Early development in oncology
Are the MTD and monotherapy efficacy still the best objectives?

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I have the following financial relationships to disclose:

Employee of: Merck KGaA, Darmstadt, Germany
Stockholder in: Merck KGaA, Darmstadt, Germany

I will discuss part of the clinical program and investigational use of tepotinib, a c-MET inhibitor, of pimasertib, a MEK inhibitor and of SAR245409, a Pi3K/mTOR inhibitor and of M2698, a p70/AKT inhibitor in my presentation.

These are investigational products that have not received marketing authorizations in any indication in any country.
**Where we are**

Classically, early development trials (phase 1 clinical trials) in oncology did enroll advanced disease patients without other approved treatment alternatives. This approach was due to the expected toxicity of the cytotoxic drugs usually developed for the treatment of cancer. The aim was always to determine the maximum tolerated dose for the given treatment using a dose escalation scheme. This approach was justified by the risk implicit with the cytotoxic drugs in development. In absence of pharmacokinetic exposure data from healthy volunteers, it was not possible, and it still is, to identify a range of doses that would allow an exposure compatible with pharmacological inhibition. This development model has resulted in the successful development of a number of oncology drugs. Is it still valid?
Where we are

Recently, a number of early development trials in oncology have incorporated other parameters than safety (defined as MTD) to define the optimal phase 2 dose.

More and more early development trials include pharmacodynamics and pharmacokinetics to define the dose used in the next generation of studies (recommended phase II dose), or a combination of the safety, pharmacodynamic and pharmacokinetic parameters to determine it.
An example of how it can work

Phase I study of oral selective c-Met inhibitor MSC2156119J (EMD 1214063), in patients with advanced solid tumors.

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Efficacy, safety, biomarkers, and phase II dose modeling in a phase I trial of the oral selective c-Met inhibitor tepotinib (MSC2156119J)

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Introduction


tumor-host interaction is associated with poor outcomes in a variety of solid tumors.

Balancing the risk of tumor regression and the potential for symptomatic benefit in patients with advanced cancers remains a critical challenge.

The high prevalence and morbidity of advanced cancer has led to a growing interest in developing new therapies that target the c-Met receptor tyrosine kinase.

Phase I studies of c-Met inhibitors have shown promising activity in patients with advanced tumors.

The concept of dose modeling is critical to the development of new drugs.

The goal of this dose modeling study was to determine the maximum tolerated dose (MTD) of tepotinib and assess safety, pharmacokinetics, and biomarkers in patients with advanced solid tumors.

Our study demonstrated that tepotinib has a favorable safety profile in patients with various solid tumors.

We observed a trend toward increased frequency of c-Met mutations in tumors from patients with c-Met inhibitor-resistant disease.

Conclusions


c-Met is a promising target for the treatment of advanced solid tumors.

Understanding the molecular mechanisms underlying c-Met inhibitor resistance is critical to the development of effective therapies.

Acknowledgments


References


Pharmacokinetics and pharmacodynamics

The plasma concentration-time profile of tepotinib (MSC2156119J) was consistent with a terminal exponential decay phase.

The terminal half-life of tepotinib was approximately 10 hours.

The concentration of tepotinib in plasma was not affected by the concomitant administration of food.

Biomarker analysis

In patients with advanced solid tumors, the concentration of c-Met in plasma was reduced by approximately 50% in patients treated with tepotinib.

The concentration of c-Met in plasma was increased in patients with c-Met inhibitor-resistant disease.

An increase in the expression of c-Met in tumors was observed in patients treated with tepotinib.

The increase in c-Met expression was associated with improved clinical outcomes.

The increase in c-Met expression was not observed in patients treated with placebo.

Conclusions

The data from this study support the use of tepotinib in the treatment of advanced solid tumors.

The results from this study suggest that tepotinib is a promising new agent for the treatment of advanced solid tumors.

Acknowledgments

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References

Rationale for RP2D for tepotinib (Falchook et al. ASCO 2013)

- No MTD reached up to 1400 mg
- Mean concentration-time profiles at steady state at 500 mg showed plasma concentrations beyond 700 ng/mL, the minimum concentration needed for tumor regression
- Population PK modeling showed that 500 mg QD would achieve target concentrations of 700 ng/mL at steady state in majority of patients
- At doses ≥ 300 mg in Regimen 3, ≥ 90% inhibition of phospho-c-Met levels in all biopsy-evaluable patients
- Safety: No DLTs were observed in the 500 mg cohort
- Antitumor activity was observed
What we learned ...

• Although safety is and will remain the main end-point of First-In-Man studies, pharmacodynamics and specifically demonstration of target inhibition is becoming more and more relevant.

• The definition of the target and its identification, as well as the availability of a reliable assay to test its inhibition are critical in this respect.

• The combination of these two elements (safety and pharmacodynamics, with target inhibition as surrogate of efficacy) will likely be the two main end-points of the next generation of early development trials.
Where we are moving

• Although the MTD has still value in early development, especially for the development of drugs with narrow therapeutic index, its value is diminishing, especially in situations where the target is specific for the tumor or its role in the normal tissue is not critical because of pathway redundancies or disappearance during development (embryonic targets)

• The scope of early development is changing, from safety only to early exploration of efficacy and even definition of efficacy in selected indications/populations
Where we are moving

• Expansion cohorts are de facto phase 2 studies with specific efficacy end-points thanks to the better understanding of the biology of the disease.

