

# TPS3177: <sup>177</sup>Lu-edotreotide versus everolimus in patients with advanced neuroendocrine tumors of lung or thymic origin: The phase 3 randomized LEVEL, GETNE-T2217 trial

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## BACKGROUND

Everolimus is the only approved drug for the treatment of patients with neuroendocrine tumors (NETs) of lung and thymic origin, showing a median progression-free survival (PFS) of 9.2 months<sup>1</sup>. Retrospective data for peptide receptor radionuclide therapy (PRRT) have demonstrated promising activity in somatostatin receptor (SSTR)-positive lung NETs<sup>2,3</sup>.

## TRIAL DESIGN

LEVEL Trial is a randomized, prospective, international, open-label, phase 3 study comparing everolimus and <sup>177</sup>Lu-edotreotide in advanced SSTR+ lung and thymic well differentiated NETs with high expression of somatostatin receptors confirmed by PET somatostatin receptor imaging. Eligible patients are randomly assigned 3:2 to 6 cycles of <sup>177</sup>Lu-edotreotide (7.5±0.7 GBq / cycle) or to oral everolimus 10 mg once daily until progression (PD) or unacceptable toxicity. Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) scans are performed every 12 weeks until PD (Figure 2-3).

## STUDY SCHEME

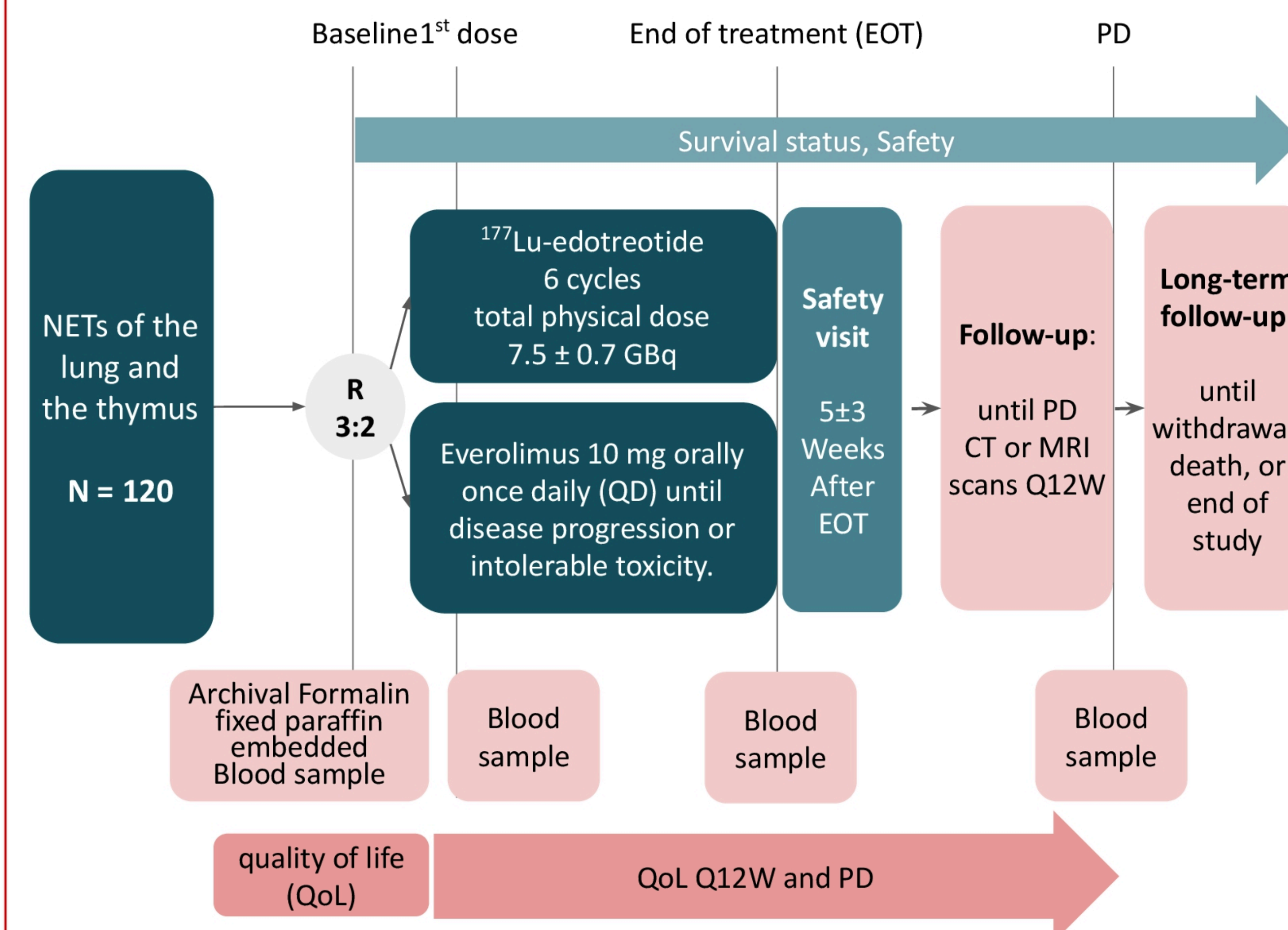


Figure 2. Study scheme of the LEVEL trial

## OBJECTIVES

### Primary:

- To demonstrate the efficacy of PRRT with <sup>177</sup>Lu-edotreotide in comparison with everolimus assessing the progression-free Survival (PFS), defined as the time from randomization until adequately documented PD according to RECIST v1.1 or death, whichever occurs first.

### Secondary:

- To determine relevant outcomes as overall response rate (ORR), disease control rate (DCR), duration of response (DoR) and Overall Survival (OS).
- To evaluate safety based on the frequency and severity of adverse events and Treatment-emergent adverse events (TEAEs). To assess health-related quality of life (HRQoL).

### Exploratory objectives:

- To determine molecular or clinical predictive biomarkers of response to <sup>177</sup>Lu-edotreotide.

