The combined use of propensity score matching and a joint tumor growth dynamics (TGD) - Overall Survival (OS) model to benchmark the efficacy of new treatments for advanced renal cell carcinoma (RCC)

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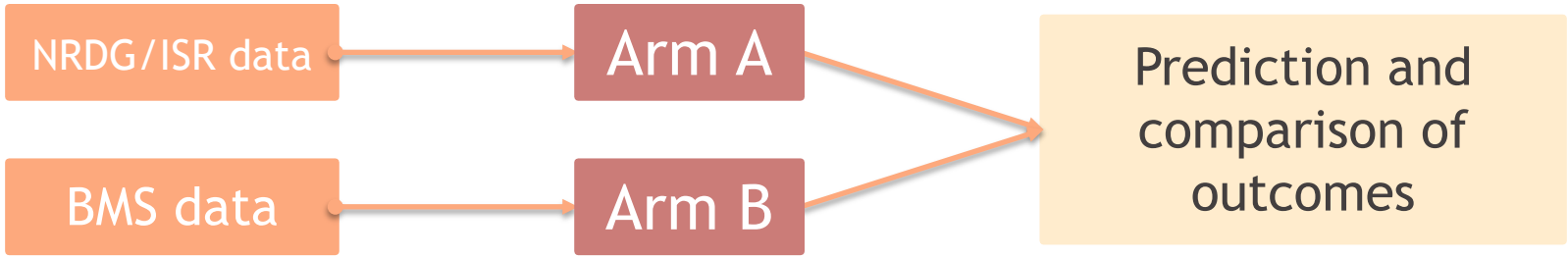
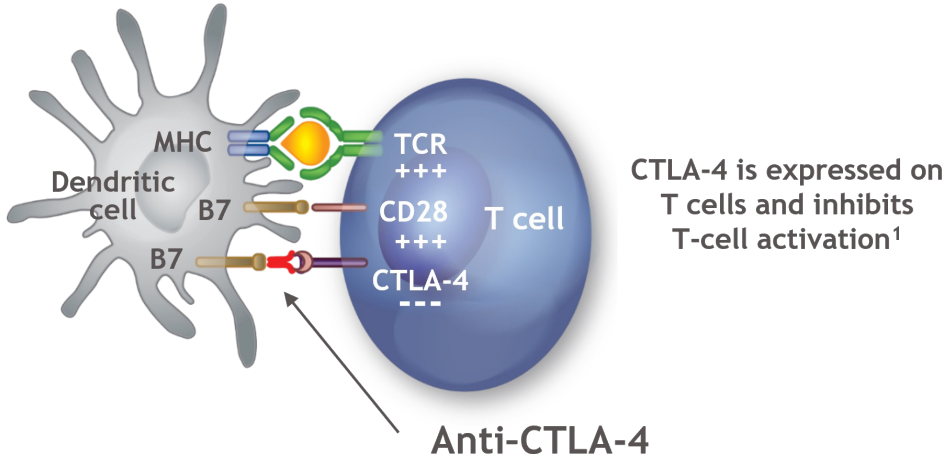
Background

- Non-registrational data generation (NRDG) and investigator sponsored research (ISR) studies typically have a small number of patients, are single arm studies, and have short-term follow-up of overall survival (OS) due to the nature of the research
- These limitations make it difficult to compare overall survival data from NRDG/ISR studies to an appropriate benchmark treatment
- The present work is to establish feasibility of using a joint tumor growth dynamic model (TGD-OS) to extrapolate OS and generate a synthetic control arm from historical data by propensity score modeling

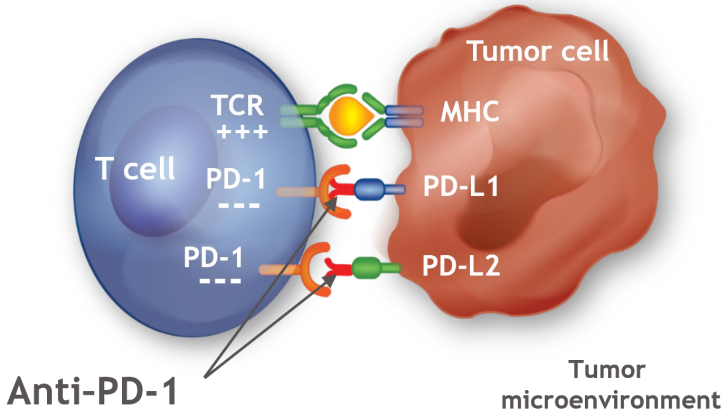


Introduction to disease and treatments

- Renal cell carcinoma (RCC)
  - 90% of kidney cancer
  - 30% manifest itself as metastatic disease (mRCC)
  - Karnofsky performance score (KPS) 0-100 is a measure of functional impairment
  - MSKCC/Motzer risk score (0-5) is calculated based on 5 independent measurements
  - IMDC—International metastatic RCC database consortium score (0-4)
- Treatment paradigms for mRCC
  - Tyrosine kinase inhibitors (TKIs): sunitinib (anti-VEGFR2, PDGFR and KIT) …
  - Immuno-oncology (IO) therapies: ipilimumab (Ipi,I) and nivolumab (Nivo,N) …