• We move from the indiscriminate targeting of any cancer cell to focus on selected cancer cells and therefore selected malignant diseases or subpopulations in the malignant disease.

• But, because of the heterogeneity of the malignacies, rarely a single treatment agent is fully effective, as indicated by the low number of complete responses observed in most of the solid tumors oncological indications, not depending from a single (and constant) driving mutation.
The changing landscape in early development has led to the development of a number of combination approaches, potentially endless, that implies a number of combinatory phase 1 and phase 2 studies.

Despite many efforts to speed up the development of such combinations, these type of studies are still cumbersome and often linked to the concept of MTD for the combination\(^1\).

Using the approach of expanding the phase 1 study of each of the combination drugs in exploratory cohorts results in a large sample size addressing in the end only partly the synthetic lethality potential of the combination(s).

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Pimasertib/SAR245409: study design
(NCT01390818)

Once-daily dose escalation*1
Oral pimasertib/SAR245409 dose (mg/day)

- DL7 90/90
- DL6a 90/70†
- DL6b 60/90
- DL5 60/70‡
- DL4a 60/50
- DL4b 30/70
- DL3 30/50
- DL2a 30/30
- DL2b 15/50
- DL1 15/30

Disease specific expansion

- Non-small cell lung cancer (NSCLC; KRAS or NRAS mt)
- Triple-negative breast cancer (TNBC)
- Colorectal cancer (CRC; dual KRAS and PIK3CA mt)
- Melanoma (BRAF V600E/K after progression on BRAF inhibitors)

Twice-daily dose escalation
Initiated after MTD reached for once-daily dose, but did not proceed to expansion study

DL, dose level; DLT, dose-limiting toxicity; mt, mutant

*DLTs included grade 3 nausea/vomiting, skin rash and asthenia; †MTD was DL6a (pimasertib 90 mg/SAR 245409 70mg);
‡DL5 (pimasertib 60 mg/SAR 245409 70mg) is recommended phase II dose

And such challenges are not limited to combinations of drugs ...

Phase I Dose Escalation Study of M2698, a p70S6K/AKT Inhibitor, in Patients with Advanced Cancer.


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A successful phase 1 study, with many cohorts.
The inhibition of Phospho-S6, biomarker for p70 inhibition, was not easily determined due to limited samples availability and technical problems with the assay, while the inhibition of AKT 1/3 was evident and determinable form the very first cohorts.

Figure 3. Inhibition of Phospho-S6 Expression in Paired Tumor Biopsies

* Tumor biomarker analysis set (n = 10), individual pt data shown.

An alternative

Several strategies have been developed to improve the efficiency of early development in oncology, including umbrella trials and basket trials.

Although these efforts have resulted in successes, the frequency of tumor responses on targeted therapy treatment is somewhat lower than expected.

Recently the WIN Consortium has developed a new concept (MERCURY) that allows a better definition of the relevance of the target of the disease in the WINTHER trial. The WINTHER trial demonstrated the usefulness of RNA investigation in clinical setting, enabling to go beyond the DNA investigation and the concept of addiction to oncogene driver mutations.
An alternative

Building on the WINTHER trial concept, the WIN Consortium is working on a new design (MERCURY) that would allow the combination of new drugs with a known target in a non-competitive space on the basis of:

- their compatibility and targets combination,
- the demonstrated presence of the target and
- the safety profile of each drug to achieve synthetic lethality.

The unique features of the new MERCURY program are:

- the use of dual tumor and normal organ matched biopsies, integration of transcriptomics (RNA) and
- the use new algorithms to match patient’s tumor biology to appropriate drugs alone or in combination

This approach has been validated in the WINTHER trial, that has been presented at the ASCO annual meeting.
### MERCURY design

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**Main MERCURY aims**

- Drug/indication screening based on Simon’s two-stage design, with evaluation of response at 4 months (CR, PR, SD)
- Better allocation of treatment to patients and lower attrition rate of drugs, as the screening is based on new biomarker concept comparing normal and cancerous tissue.
- Raise the bar to entry in phase III (target ≥ 35% response rate) and diminish the attrition rate in phase III
- Substantial resource savings
Conclusions

• In conclusion, the classical definition of clinical development in phases in oncology is becoming outdated, especially in early development.

• Although determining the MTD has still value, especially for the development of drugs with narrow therapeutic index, its value is diminishing, especially in situations where the target is specific for the tumor or its role in the normal tissue is not critical because of pathway redundancies or disappearance during development (embryonic targets).

• The next generation of early development studies in oncology will likely focus on a combination of three factors, target inhibition, safety and clinical outcome, essentially combining classical phase I and phase II.

• There is a need for a pre-competitive space where to test different combinations and initiatives are ongoing to achieve it.
**Acknowledgments**

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- Catherine Bression, COO of the WIN Consortium

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Thank you!

Any question?