

Applications of an Immunogenicity QSP Platform: Predictive Modelling for ADA and PK Impact for Biotherapeutic Combinations

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Background

- The development of anti-drug antibodies (ADA) can significantly alter the pharmacokinetics (PK), reduce efficacy and compromise safety.
- Immunogenicity (IG) is currently mitigated in the preclinical phase by using *in silico* prediction tools and *in vitro* assays to guide protein engineering and compound selection, and in the clinic through dose optimisation, tolerance induction, close monitoring, and co-medication with immunosuppressants [1].
- Mitigation strategies do not address biotherapeutics that are dosed in combination, where the IG risk can be even more uncertain through synergistic effects, particularly for immuno-modulatory drugs [2].
- The IG Simulator is a quantitative systems pharmacology (QSP) model [3,4] that aims to predict ADA production and its impact to PK for management of clinical immunogenicity (Figure 1A).
- Nivolumab, a PD-1 inhibitor, and ipilimumab, a CTLA-4 inhibitor, are immunotherapies approved for several oncology indications either as monotherapies or in combination. In the CheckMate-067 clinical trial for advanced melanoma (NCT01844505), treatment-emergent anti-nivolumab ADA incidence increased when used in combination with ipilimumab versus nivolumab monotherapy [5,6].
- While uncertainty exists [7,8], there is evidence to suggest ipilimumab binding to CTLA4 on Tregs could increase CD4+ T cell activation and antibody production and is a plausible mechanism to explain the increase in nivolumab ADA when dosed in combination [9,10,11,12].

Objective

- to update the IG Simulator to model the contribution of CTLA4-dependent cell activities via Tregs to the development of nivolumab ADA
- to use the updated model to test the hypothesis that inhibition of Treg proliferation by ipilimumab can explain increased nivolumab immunogenicity for combination versus monotherapy.

Methods

- PK of nivolumab and ipilimumab were modelled using a physiologically-based PK (PBPK) model [14], with time-varying clearance captured by a sigmoid $E_{\max}$ function [15,16].
- The PBPK model parameters were integrated with predicted MHCII binding constant from *in silico* risk assessment of nivolumab T cell epitopes within the IG Simulator (Figure 1A).
- The IG Simulator was expanded to include a mechanistic model of T regulatory cell activation and activity previously described in [13] (Figure 1B).
- The inhibition of Treg proliferation rates because of CTLA-4 inhibition by ipilimumab was integrated using an inhibitory $E_{\max}$ model using the reported *in vitro* IC_{50} [10] (Figure 1B).
- Simulations were performed to predict the incidence of anti-nivolumab immunogenicity and the impact of ADA on nivolumab PK for clinical dosing regimens of nivolumab administered alone or in combination with ipilimumab.

Results

- The PBPK model captured the clinical plasma concentration profiles of nivolumab and ipilimumab when used administered alone or in combination (Figure 2).