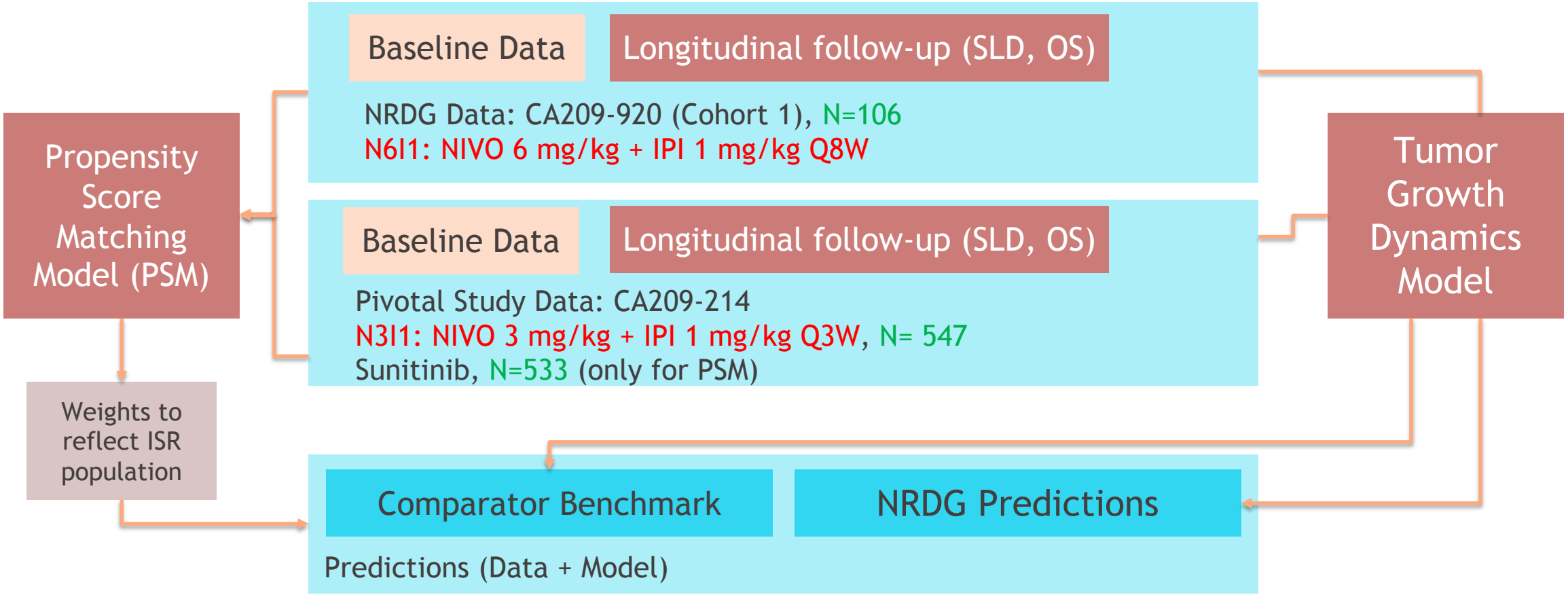
CTLA-4 is expressed on T cells and inhibits T-cell activation[1]



PD-1 expression on tumor-infiltrating lymphocytes interacting with PD-L1/ PD-L2 is associated with reduced effector function

Combined Modeling Approach (TGD-OS + PSM)

- A previously developed joint TGD-OS model for advanced RCC was refined (slide 4 and 5)
- The fitted joint TGD-OS model was then used to predict OS of RCC patients in Cohort 1 of NRDG study CA209-920 (NCT02982954) in which subjects received an investigational dosing regimen (N6I1)
- The predicted OS for CA209-920 (Cohort 1) was benchmarked against the approved NIVO + IPI treatment regimen (N3I1) investigated in the registrational study of CA209-214 by utilizing a propensity score model (PSM)



Joint TGD-OS model (1/2)

Joint TGD-OS model was developed with data from 1275 subjects from historical RCC studies, including CA209-214