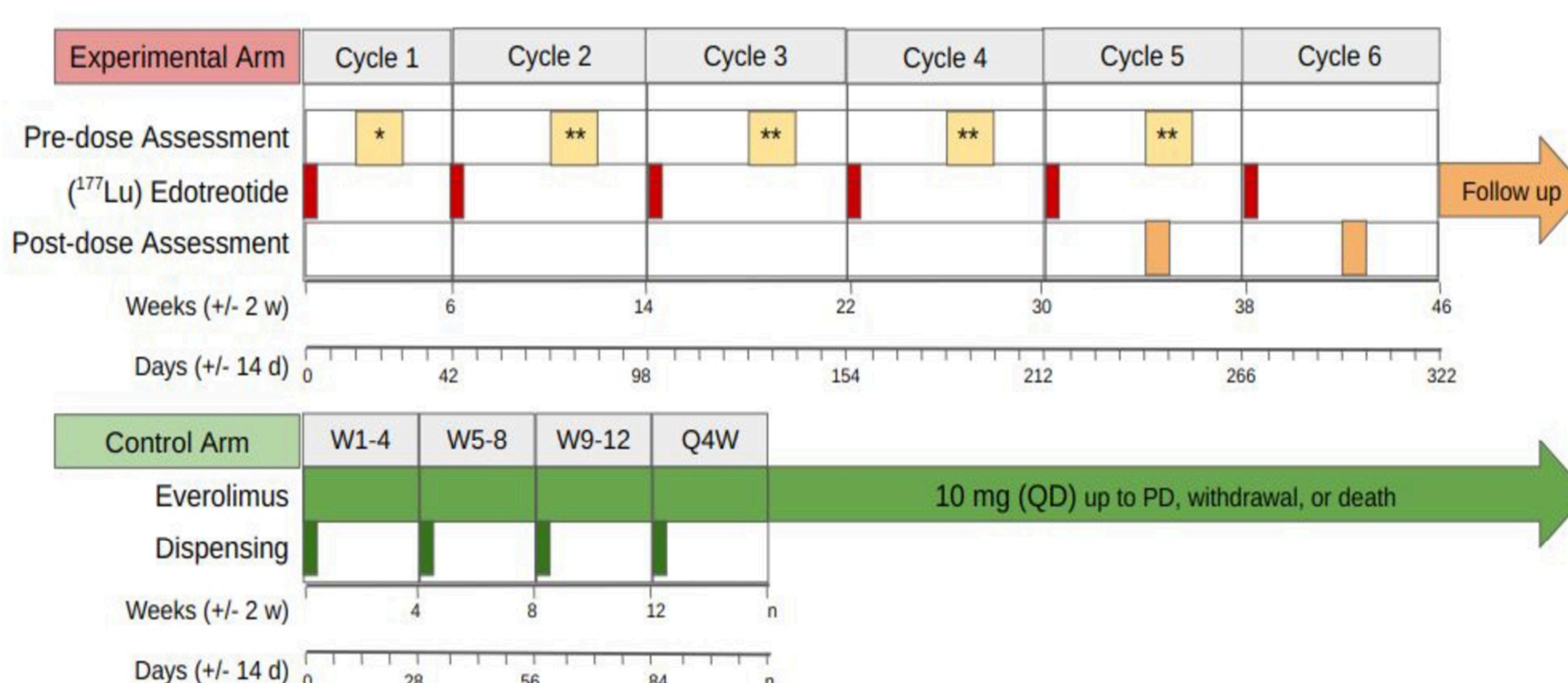


Figure 3. Scheme of study treatment

## PATIENT SELECTION

- ❖ Patients ≥18 years and ECOG 0-1
- ❖ Histologically confirmed metastatic or locally advanced unresectable well/moderately differentiated NET of lung or thymus origin
- ❖ Have an archival tissue sample (if not a new biopsy tissue sample should be provided).
- ❖ Appropriate pathological features based on WHO classification, and description of proliferation activity.
- ❖ In SSTR imaging all RECIST v1.1 selected target lesions and all other lesions considered dominant should be SSTR+.
- ❖ Lesions must have shown radiological evidence of disease progression in the 12 months prior to inclusion in the study.
- ❖ Patients may be included in first-line therapy (systemic treatment naïve) or may have experienced progression on somatostatin analogues or additional systemic treatments (maximum of 2 prior systemic anti-tumor treatments). Somatostatin analogues for symptoms control in functioning tumors are allowed.

