Utilizing receptor occupancy and tumor penetration for the phase 2 dose selection of monoclonal antibodies targeting solid tumors

T-006

Jaeyeon Kim[1], Fariba Khanshan[1], Yu-Yun Ho[2], Andrew Stein[1]

[1]Novartis Institutes for Biomedical Research, Cambridge, MA, United States; [2]Novartis Pharmaceuticals Corp., East Hanover, NJ, United States

Objectives

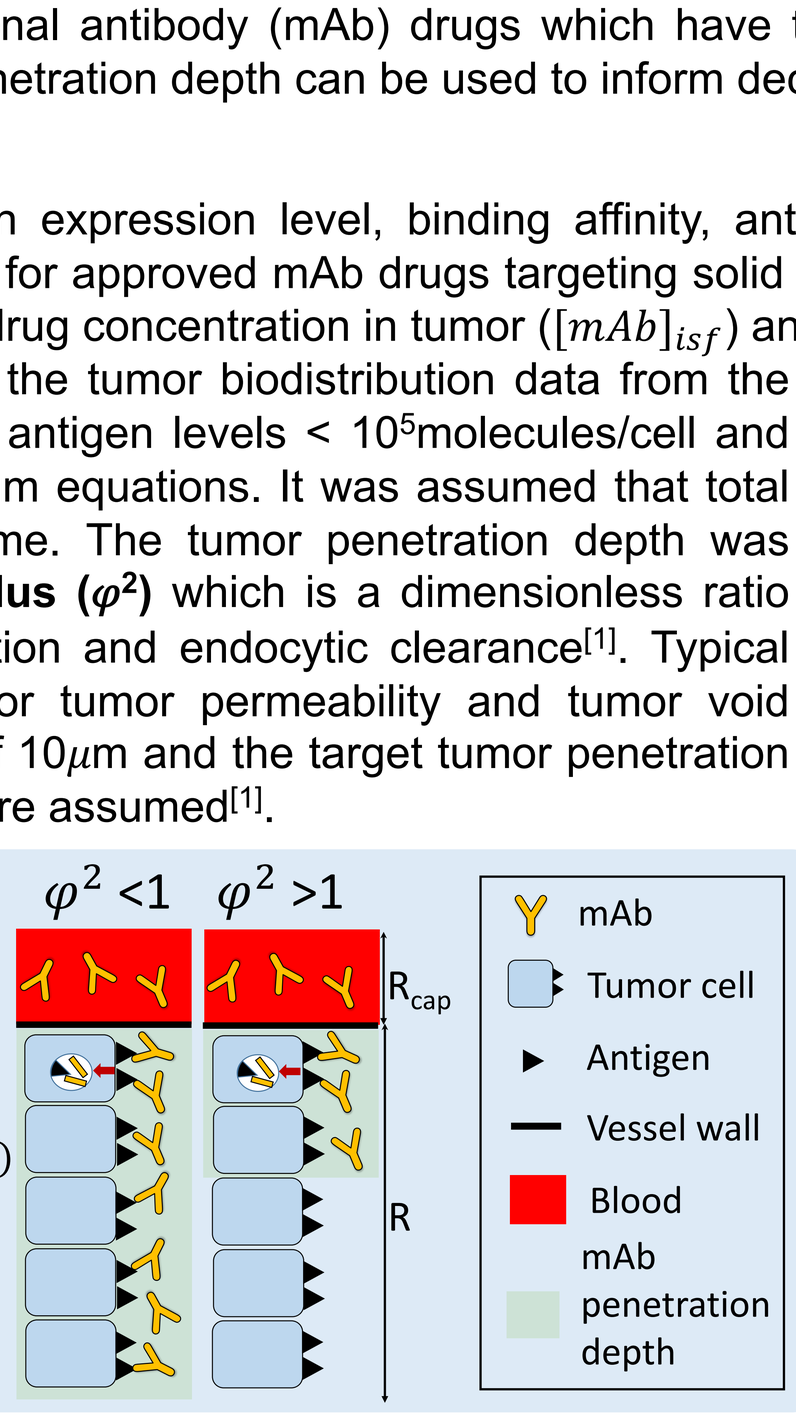
As more targeted therapies with better safety profiles are developed in oncology, a maximum tolerated dose often cannot be determined and therefore, different strategies for selecting a recommended phase 2 dose (RP2D) are needed beyond the conventional approach using maximum tolerated dose (MTD). While efficacy data can in principle be useful for guiding dose selection, the heterogenous population in many oncology phase 1 studies often does not yield rich enough data for efficacy to guide the dose selection. For monoclonal antibody (mAb) drugs which have the above properties, it is hypothesized that receptor occupancy (RO) and tumor penetration depth can be used to inform decision making regarding the RP2D.

