Computing tumor growth rate (TGR) across pre- and post-treatment periods uncovers anti-tumor activity in patients treated by a pan-CDK inhibitor roniciclib (BAY1000394)

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Methodology

We analyzed the TGR of solid tumors from patients prospectively enrolled in a dose-escalation phase I trial investigating the pan-CDK inhibitor roniciclib (BAY1000394) on a 24-days on 28-days off 1 treatment cycle.

Only patients who had tumor imaging evaluation at least one month before the onset of the experimental treatment, a baseline (start of the experimental treatment) tumor imaging, and at least one tumor evaluation after 2 cycles of treatment were eligible.

Patient consent was obtained prior to analysis.

We computed the TGR across clinically relevant treatment periods, as described by Ferti et al (Clin Cancer Res 2014):

- TGR REFERENCE assessed during the wash-out period
- TGR EXPERIMENTAL assessed during the first cycle of treatment (∼1 evaluation)

We compared these results to RECIST 1.1-based response evaluation:

- Each patient was used as his/her own control.
- *Pts with non-measurable disease at baseline were excluded in case of new lesions, TGR was computed only on the target lesions.

Histology of primary tumor sites (n) and corresponding TGR evaluation

- Ovarian adenocarcinoma: 3 (9, 11)
- Small cell lung Cancer: 2
- Non-small cell lung cancer: 8
- Cholangiocarcinoma: 8
- Colon adenocarcinoma: 12
- Skin melanoma: 1
- Bladder carcinoma: 10
- Gastric carcinoma: 8
- Thymic carcinoma: 6

Background

The ability of Response Evaluation Criteria in Solid Tumors (RECIST 1.1) to evaluate the activity of novel molecular targeted agents is highly discussed as these drugs may induce tumor density or perfusion changes responsible of long-lasting stabilizations rather than tumor shrinkage.

Mainly, RECIST 1.1 does not take into account the posttreatment tumor kinetics and may provide incomplete information about experimental drug activity.

We and others have previously reported on the potential value of Tumor growth rate (TGR) for a dynamic and quantitative assessment of the tumor response in phase I trials.

We found that patients with non-measurable disease at baseline were excluded in case of new lesions, TGR was computed only on the target lesions.

The tumor growth rate (TGR) was defined as an increase in tumor volume during 1 month.

TGR = \( \frac{dV}{dt} = \frac{\ln(V_f/V_0)}{t} \)

where

- \( dV \) is the variation in tumor volume,
- \( V_0 \) and \( V_f \) the tumor volume at time \( 0 \) and at time \( t \),
- \( t \) the time in months elapsed between time \( 0 \) and time \( t \).

Conclusions

TGR analysis in this cohort suggests anti-tumor activity of the pan-CDK inhibitor roniciclib (BAY1000394) in patients with small cell lung, bladder, thymic and colon adenocarcinoma tumor types.

This result, not previously identified with RECIST 1.1, suggests TGR analysis is a promising tool to guide the go/no-go decision-making in the early drug development.

To address more definitive conclusion is hampered by the very small number of patients: only 12 evaluable pts for TGR in the 32 pts enrolled in the protocol BAY1000394.

Some patients exhibited signs of drug activity (decrease of TGR) but progressed with occurrence of new lesions at the first evaluation. This suggests a different biology for fixed lesions (i.e. target lesions) versus infraclinical and infra-radiological lesions.