Modeling of pemetrexed maintenance de-escalation strategies using digital twins-based in silico clinical trials in FLAURA2 regimen as front-line treatment of metastatic EGFR-mutated non-small cell lung cancer

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Introduction

- FLAURA2 clinical trial (NCT04035486) showed that adding platinum–based chemotherapy (CDDP) and pemetrexed (PMX) to osimertinib (osi) improves PFS in EGFR-mutated (EGFRm) advanced NSCLC and demonstrated a 4-year benefit in overall survival [1,2].
- Real-world applicability motivates defining how long PMX should be maintained after induction, given potential cumulative toxicity and quality-of-life considerations in a broader patient population
- A previously developed and validated mechanistic disease model of EGFRm NSCLC enables credible prospective simulation of trial outcomes under alternative strategies.
- Objective: Quantify the impact of PMX-maintenance duration on PFS after four induction cycles of CDDP + PMX + osi

Methods

Model & credibility

We used a pathophysiology-based NSCLC QSP model coupled to treatment models for osi, CDDP, and PMX Fig. 1). Credibility of the model in the current context of use was assessed by comparing the simulation results with publicly available FLAURA2 and PAPILLON clinical trials results [3-4].

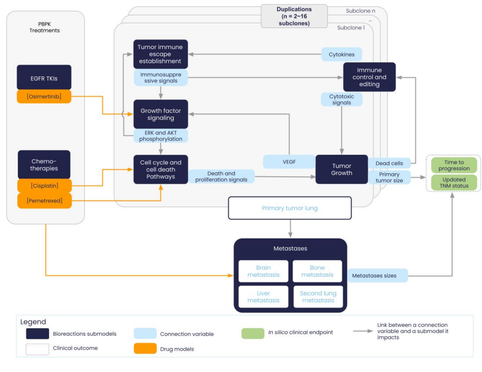


Figure 1: Structure of the EGFRm NSCLC model, integrated with 3 treatment models: osi, CDDP and PMX.

Virtual population (digital twins)

Generated to reflect heterogeneity in baseline disease/tumor dynamics, PK variability, and resistance emergence; aligned with first-line EGFRm advanced NSCLC characteristics relevant to FLAURA2 original trial.

Design of the in silico clinical trial

- **Induction (all arms)**: 4 cycles Q3W of CDDP + PMX (500 mg/m²) + osi (80 mg QD).
- **Maintenance exploration**: Arms with osi + 0 to 50 maintenance PMX cycles
- **Comparator**: osi + CDDP + PMX maintenance consistent with FLAURA2

Endpoint & analysis

- **Primary endpoint**: PFS by RECIST 1.1.
- Kaplan–Meier estimation; median PFS with 95% intervals.
- Multiple-comparison control using false discovery rate (FDR) across explorations; α=0.05 after correction.

Results

Model credibility assessment

- The external validation for the CDDP + PMX exposure has been done by reproducing the CDDP + PMX arm clinical outcomes of the PAPILLON trial (Fig. 2)
- The model has been externally and prospectively validated by reproducing FLAURA2 clinical outcomes for both osi and osi + CDDP + PMX arms (Fig. 3)

Digital-twin trials testing maintenance durations

- **Overall pattern**: results indicates that continuing PMX with osi beyond induction yielded a moderate but still significant improvement in PFS *vs* osi alone maintenance strategy after induction (Fig.4).
- **Significance window:** After FDR correction, most schedules within 0–10 cycles of PMX maintenance showed a PFS gain versus historical FLAURA2 arm. Additional PMX over 10 cycles produce a slightly incremental PFS benefit after multiplicity adjustment (Fig. 5).