Longitudinal Model for SLD

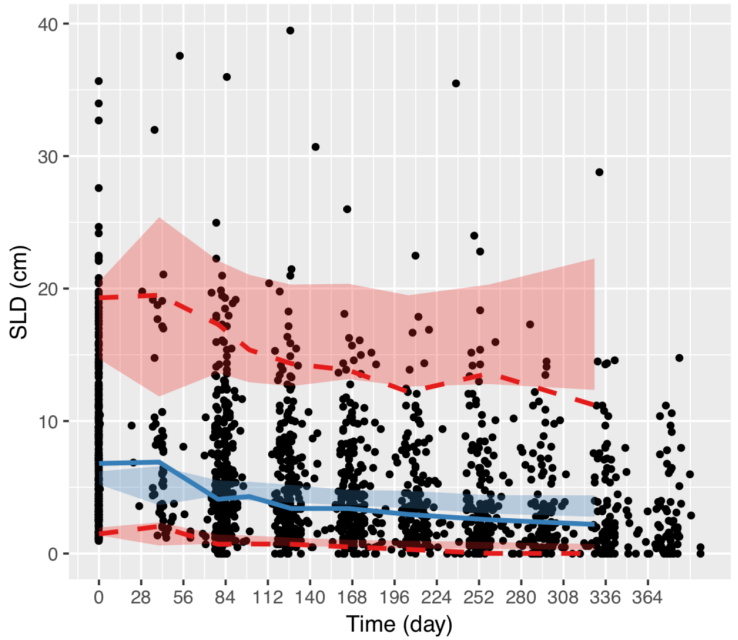
- Mixture Wang model (Feng et al. CPT PSP 8 (2019):825-834)

$$\hat{y}_{ij,t} = TB0_{i,l} \times \exp\left(-\mathrm{TS}_{i,l} t_{ij}\right) + \mathrm{TG}_{i,l} t_{ij} + \mathrm{TLIM}_{i,l}$$

Where i indexes patients, j indexes observations, l = 1,2,3 indexes sub-population

  - $TB0_{i,l}$ - is the baseline tumor burden
  - $TS_{i,l}$ - tumor shrink rate (1/week)
  - $TG_{i,l}$ - tumor growth rate (cm/week)
  - TLIM - the approximate tumor limit of patient

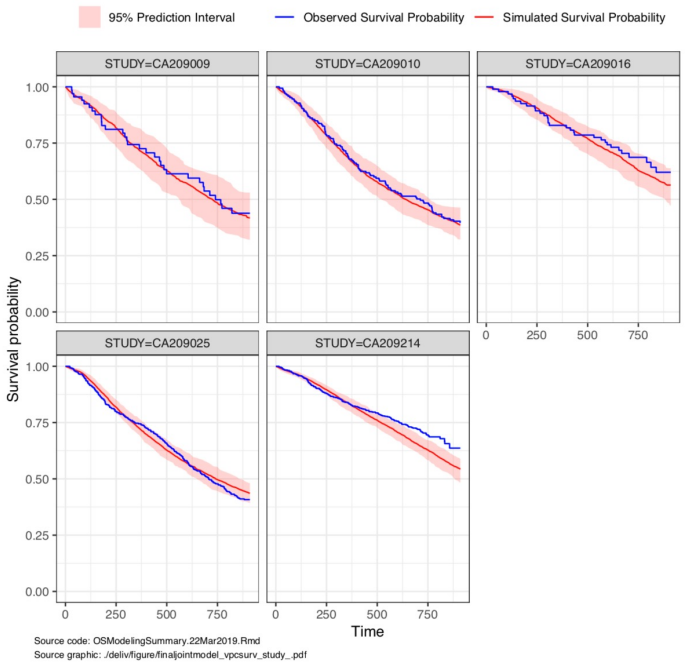
- The following covariates were included based on either improved model performance on BIC or covariates of clinical interest
  - TB0~ Albumin + KPS ((< 90, ≥ 90)
  - TS ~ Line of therapy + Number of Index Lesions + PDL1 status
  - TG ~ Albumin + Line of therapy + Number of Index Lesions + PDL1 status



Joint TGD-OS model (2/2)

Model for OS

- Parametric (log-logistic) model was selected as it showed lowest BIC compared with the other models (Weibull and Gompertz)
- Time-varying tumor size and Tumor growth and shrinkage were included on the hazard
- Covariates were included by backward elimination from the full model based on BIC
  - MSKCC risk score
  - KPS (< 90, ≥ 90)



Hazard of death at time *t* for patient *i*

$$h_i(t|x_i) = \frac{\left(\frac{\gamma}{\lambda_i(t)}\right) \exp\left((\gamma-1)\log\left(\frac{t}{\lambda_i(t)}\right)\right)}{1+\exp\left(\gamma \log\left(\frac{t}{\lambda_i(t)}\right)\right)}$$

$$\text{where } \log\lambda_i(t) = x_{OS,i}^{t}\beta + \text{TumEff}_i(t) + \text{NewLeff}_i(t)$$