Methods

The molecular properties (e.g., antigen expression level, binding affinity, antigen internalization rate) and typical patient exposures (e.g., trough concentrations) for approved mAb drugs targeting solid tumors were collected from the literature. **RO** was computed based on the interstitial drug concentration in tumor ($[mAb]_{isf}$) and the binding affinity (K_d). The interstitial drug concentration was predicted based on the tumor biodistribution data from the literature ($[mAb]_T = 0.3[mAb]_{blood}$[2] for antigen levels < 10^5molecules/cell and $0.8[mAb]_{blood}$[3] for Her2) and equilibrium equations. It was assumed that total antigen levels do not change over time. The tumor penetration depth was calculated based on the **Thiele modulus (φ^2)** which is a dimensionless ratio between time scales for target saturation and endocytic clearance[1]. Typical values for an IgG mAb were used for tumor permeability and tumor void fraction[1]. The capillary vessel radius of 10μm and the target tumor penetration depth of 100μm from the vessel wall were assumed[1].

$$\boldsymbol{\varphi^2 = \frac{k_e R^2([Ag]_T/\mathcal{E})}{2PR_{cap}[mAb]_{blood} + DK_d}}$$

k_e: Endocytic antigen (target) clearance rate
R: Target tumor penetration depth (100μm[1])
$\mathcal{E}$: Tumor void fraction (0.2[1])
P: Tumor permeability (3nm/s[1])
D: mAb Diffusion coefficient (10μm^2/s)
R_{cap}: Capillary vessel radius (10μm[1])