Figure 2: Kaplan-Meier curves of observed PFS and simulated TTP for the platinum + PMX arm of PAPILLON trial
Red curve : CDDP + PMX in PAPILLON trial ; Yellow curve : CDDP+PMX simulated

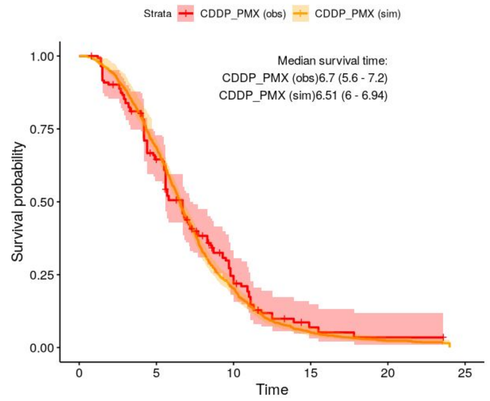


Figure 3: Kaplan-Meier curves of observed PFS and simulated TTP for FLAURA2 trial (both arms).
Dark blue and red curves : FLAURA2 trial arms; Light blue and yellow curves : simulated arms

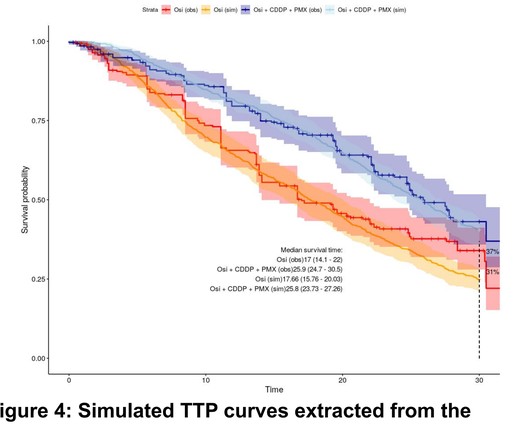


Figure 4: Simulated TTP curves extracted from the digital-twin trial testing maintenance duration strategies after four induction cycles of platinum + PMX + osi. Blue : FLAURA 2 osi arm; Purple : FLAURA2 CDDP + PMX + osi arm; Green : alternative CDDP + PMX + osi arm with 10 cycles of PMX maintenance.

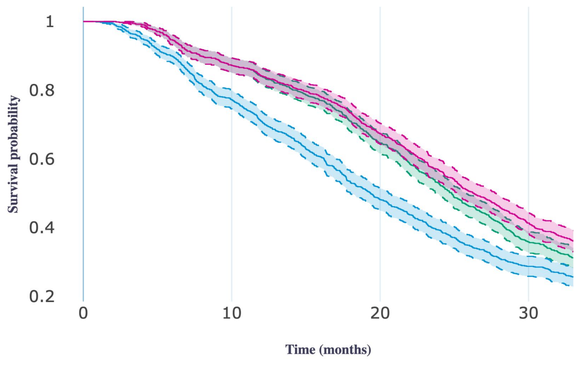
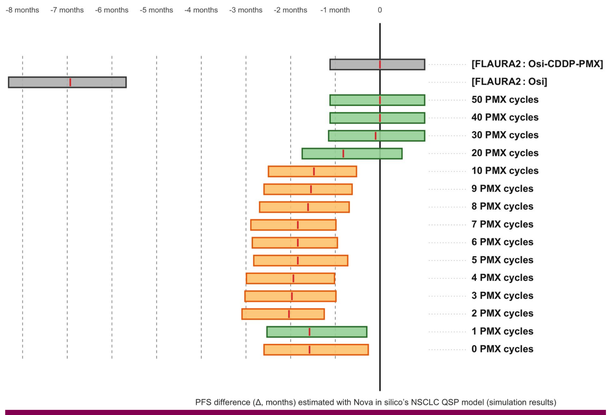


Figure 5. Forest plot of differences (Δ, months) in median survival versus the historical FLAURA2 arms. The two top rows are the simulations results of historical comparators (grey). Remaining rows are alternative Osi-CDDP-PMX arms ordered by number of simulated maintenance PMX cycles. The red tick marks the point estimate (median Δ); the box spans the 95% CI. The solid black line indicates 0 (no difference); dashed guides show −8 to -1 months differences. Orange boxes indicate significance after Benjamini–Hochberg FDR multiple testing correction, green boxes indicate non-significance.



Conclusions

- Digital-twin simulations indicate that maintaining PMX for ~10 cycles after induction confers a PFS benefit versus osi-only maintenance and aligns with FLAURA2 results (the median number of total PMX cycles was 12) . Additional cycles of PMX maintenance (>10) only yield a modest incremental benefit in these simulations.
- The usage of this mechanistic model supports the exploration of PMX-maintenance duration and mimics the FLAURA2 findings especially regarding the overall PMX exposure.

References

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