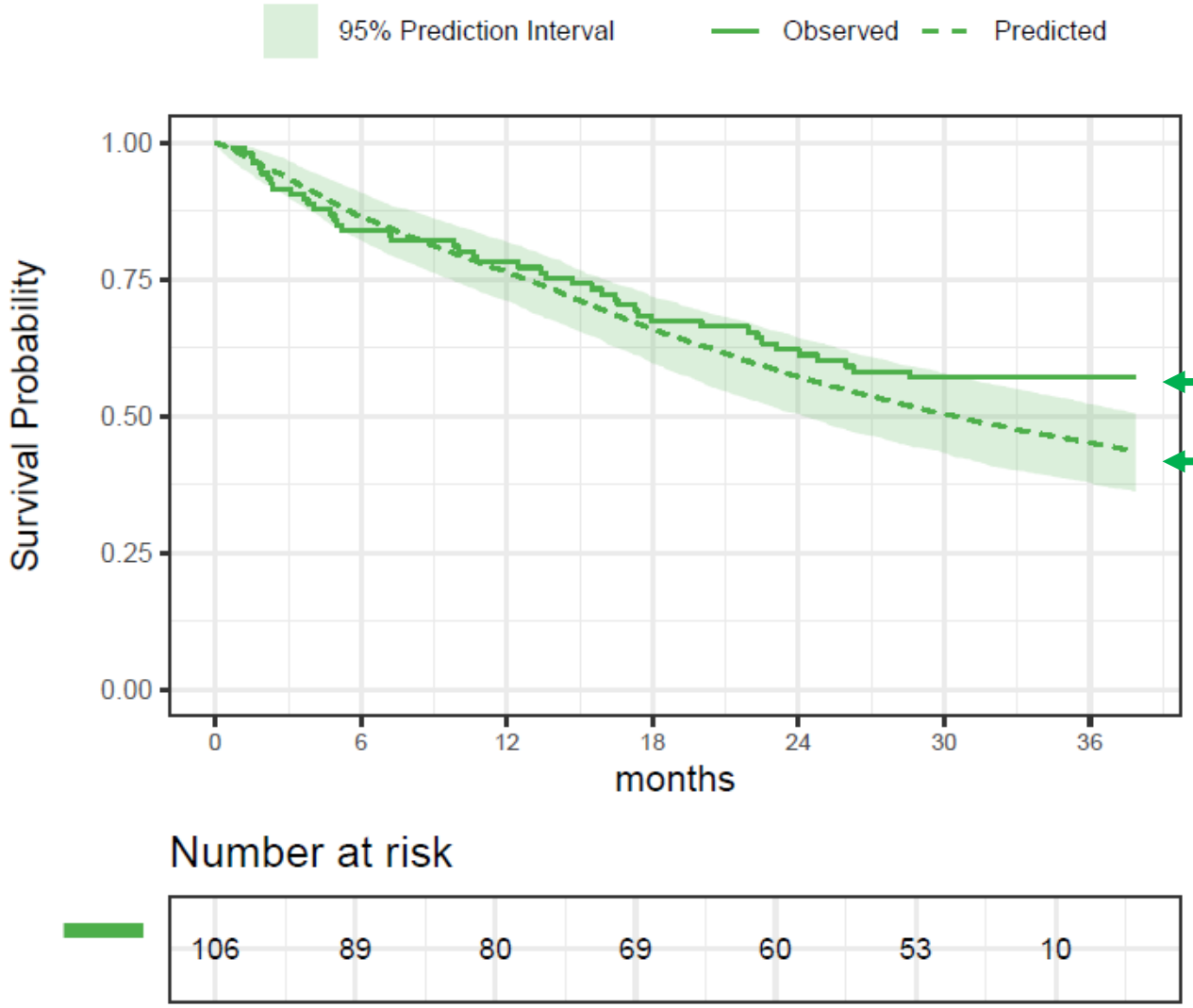
- γ : shape parameter
- $x_{OS,i}$: baseline covariates of patient *i*
- TumEff (t) : effect of time-varying absolute tumor size derived from the TGD model

$$\theta_{ATS}\log\left\{\frac{y_{i,j,t}(t)}{10}\right\}$$

- NewLEff(t) : time-varying effect of the appearance of new lesions

$$\text{NewLEff}_i(t) = \begin{cases} 0 & t < t_{i,\text{NEWL}} \\ \theta_{\text{NEWL}} & t \geq t_{i,\text{NEWL}} \end{cases}$$

