Use Of A Population Pharmacokinetic Modelling And Simulation Approach To Identify Flat Doses Of Domvanalimab In Phase 3 Studies

PRESENTER:

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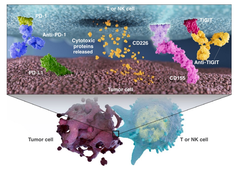


INTRODUCTION

- Domvanalimab (AB154) is an Fc-silent humanised IgG1 mAb designed to block the interaction of T-cell Immunoglobulin and ITM Domain (TIGIT) with CD112 and CD155, reducing inhibition of T cells and NK cells and, thereby, promoting antitumour activity
- Domvanalimab, in combination with zimberelimab, an investigational anti-PD-1 mAb, is being developed in multiple oncology indications, including non-small cell lung cancer (NSCLC) and upper gastrointestinal tract cancers; clinically meaningful improvement in objective response rate & progression-free survival was demonstrated compared to zimberelimab monotherapy in NSCLC patients[1]
- Domvanalimab was dosed based on body weight in early phase clinical studies; a model-informed drug development (MIDD) approach is used to provide justification for flat-dosing regimen, improving the ease of use and administration

OBJECTIVES

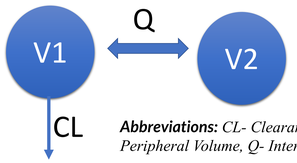
- To develop a population pharmacokinetics (PK) model for domvanalimab
- To derive flat doses of domvanalimab using MIDD approach to employ in future clinical studies

METHODS: Clinical Studies with Domvanalimab PK Data

Study	AB154CSP0001	AB154CSP0002 (ARC-7)
Study design	Phase 1, multicenter, open-label, dose-escalation study to evaluate the safety, tolerability, PK, PD, and clinical activity of domvanalimab as monotherapy and in combination with zimberelimab	Phase 2, multicenter, randomized, open-label, proof of concept study evaluated zimberelimab, zimberelimab+domvanalimab, and zimberelimab+domvanalimab+ etrumadenant
Population	Patients with advanced solid tumors	Metastatic (Stage IV) squamous or non-squamous non-small cell lung cancer (NSCLC)
Number of subjects*	69	42
Number of PK observations	786	507
DOM dosing regimen	0.5 mg/kg, 1 mg/kg, 3 mg/kg (monotherapy, Q2W); 1 mg/kg, 3 mg/kg, 10 mg/kg, 1200 mg (Q3W, with zimberelimab), 15 mg/kg, 20 mg/kg and 1500 mg (Q4W, with zimberelimab)	10 mg/kg Q2W or 15 mg/kg Q3W (In combination with zimberelimab and zimberelimab+etrumadenant)
ClinicalTrials.gov identifier	NCT03628677	NCT04262856

*Number of subjects who have received at least one dose of Dom treatment and for whom PK data are available at time of PK analysis

METHODS: Population PK Model Structure



Abbreviations: *CL- Clearance, V1- Central Volume, V2- Peripheral Volume, Q- Inter-compartmental Clearance*

