Equivalent survival benefits from first-line and second-line use of CDK4/6 inhibitors in HR+/HER2- advanced breast cancer: A computational analysis of phase 3 trials

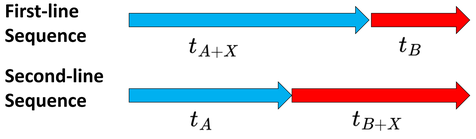
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Drugs often have approvals in both relapsed/refractory and treatment-naïve cancers. When are they most beneficial?

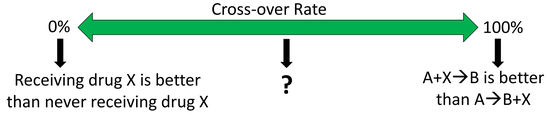
- After demonstrating efficacy in previously-treated disease, drugs are often evaluated in combination with first-line standard of care. Effective drugs may receive regulatory approval in both settings.
- Outside of time-limited (e.g. curative) treatment, continuous use of first-line multidrug combinations can elicit higher rates of adverse events and increased costs to patients and healthcare systems[1].
- Essential to determine whether there are greater survival benefits from first-line use compared to second-line use.



A: First-line standard of care
B: Second-line standard of care
X: New investigational drug

Overall Survival in first-line trials could answer this question, but rarely does

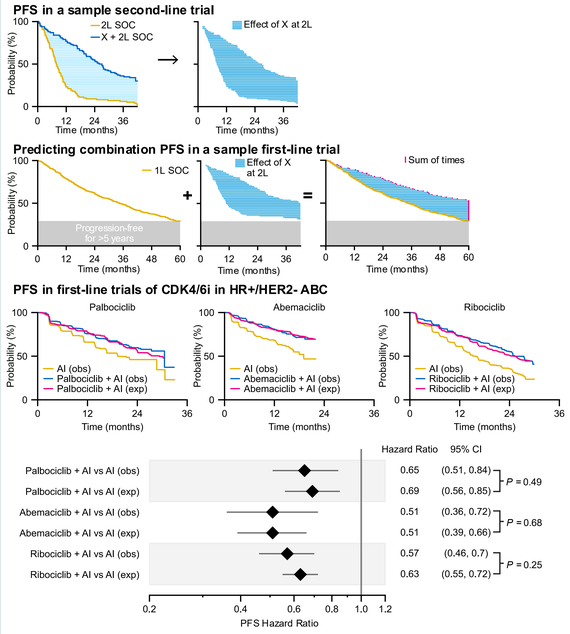
- Overall Survival (OS) is affected by rate of cross-over, that is, how many patients randomized to control can receive the investigational drug post-progression
- If 100% of control patients in a first-line trial cross-over and receive the investigational drug (X) at second-line, OS compares the ability of first-line (A+X→B) versus second-line (A→B+X) sequences to prolong time to death.
- If 0% of control patients cross-over, OS compares whether receiving drug X prolongs time to death more than never receiving drug X.
- Cross-over rates are commonly in between and render OS results difficult to interpret
- The meaning of an Overall Survival advantage of A+X vs A depends on cross-over:



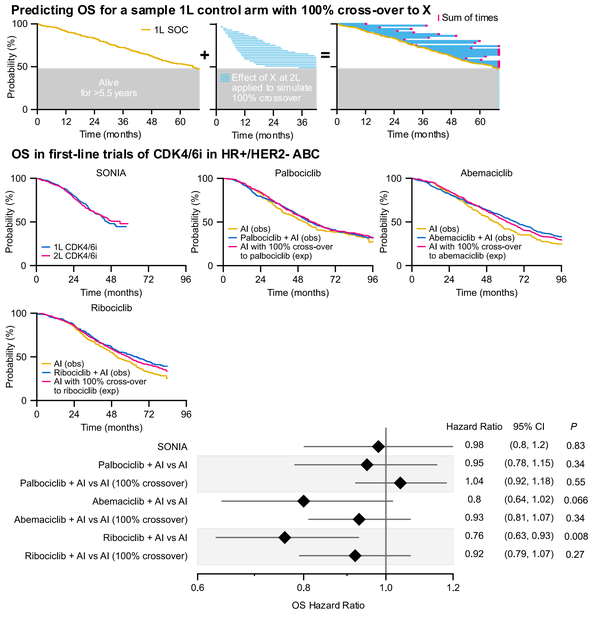
CDK4/6 inhibitors have first-line and second-line indications in HR+/HER2- advanced breast cancer (ABC)