Observed and Predicted OS of CA209-920 (NRDG Study) using TGD-OS Model



Observed overall survival in ***2020***

Predicted OS using tumor size data in ***2018*** as input into the joint TGD-OS model

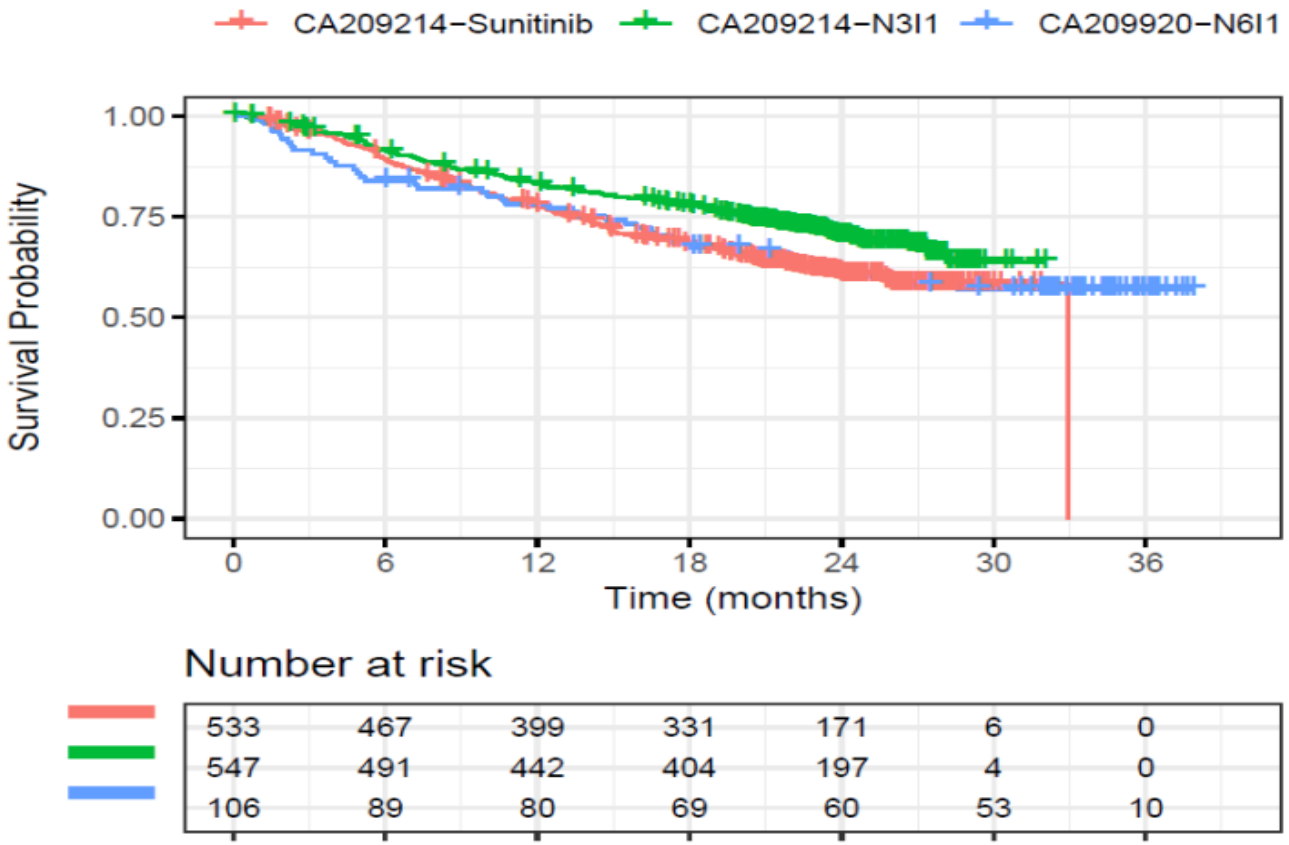
TGD-OS model using tumor size data in 2018 adequately predicted OS curve in 2020

KM Curve of OS in CA209-214 and 920 (Unweighted)

- OS of N6+I1 (CA209-920) appears less favorable than that of N3+I1 (CA209-214) based on cross-study comparisons
- Results of cross-study comparison could be misleading, due to imbalances in subject characteristics