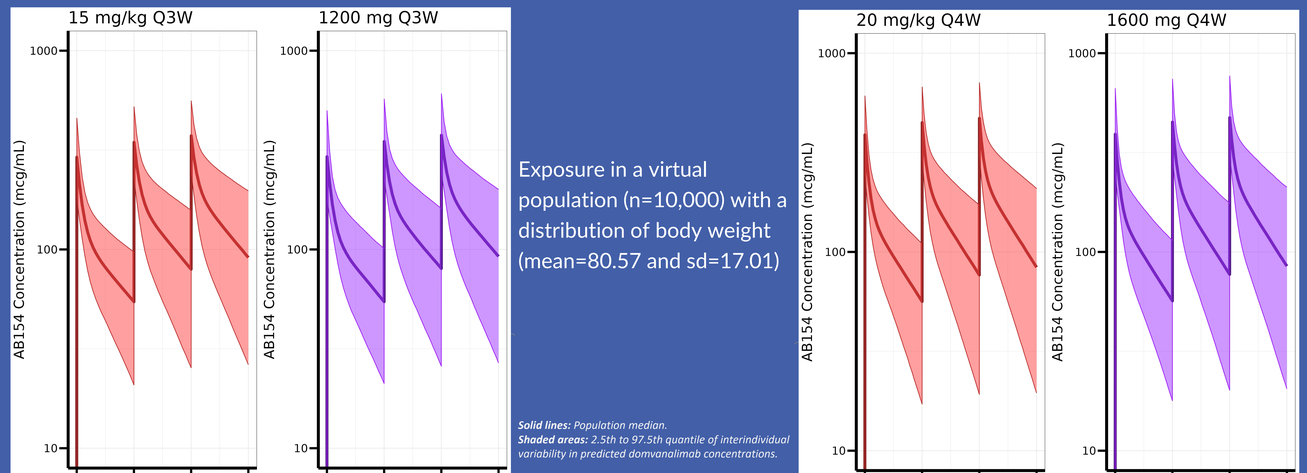
RESULTS

- A two-compartment model with weight as covariate on clearance and central volume of distribution was selected as the final model
- Simulations indicated that the overall difference in geometric means of all summary exposure measures between the weight based and flat dose regimens was < 1% when comparing 1200 mg Q3W to 15 mg/kg Q3W, and 1600 mg Q4W to 20 mg/kg Q4W regimens.

Key Findings

- **Population PK model-based simulations indicate that domvanalimab flat doses of 1200 mg Q3W and 1600 mg Q4W will result in similar exposure to 15 mg/kg Q3W and 20 mg/kg Q4W, respectively.**
- **Flat doses of 1200 mg Q3W and 1600 mg Q4W are being studied in ongoing Phases 2 and 3 clinical trials in multiple cancer indications**

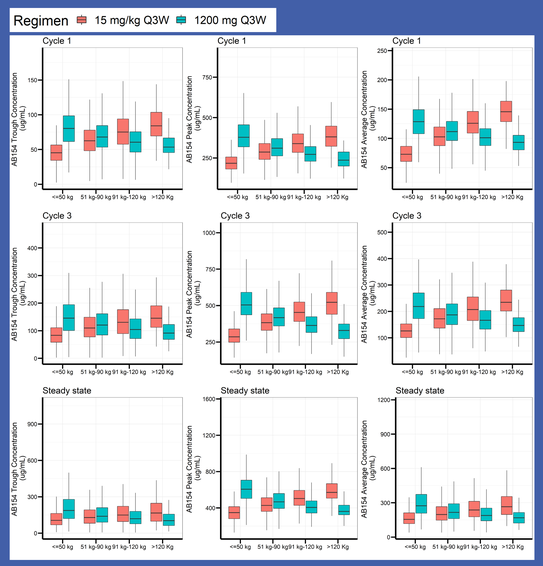
Simulations indicate that flat doses of 1200 mg Q3W and 1600 mg Q4W result in similar exposure as 15 mg/kg Q3W and 20 mg/kg Q4W, respectively.

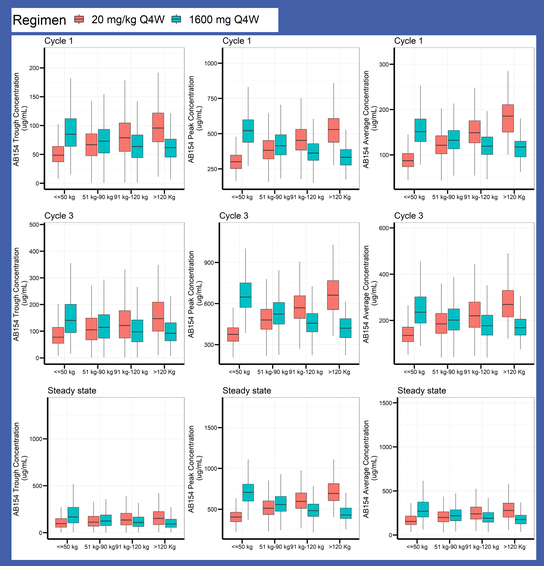


Exposure in a virtual population (n=10,000) with a distribution of body weight (mean=80.57 and sd=17.01)

Solid lines: *Population median.*
Shaded areas: *2.5th to 97.5th quantile of interindividual variability in predicted domvanalimab concentrations.*

Exposure of domvanalimab in different body weight groups indicate similar ranges of exposures at flat and weight-based dosing