- Palbociclib, abemaciclib, and ribociclib currently have first- and second-line approvals in HR+/HER2- ABC[2-7], and while all drugs significantly improve Progression-Free Survival (PFS), they have had mixed abilities to significantly improve OS in phase 3 trials and ~30% cross-over
- The phase 3 SONIA trial directly compared first- and second-line CDK4/6i treatment sequences and found that while first-line CDK4/6i improve PFS, first-line sequences did not significantly improve OS or time to second progression (PFS2) compared to second-line CDK4/6i; however, first-line sequences were associated with a >50% increase in grade 3+ adverse events and increased time on CDK4/6i therapy by ~16 months.
- SONIA primarily studied palbociclib (>90%), calling into question generalizability of findings

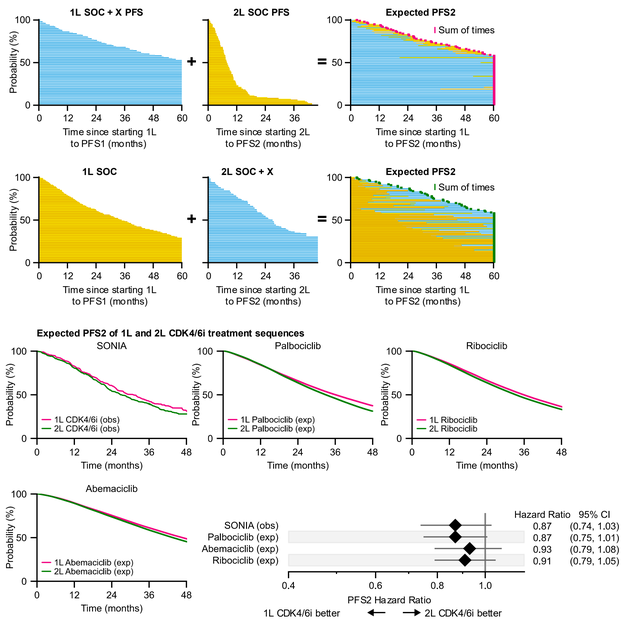
Predicting first-line CDK4/6i PFS using second-line CDK4/6i PFS benefits



Accounting for the influence of incomplete cross-over on first-line Overall Survival



Simulating head-to-head trials of first-line vs second-line CDK4/6i sequences using phase 3 trial data at first- and second-line



Conclusions

- For all approved CDK4/6i, observed first-line CDK4/6i PFS does not significantly differ from predicted PFS under the null hypothesis that CDK4/6i prolong time to progression equally well at first- and second-line
- For all approved CDK4/6i, first-line CDK4/6i are not expected to significantly improve OS compared to a first-line AI arm with 100% cross-over to second-line CDK4/6i
  - Consistent with findings of SONIA
  - Suggests OS advantage seen in first-line trials is partially a consequence of limited subsequent access, not superior efficacy of first-line use
- Simulations of head-to-head trials do not predict significant differences in PFS2 between first-line and second-line CDK4/6i sequences, but do predict second-line sequences reduce median time on CDK4/6i by 19.3, 13.4, and 10.6 months for palbociclib, abemaciclib, and ribociclib, respectively
  - Further consistent with SONIA findings
- Future work will investigate the impact of targeted therapies (*ESR1* and *PIK3CA* mutations) on optimal time to deploy CDK4/6i
- Based on CDK4/6i activity in randomized phase 3 trials, second-line CDK4/6i use is a clinically viable option for patients in whom attrition is not a concern and may be preferrable for many patients due to increased tolerability and affordability

References

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