Covariate	Categories	CA209214-Sunitinib	CA209214-N3I1	CA209920-N6I1
		N = 533	N = 547	N = 106
IMDC	poor	95 (17.8)	101 (18.5)	20 (18.9)
IMDC	intermediate	332 (62.3)	327 (59.8)	86 (81.1)
IMDC	favorable	106 (19.9)	119 (21.8)	
Karnofsky	less than 80	52 (9.76)	54 (9.87)	1 (0.943)
Karnofsky	80	95 (17.8)	82 (15.0)	24 (22.6)
Karnofsky	greater than 80	386 (72.4)	411 (75.1)	81 (76.4)
Line of therapy	1st line	529 (99.2)	535 (97.8)	104 (98.1)
Line of therapy	2nd line	4 (0.750)	12 (2.19)	2 (1.89)
MSKCC	poor	50 (9.38)	42 (7.68)	30 (28.3)
MSKCC	intermediate	210 (39.4)	209 (38.2)	41 (38.7)
MSKCC	favorable	273 (51.2)	296 (54.1)	35 (33.0)

Covariate	CA209214-Sunitinib	CA209214-N3I1	CA209920-N6I1
Age (years)	60.8 (10.1) [21.0,85.0]	61.2 (9.65) [34.0,85.0]	62.8 (9.43) [40.0,84.0]
Albumin (g/dL)	4.04 (0.506) [2.00,5.10]	4.09 (0.488) [1.80,5.20]	3.68 (0.951) [0.00,4.90]
Abs lymphocyte ct (1000/muL)	1.62 (0.625) [0.400,3.81]	1.65 (0.638) [0.300,4.36]	1.52 (0.708) [0.00100,6.10]
Bodyweight (kg)	82.4 (19.7) [34.1,168]	82.4 (18.9) [42.5,177]	91.8 (20.3) [50.1,148]
BL SLD (cm)	8.23 (6.31) [1.00,35.9]	8.17 (5.99) [1.00,35.7]	10.2 (6.95) [1.20,27.3]



Generate a synthetic control arm by propensity score modeling

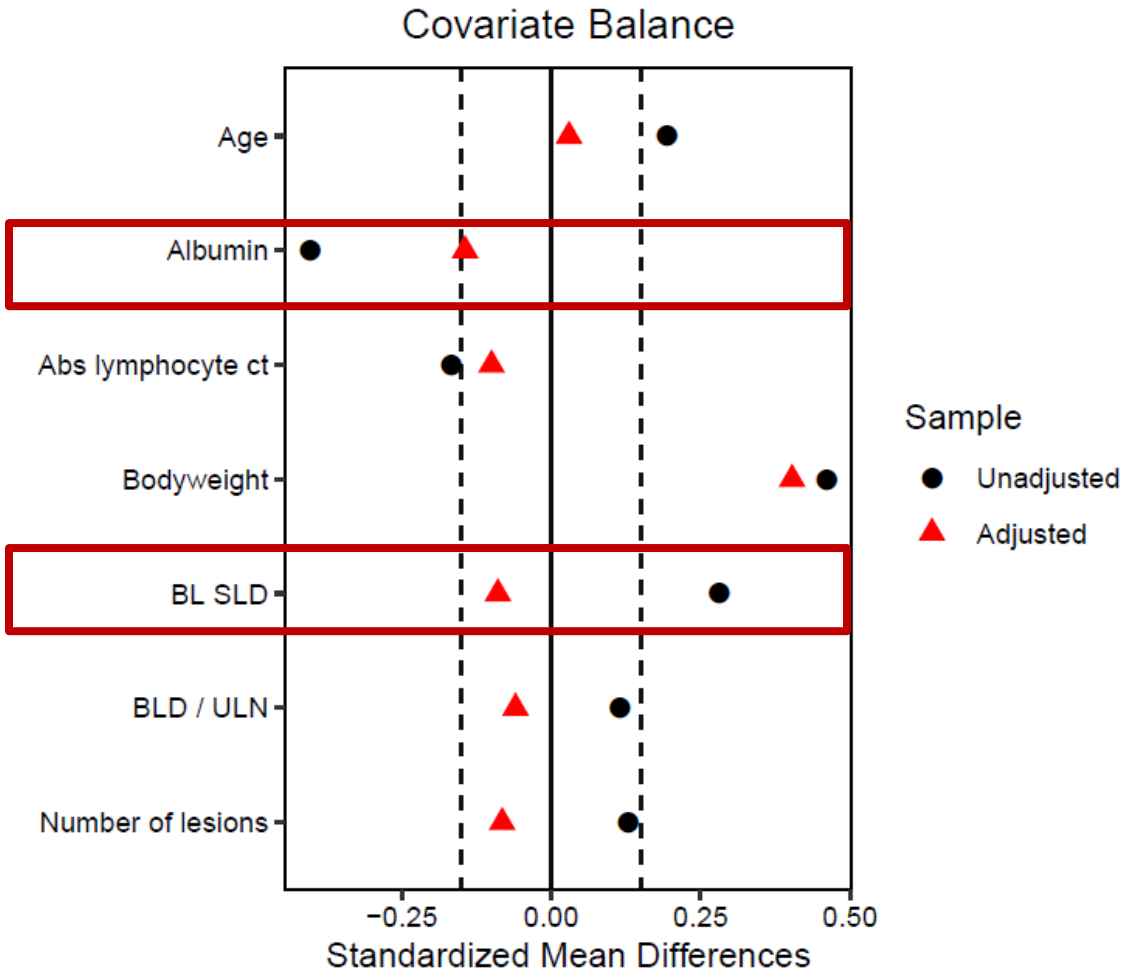
- Goal: Estimate the survival distribution and hazard ratio for the CA209-214 regimen ***had it be tested in CA209-920 population and compared to CA209-920 regimen***
- Achieved this through a weighted Kaplan-Meier estimate using average treatment effect in the treated (ATT) weights
- The ATT weights are a function of
  - The conditional probability of a subject selected randomly from the pooled population coming from the CA209-920 study, conditional on baseline covariates (***propensity score***)
  - The proportion of subjects in the pooled population who were in the CA209-920 study