$$\boldsymbol{RO = \frac{[mAb]_{isf}}{[mAb]_{isf} + K_d}}$$

$$\boldsymbol{[mAb]_{isf} = \frac{-b + \sqrt{(b)^2 + 4K_d[mAb]_T}}{2}}$$

where $b = [Ag]_T + K_d - [mAb]_T$

Following equations were solved to give the above equation for $[mAb]_{isf}$

$[mAb]_T = [Ag{:}mAb] + [mAb]_{isf} = 0.3[mAb]_{blood}$

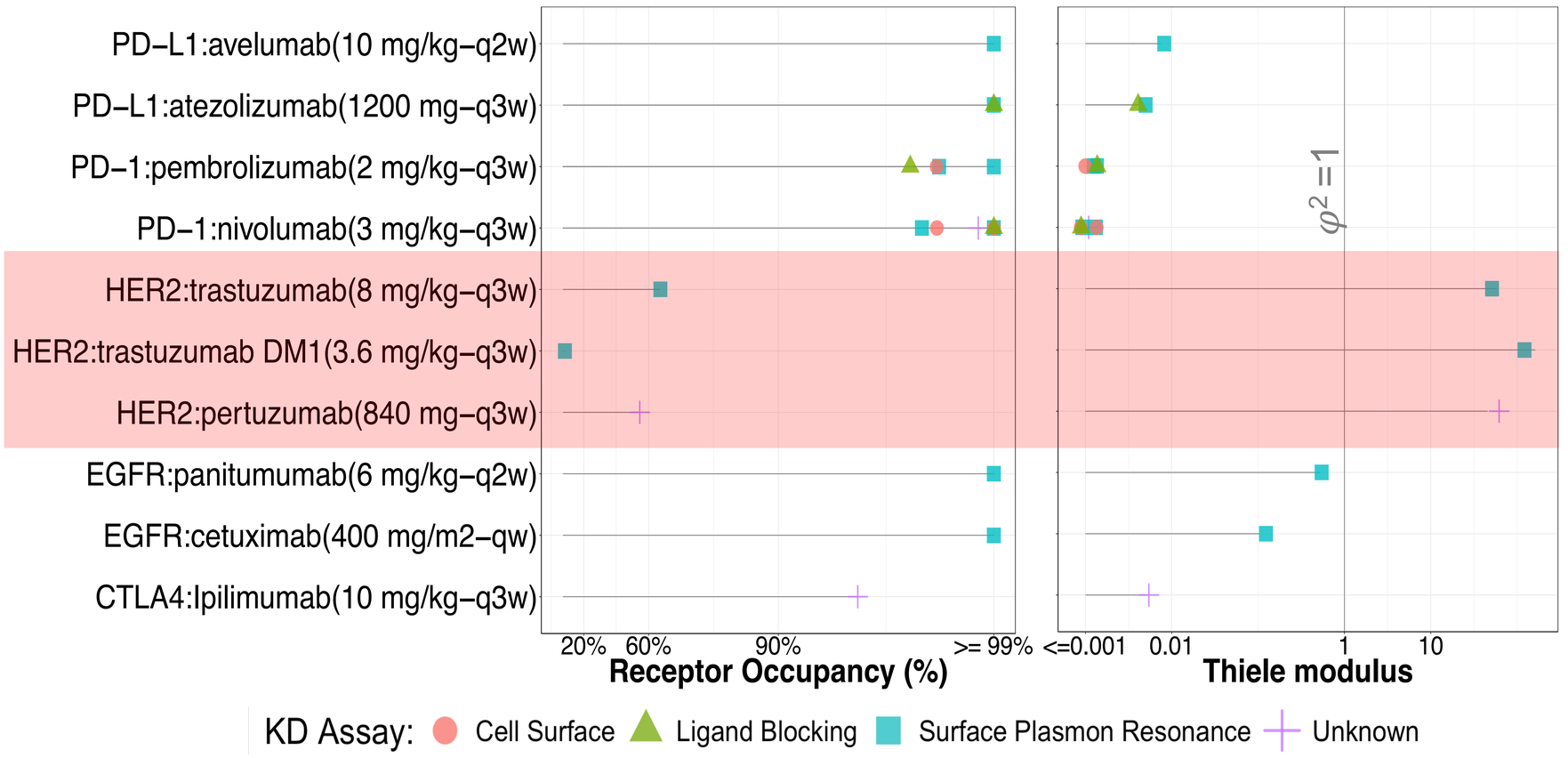
$[Ag]_T = [Ag{:}mAb] + [Ag]$

$K_d = \frac{[Ag][mAb]_{isf}}{[Ag{:}mAb]}$

$[mAb]_{blood}$: mAb conc. in blood
$[mAb]_{isf}$: mAb conc. in tumor interstitial fluid
$[mAb]_T$: Total mAb conc. in tumor
$[Ag]_T$: Total antigen conc. in tumor
$[Ag]$: Free antigen conc. in tumor
$[Ag{:}mAb]$: Bound mAb-Ag conc. in tumor
K_d: Binding Affinity

Summary of Results and Conclusions

- Most mAbs achieved RO>90% and φ^2 <1 at the approved dose levels suggesting their use as a surrogate RP2D guidance for mAbs targeting solid tumors when dose is not limited by safety concerns
- When drug is not in excess for its target (e.g., Her2), achieving complete receptor occupancy and penetration is difficult
- Lower RO might be sufficient for mAbs inducing ADCC or conjugated with cytotoxins (i.e., ADCs)



References

[1]Thurber GM, et al. Adv Drug Deliv Rev 2008;60:1421-1434; [2]Deng R, et al. MAbs 2016;8(3):593-603; [3]Mandler R et al. Cancer Res 2004;64:1460-1467