysis was perform during chronic phase on peripheral blood samples. We used a 30 myeloid gene panel (*TET2, ASXL1, DNMT3A, FLT3, NPM1, CEBPA, IDH1, IDH2, RUNX1, TP53, JAK2, MPL, CALR, KRAS, HRAS, NRAS, PTPN11, CBL, BRAF, SF3B1, SRSF2, U2AF1, ZRSR2, WT1, CSF3R, ETV6, EZH2, KIT, SETBP1, ABL1*).
**Results:** At diagnosis, median age was 49 years (range: 17-80), with a female prevalence (64%); median platelet count was 727,6 x$10^9$/L, while hemoglobin and leukocyte count were normal; 4 (14%) patients had symptoms, 2 (7%) had splenomegaly and 12 (43%) had ≥1 cardiovascular risk factor; 2 (7%) had arterial thrombosis. According to r-IPSET, 3 (10,7%) were at high risk, 8 (28,6%) at intermediate and 17 (60,7%) at very low. With a median follow up of 4 years (range: 1-30), 4 (14%) adverse events were noted in 4 patients (1 arterial thrombosis, 1 major bleeding, 1 leukemic progression, 1 death). In total, NGS revealed 16 mutations and 7 variants of uncertain significance in 14 (50%) patients. Among the former, the majority were DTA (DNMT3A, ASXL1, TET2; n=9) and non-canonical driver genes (JAK2, CALR, MPL; n=4) mutations. Overall 15-years OS and EFS were 84% and 64%. Patients with ≥3 additional mutations (n=3) had inferior 5-years OS (67% vs 100%, p=0.011) and EFS (67% vs 100%, p<0.001, Figure 1A) compared to others (n=25). Patients with ≥1 DTA mutation (n=6) had inferior 10-years OS (50% vs 100%, p=0.046) and EFS (50% vs 100%, p=0.009, Figure 1B) compared to others (n=22). Patients with non-canonical driver mutation had inferior 10-years OS compared to “true” TN (50% vs 100%, p=0.046).
**Conclusions:** Our results support the importance of NGS use in ET diagnosis to find out the presence of non-canonical driver gene mutations and to provide a “proof of clonality” in TN cases. The presence of additional mutations with prognostic significance might allow an accurate risk stratification, according to recent MIPSS-ET model. Similarly to previous studies, we confirmed the greater the number of mutations, the higher the risk of adverse events. Finally, larger studies might better elucidate the distinct contribution of age and DTA mutations – strictly connected in clonal hemopoiesis – on adverse events and survival in ET.

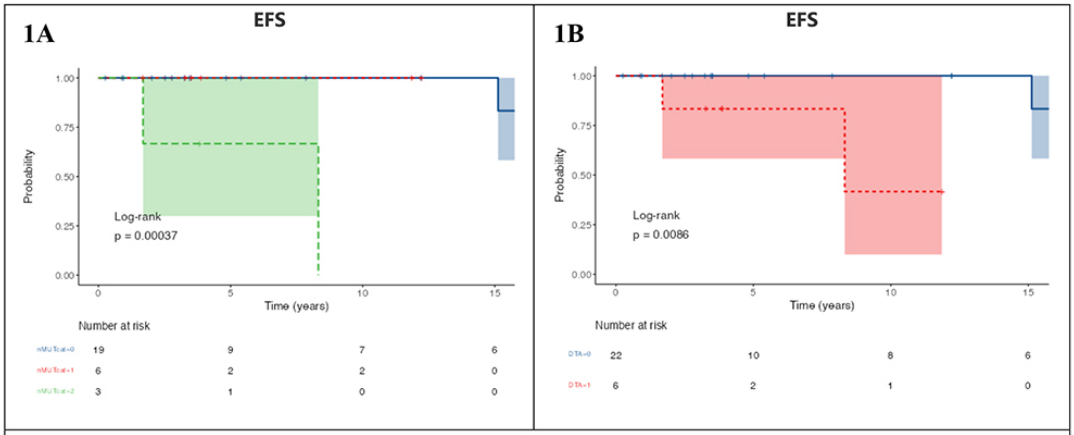


**Figura 1A.** Pazienti con almeno 3 mutazioni addizionali (curva verde) hanno minore EFS rispetto a chi ha 1-2 mutazioni (curva rossa) e a chi non ha alcuna mutazione (curva blu). **Figura 1B.** Pazienti con almeno una mutazione DTA (curva rossa) hanno minore EFS rispetto a chi ha mutazione non-DTA o non ha alcuna mutazione (curva blu).