TRIAL SYNOPSIS

Effects of TAMoxifen on the Mutant Allele Burden and Disease Course in Patients with MyeloprolifeRatIve Neoplasms

TAMARIN

Trial Design

A multicentre phase II, single stage A'herns design clinical trial to assess the safety and activity of tamoxifen in MPN.

Outcome Measures

Primary outcome

- Reduction in the peripheral blood JAK2V617F, CALR 5bp insertion (exon 9), or CALR 52bp deletion (exon 9) mutant allele burden of ≥50% at 24 weeks

Secondary outcomes

- Reduction in the peripheral blood mutant allele burden of ≥50% at 12 weeks
- Toxicity measured as the number of grade 3 and 4 adverse events reported
- Thrombotic events of any grade reported and validated
- Duration of haematological response [1-2]
- Proportion of patients in each response category according to IWG-MRT response criteria for MF [2] and 2013 ELN response criteria [3] for ET/PV at 24 weeks
- Proportion of patients showing an improvement in response category at 24 weeks compared to baseline [1-2]

Exploratory outcomes

- Change in allele burden between weeks 12, 24 and baseline.
- Proportion of patients showing a decrease in requirement for cytoreduction at 24 weeks compared to baseline
- Proportion of patients showing a decrease in allele burden of ≥50% at 36 and 48 weeks compared to baseline
- Duration of reduction in the mutant allele burden, defined as time from first observed reduction of ≥50% until reduction from baseline becomes <25% or patient's death
- Expression (RNAseq), DNA-protein interaction (ChipSeq) and methylation studies focused on oestrogen receptor signalling in haematopoietic progenitors obtained from peripheral blood and bone marrow before (peripheral blood only) and after tamoxifen treatment.

Patient Population and Sample Size

A total of 42 patients with an MPN with at least a 20% JAK2V617F,CALR 5bp insertion (exon 9) or CALR 52bp deletion (exon 9) allele burden in peripheral blood granulocyte DNA (as determined centrally), stable disease (haematological PR/CR for ET/PV patients and no evidence of disease progression for MF patients) that meet the eligibility criteria will be recruited over 28 months.

Of the 42 patients, we will aim to achieve a minimum of 15 PV patients, 10 ET patients and 5 MF patients.

Main Inclusion and Exclusion Criteria

Inclusion Criteria

- Age ≥ 60 years (men aged between 50-59 may also be considered following discussion with the Chief Investigator)
- Women must be post-menopausal (defined as amenorrhoeic for at least 12 consecutive months following cessation of all exogenous hormonal treatments)
- Confirmed diagnosis of JAK2-V617F , CALR 5bp insertion (exon 9), or CALR 52bp deletion (exon 9) positive Essential Thrombocythaemia (ET), Polycythaemia Vera (PV) or Myelofibrosis (MF) (primary or secondary) for ≥ 6 months
- JAK2-V617F, CALR 5bp insertion (exon 9), or CALR 52bp deletion (exon 9) mutant allele burden ≥ 20% in peripheral blood granulocyte DNA at study entry (**assessed via central review**)
- WHO performance status 0-2
- For patients with PV or ET, maintenance of platelet count ≤600 x 10^9/L, WBC ≤25 x 10^9/L and venesection requirements ≤1 per month for the previous 3 months prior to registration, without introduction of any new therapeutic agents for their MPN for 6 months prior to registration
- For patients with MF, there must not have been any evidence of disease progression* for the previous 6 months (prior to registration) and no new therapeutic agents for their MPN introduced during this period.

TRIAL SYNOPSIS

- Patients receiving cytoreductive therapy (with the exception of interferon alpha or investigational agents) for their MPN (not solely aspirin or venesection)
- Adequate hepatic function, defined as:
  - bilirubin ≤ 1.5 x upper limit of normal (ULN) (patients with elevated bilirubin due to Gilbert's syndrome are eligible)
  - AST/ALT/ALP ≤ 2.5 x ULN
- Adequate renal function (creatinine clearance >30 mL/min)
- Male patients must agree to use effective contraception during participation in the trial and for 2 months after the last dose of trial treatment
- Patient must be able to give written informed consent

*Defined by IWG-MRT ELN criteria (Appendix 6). Please note no baseline bone marrow is required to confirm absence of "Leukemic transformation confirmed by a bone marrow blast count of ≥20%".

Exclusion Criteria

- Leukaemic transformation (>20% blasts in blood, marrow or extramedullary site).
- Accelerated phase of disease as indicated by ≥10% blasts in the peripheral blood
- Treatment of ET, PV or MF with Interferon alpha or other investigational agents for their MPN within 6 months prior to trial entry. JAK inhibitors, such as ruxolitinib, are allowed if taken continuously for ≥6 months prior to registration (dose changes during that period will be allowed)
- Any of the following previous thrombotic events at any time:
  - Portal or other splanchnic venous thrombosis
  - Vascular access complication
  - Ischemia cerebrovascular
  - Stroke
  - Transient Ischaemic attack
  - Superficial thrombophlebitis
  - Venous Thromboembolic events including pulmonary embolism (PE) and deep vein thrombosis (DVT)
  - Peripheral vascular ischemia
  - Visceral arterial ischemia
  - Acute coronary syndrome
  - Myocardial infarction
- Previous malignancy within 5 years with the exception of adequately treated cervical carcinoma in situ or localized non-melanoma skin cancer
- Previous endometrial cancer, hyperplasia or polyps
- Prior treatment with hematopoietic stem cell transplantation
- Patients who do not carry any mutations in JAK2V617F or CALR or allele burden <20%
- Female patients receiving hormone replacement therapy
- Hypertriglyceridemia > grade 1
- Any serious underlying medical condition (at the judgment of the Investigator), which could impair the ability of the patient to participate in the trial (e.g. liver disease, active autoimmune disease, uncontrolled diabetes, uncontrolled infection (HIV, Hepatitis B and C), known genetic defect (apart from MPN) relating to venous thromboembolic events, or psychiatric disorder precluding understanding of trial information)
- Known hypersensitivity to tamoxifen or hypersensitivity to any other component of tamoxifen
- Concomitant drugs contraindicated for use with the trial drug according to the SmPC
- Known planned scheduled elective surgery during study with the exception of dental and low risk eye surgery (e.g. cataracts)

Trial Duration

All patients will receive trial treatment for 24 weeks. Following 24 weeks, they will be able to continue treatment with tamoxifen if there is clinical benefit, at the discretion of the treating Investigator and their response will be reassessed after 36 and 48 weeks of treatment as applicable. The last patient visit will be 28 days after the last administration of trial treatment.

Trials Office Contact Details

TAMARIN Trial Office

CRCTU, Centre for Clinical Haematology,
Queen Elizabeth Hospital, Edgbaston, Birmingham, B15 2TH

Tel: 0121 371 7866 Fax: 0121 371 7874 Email: TAMARIN@trials.bham.ac.uk