$$w_i = \frac{\Pr(Z_i = 1|x_i)\Pr(Z_i)}{1 - \Pr(Z_i = 1|x_i)}$$

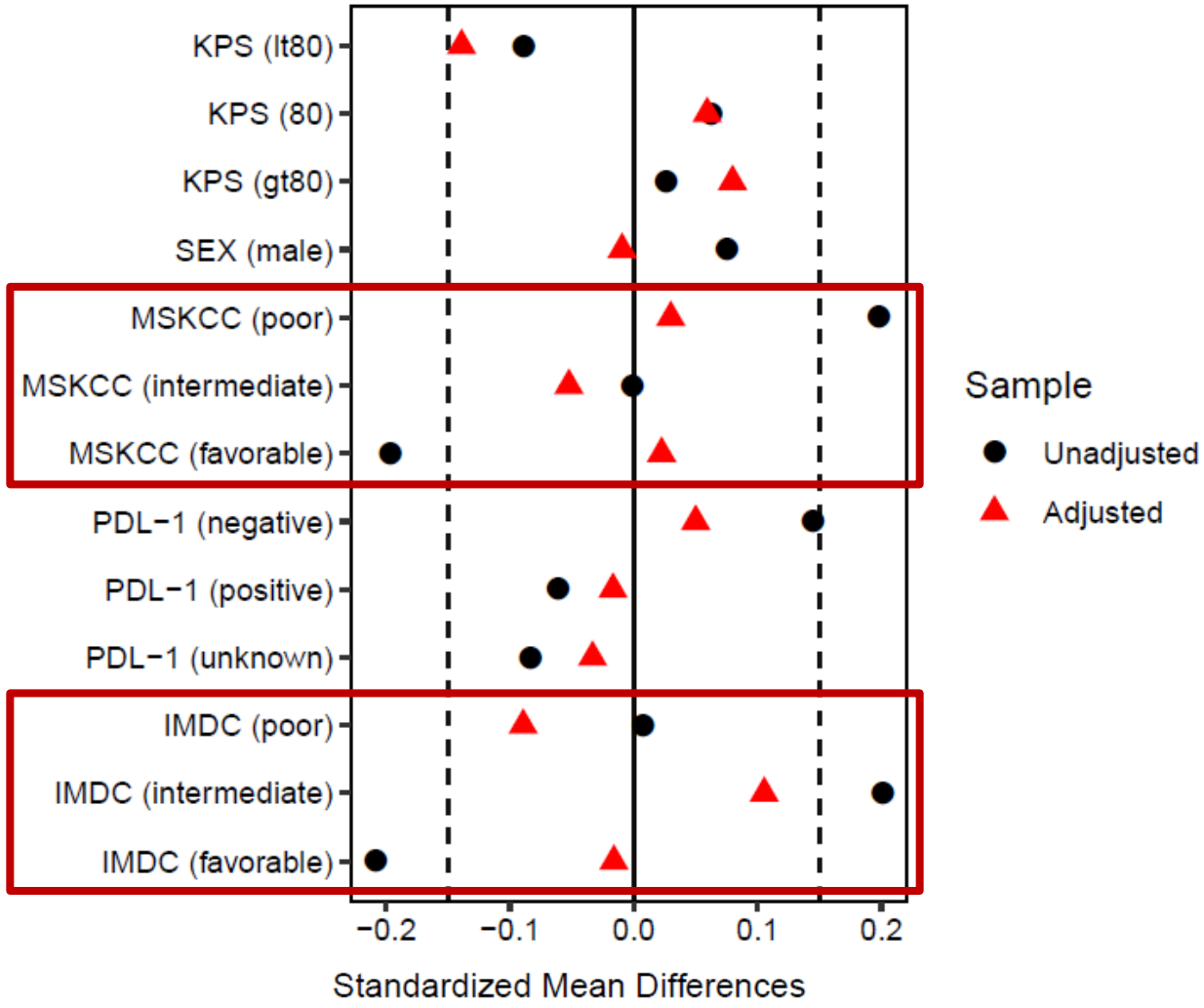
  - ATT weights weight subjects in CA209-214 relative to how similar their baseline covariates are to patients in the CA209-920 population
- The propensity scores were estimated using a random forest model (input features shown on slide 10)
- To assess how well the original and weighted CA209-214 populations compare to the CA209-920 population, plots comparing the weighted and unweighted mean differences were generated