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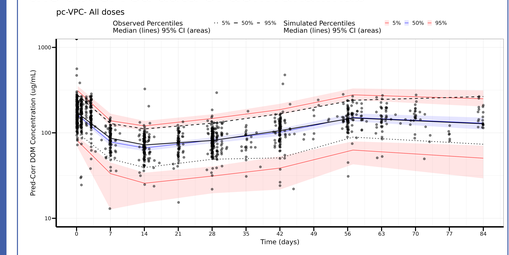
Parameter Estimates

Parameter	Parameter Estimate (%RSE)
Clearance (CL) (L/day)	0.259 (5)
Central volume (V_2) (L)	3.72 (3)
Intercompartmental clearance (Q) (L/day)	1.33 (7)
Central volume (V_P) (L)	3.55 (13)
Covariate Parameters	
Weight on V[#]	0.469 (28)
Weight on CL[#]	0.438 (43)
Interindividual Variability (%CV)	
η_{CL}	43 (24)
η_{V2}	24 (17)
η_{VP}	40 (34)
η_{Q}	40 (144)
Residual Error	
Proportional error (%CV)	23 (16)
Additive error (%CV)	7.30 (72)

%CV = percentage coefficient of variation; PK = pharmacokinetic(s); RSE = relative standard error;
[#]Based on an observed body weight range of 41 to 128 kg

Population PK model adequately described the observed data of domvanalimab



Comparison of Summary Exposures for domvanalimab following 15 mg/kg Q3W and 1200 mg Q3W

Summary Exposure	DOM 15 mg/kg Q3W GM, ug/mL (%CV)	DOM 1200 mg Q3W GM, ug/mL (%CV)	Difference in GMs, %
C_{min1}	62.1 (40)	62.6 (38)	0.80
C_{max1}	297.7 (28)	300.2 (28)	0.83
C_{avg1}	107.3 (27)	108.2 (23)	0.83
C_{minss}	127.5 (78)	128.6 (78)	0.86
C_{maxss}	449.2 (29)	453.1 (29)	0.86
C_{avgss}[a]	207.4 (51)	209.2 (51)	0.86

[a]C_{avgss} is calculated using the formula Dose/(clearance*tau), GM-Geometric mean, CV- coefficient of variation, Difference in GMs=$abs(\Delta GM)/GM_{1200\,mg\,Q3W}$
Abbreviations: C_{min1} = Trough concentration after first treatment; C_{max1} = Peak concentration on the first day of treatment; C_{avg1} = Average concentration after first treatment; C_{minss} = Trough concentration at steady-state; C_{maxss} = Peak concentration at steady-state; C_{avgss} = Average concentration at steady-state.

Comparison of Summary Exposures for domvanalimab following 20 mg/kg Q4W and 1600 mg Q4W

Summary Exposure	Domvanalimab 20 mg/kg Q4W GM, ug/mL (%CV)	Domvanalimab 1600 mg Q4W GM, ug/mL (%CV)	Difference in GMs, %
C_{min1}	64.0 (49)	64.6 (47)	0.93
C_{max1}	397.7 (28)	401.1 (27)	0.85
C_{avg1}	126.6 (28)	127.7 (25)	0.86
C_{minss}	109.3 (86)	110.2 (86)	0.82
C_{maxss}	533.3 (27)	537.9 (27)	0.86
C_{avgss}[a]	207.4 (50)	209.2 (49)	0.86

[a]C_{avgss} is calculated using the formula Dose/(clearance*tau), GM-Geometric mean, CV- coefficient of variation, Difference in GMs=$abs(\Delta GM)/GM_{1600\,mg\,Q4W}$
Abbreviations: C_{min1} = Trough concentration after first treatment; C_{max1} = Peak concentration on the first day of treatment; C_{avg1} = Average concentration after first treatment; C_{minss} = Trough concentration at steady-state; C_{maxss} = Peak concentration at steady-state; C_{avgss} = Average concentration at steady-state.

METHODS: Software

- The population PK-PD analysis was conducted using nonlinear mixed-effects modeling with the NONMEM software, version 7.5
- Graphical and all other statistical analyses, including evaluation of NONMEM outputs, were performed using R version 3.6.2 for Windows

REFERENCE

1. Johnson et al. 2022. ARC-7: Randomized phase 2 study of domvanalimab + zimberelimab ± etrumadenant versus zimberelimab in first-line, metastatic, PD-L1-high non-small cell lung cancer (NSCLC). *J Clin Oncol.* 40:36_suppl, 397600

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