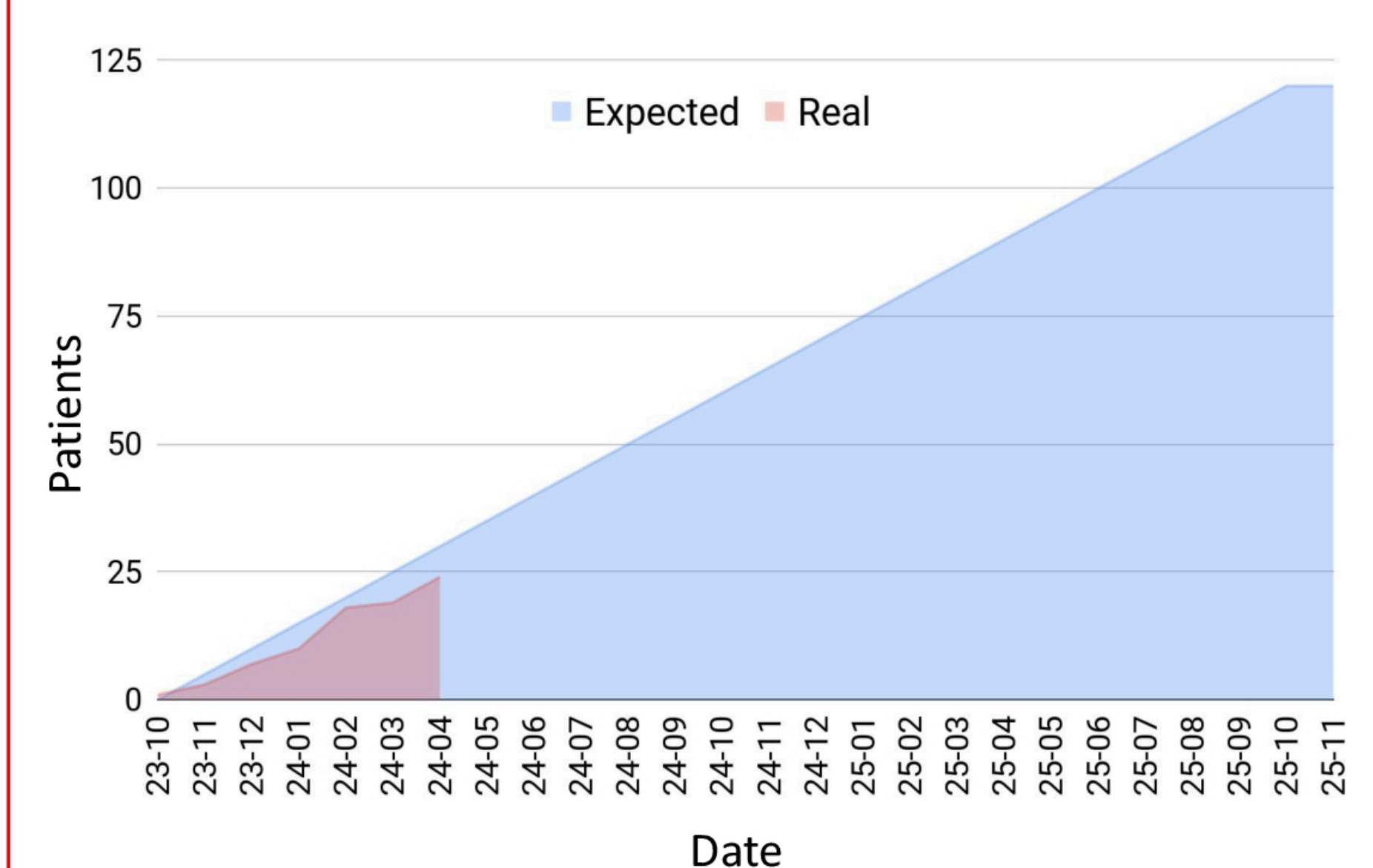


Figure 4. Prospective LEVEL trial accrual

- ❖ Patients must have adequate organ function including: neutrophil count (ANC) ≥ 1,500/mm<sup>3</sup>, platelet count ≥ 75 × 10<sup>9</sup>/l, hemoglobin ≥ 8 g/dl
  - Serum bilirubin ≤ 1.5 × upper limit of normal (ULN)
  - creatinine clearance (CrCl) ≥ 40 mL/min (Cockcroft-Gault formula)
  - alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × ULN or ≤ 5 xULN for subjects with liver metastases
- ❖ Patients with brain metastasis unless stable on treatment for > 12 w and with no evidence of raised intracranial pressure / mass effect are not eligible.

- Accrual started in October 2023
- At the date of 17 April 2024, 24 patients are already included

Figure 1. Geographic distribution of active sites in LEVEL trial.

## SAMPLE SIZE

The expected sample size is 120 patients using a two-sided group sequential Lan-DeMets with O'Brien-Fleming-like boundaries test to demonstrate statistical significant risk reduction of 46.4% (HR= 0.536) in PFS between arms, with at least 80% power and an alpha error at 5% (β=0.2, α=0.05).

## REFERENCES

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