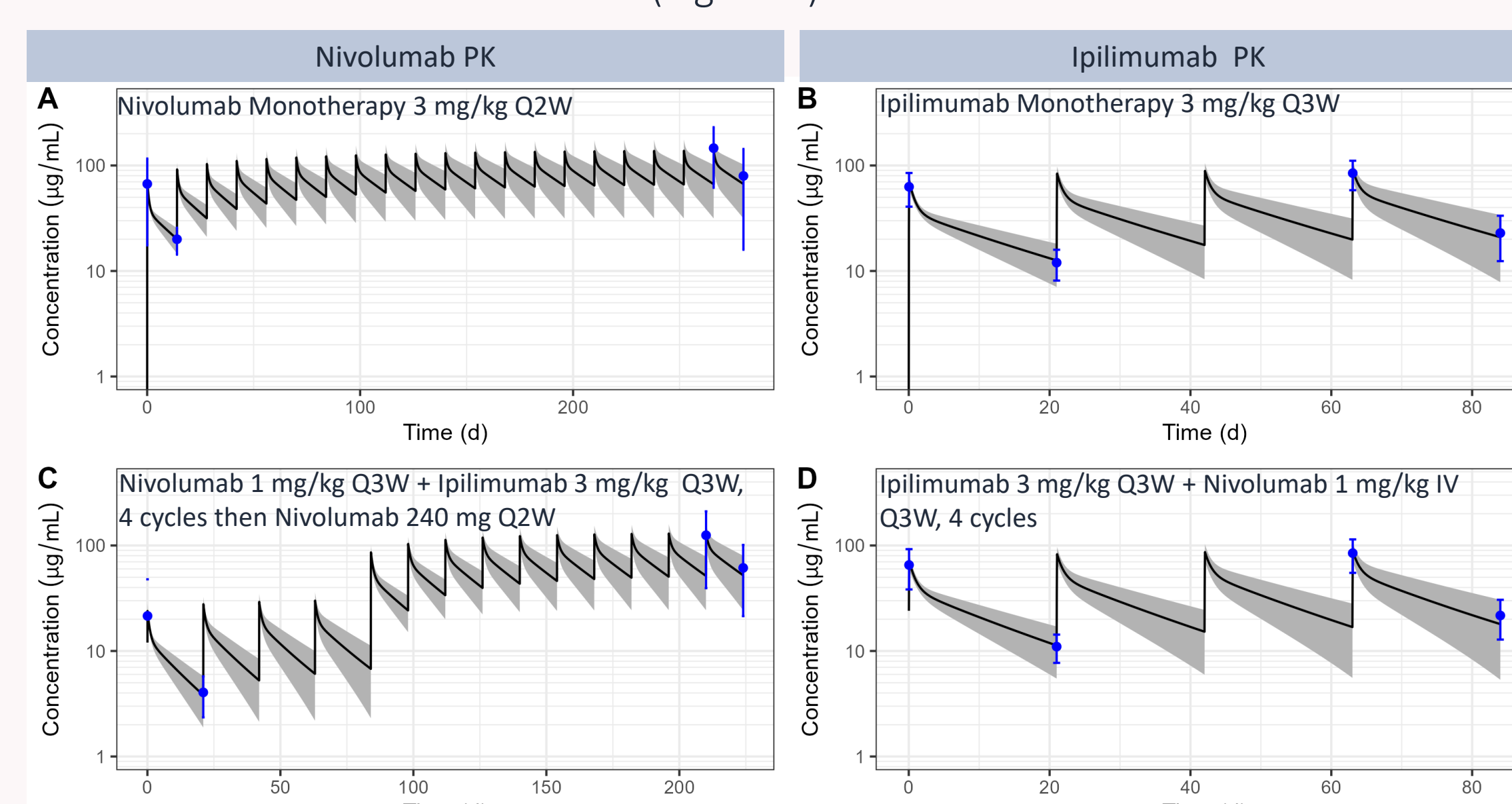


Figure 2. Predicted (lines) and observed (points [15,16]) plasma concentration (mean and SD) of (A) nivolumab 3 mg/kg IV infusion Q2W as monotherapy, (B) ipilimumab 3 mg/kg IV infusion Q3W as monotherapy, (C) nivolumab 1 mg/kg IV Q3W in combination with ipilimumab 3 mg/kg Q3W, 4 cycles then nivolumab 240 mg Q2W maintenance, and (D) ipilimumab 3 mg/kg IV Q3W in combination with nivolumab 1 mg/kg Q3W, 4 cycles.

- The original IG Simulator without Tregs, over-predicted a 96% incidence of anti-nivolumab ADA following nivolumab monotherapy versus 12.3% observed in the clinical study, which included one case (0.3% incidence) of persistent ADA (ADA positivity between 2 consecutive time points at least 16 weeks apart) [5,6]. Persistent ADA were predicted to reduce nivolumab trough concentrations, however no clinically meaningful impact of ADA on PK, safety or efficacy were previously identified [5,6] (Figure 3, left).
- Extension of the model to include Treg activation reduced the predicted anti-nivolumab ADA incidence to 11.2%. All predicted ADA were transient with no impact of ADA on nivolumab PK (Figure 3, middle).
- Concentration-dependent inhibition of Tregs cells by ipilimumab resulted in an increase in predicted ADA incidence for combination therapy to 44%, in good agreement with overall ADA incidence reported in the clinical study (44%) [5,6]. The incidence of persistent ADA is overpredicted (29% versus 5.2% observed) and only persistent ADA are predicted to reduce nivolumab trough concentrations (Figure 3, right).

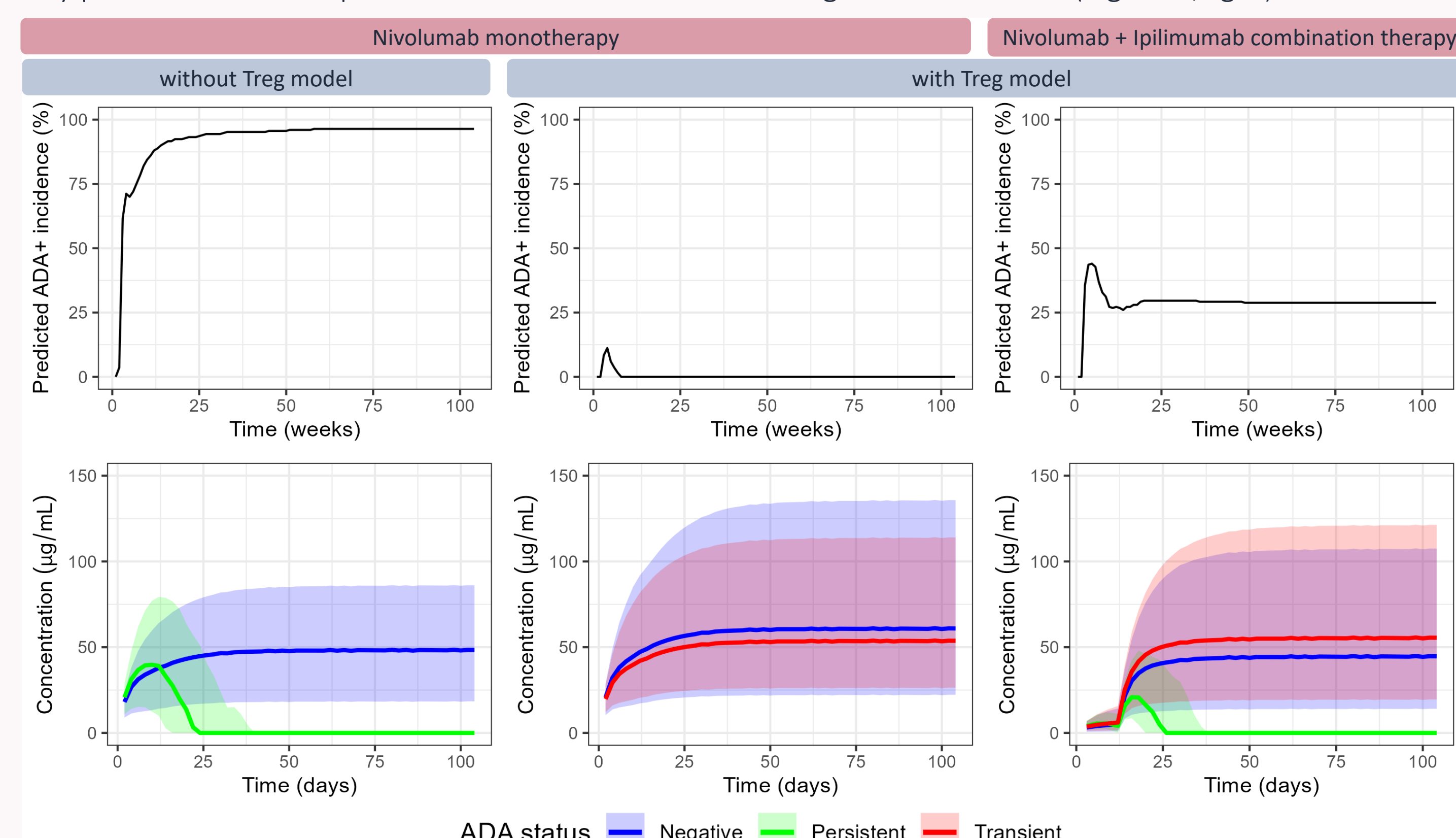


Figure 3. Predicted incidence of anti-nivolumab immunogenicity (top) and impact of ADA on nivolumab trough concentration (bottom; median and 5th and 95th percentiles) for nivolumab monotherapy (3 mg/kg IV infusion Q2W) without (left) and with (center) inclusion of the T regulatory cell model and co-therapy with nivolumab 1 mg/kg and ipilimumab 3 mg/kg Q3W for 4 cycles then nivolumab 3 mg/kg Q2W maintenance.

- Predicted incidence of anti-nivolumab ADA following combination therapy was highly sensitive to the IC_{50} for ipilimumab (Figure 4), suggesting that any uncertainty in the *in vitro* IC_{50} could significantly impact outcomes and is a possible explanation for overestimation of persistent ADA by the model.

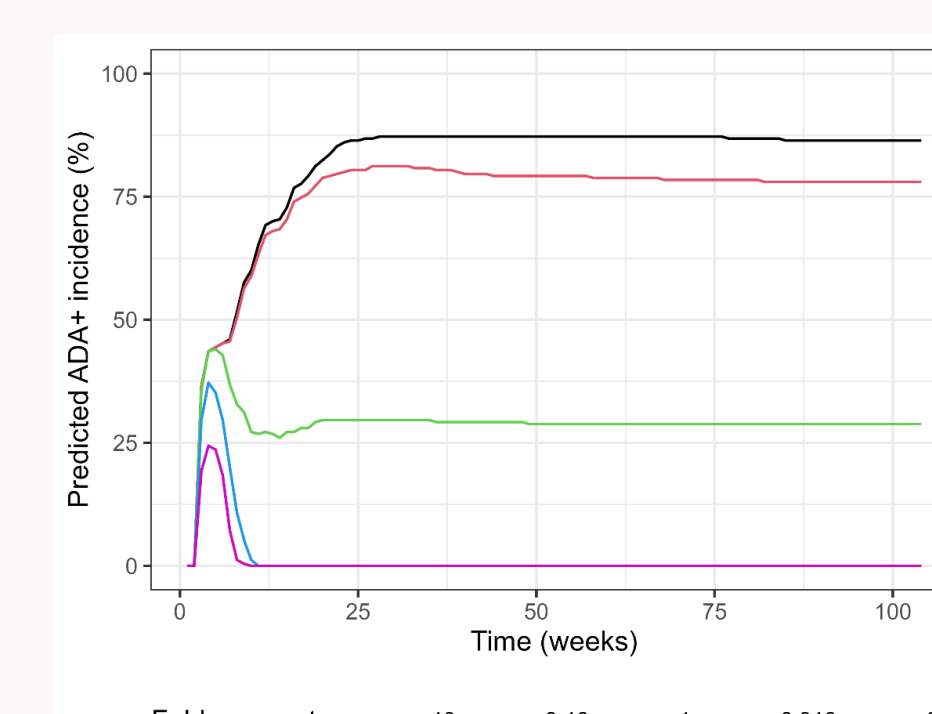


Figure 4. Parameter scan to assess the sensitivity of ADA incidence prediction to ipilimumab IC_{50} for inhibition of Treg proliferation.

Conclusions

- Results from the model support that activation of inhibitory T cell populations such as Tregs can attenuate CD4+ T cell activation and supports inhibition of Treg activity by ipilimumab as a potential mechanism to explain the increase in anti-nivolumab ADA incidence following co-therapy.
- This model framework can be utilized to evaluate other CTLA4-dependent effects on B cell activity and represents a significant advancement in developing a mechanistic basis for predicting synergistic ADA formation responses through the regulation of B cell activity.
- This understanding can inform predictions of clinical immunogenicity for other immunomodulatory biotherapeutics.

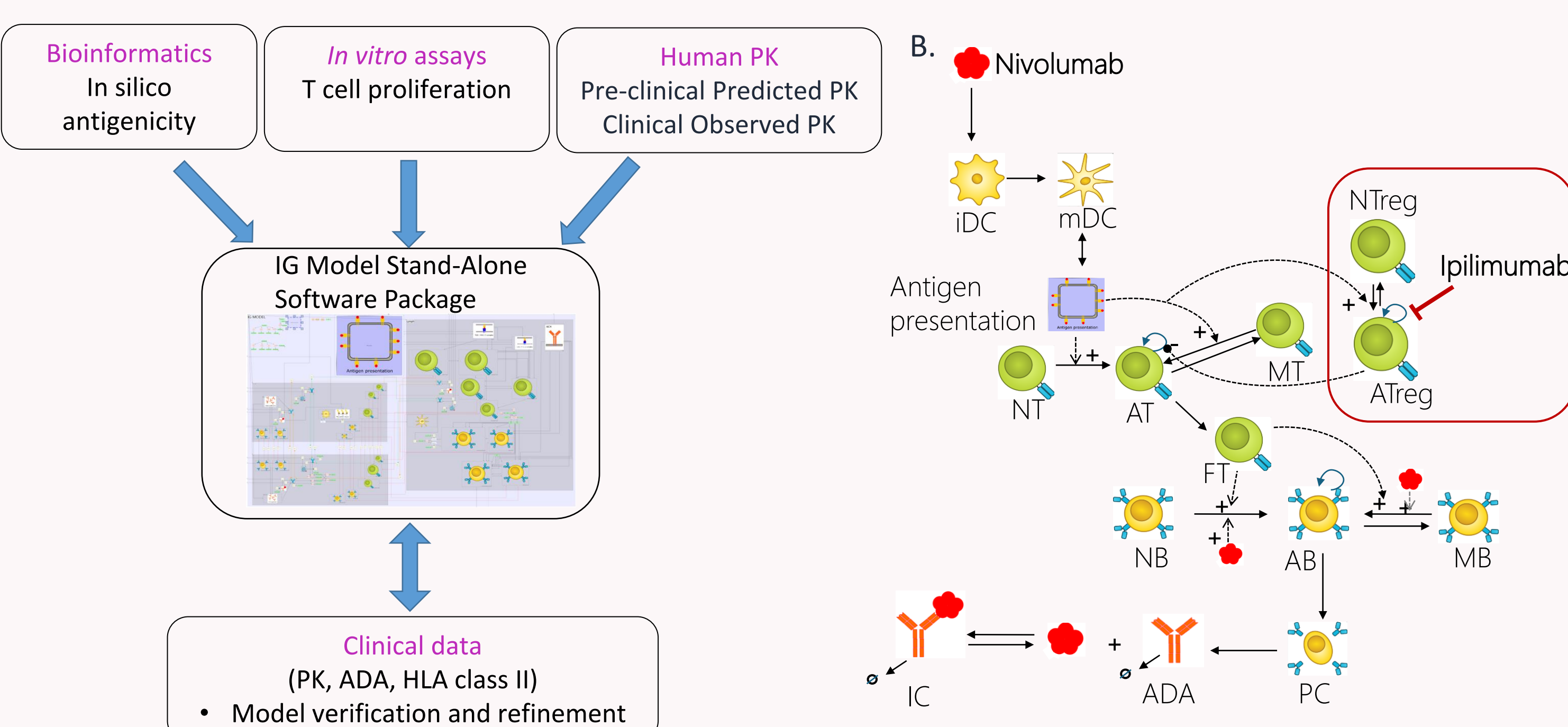


Figure 1. Summary of the IG Simulator workflow (A) and extensions to the model to integrate the contribution of Tregs and inhibition of Treg activation by ipilimumab.

iDC and mDC – immature and mature dendritic cells; NT, AT, MT and FT – naïve, activated, memory and functional T cells; NB, AB and MB – naïve, activated and memory B cells; PC – plasma cells; NTreg and ATreg – naïve and activated Tregs; IC – immune complex.

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