After Weighting, Patients Characteristics in CA209-214 More Closely Align with CA209-920

Continuous Covariates

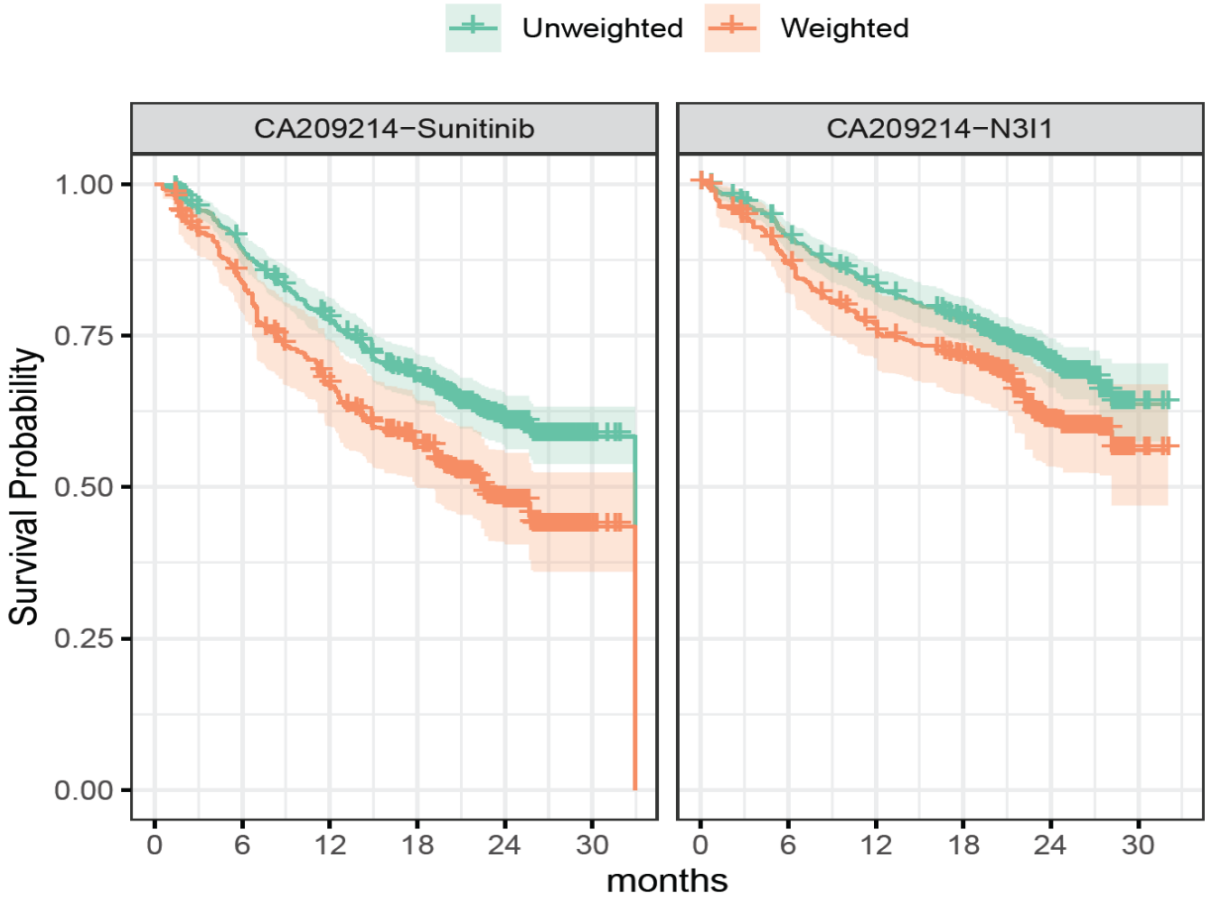


Categorical Covariates



BLD/ULN : Baseline LDH divided by Upper Limit of Normal
KPS : Karnofsky Performance Status
MSKCC : Memorial Sloan Kettering Cancer Center
IMDC : International Metastatic RCC Database Consortium

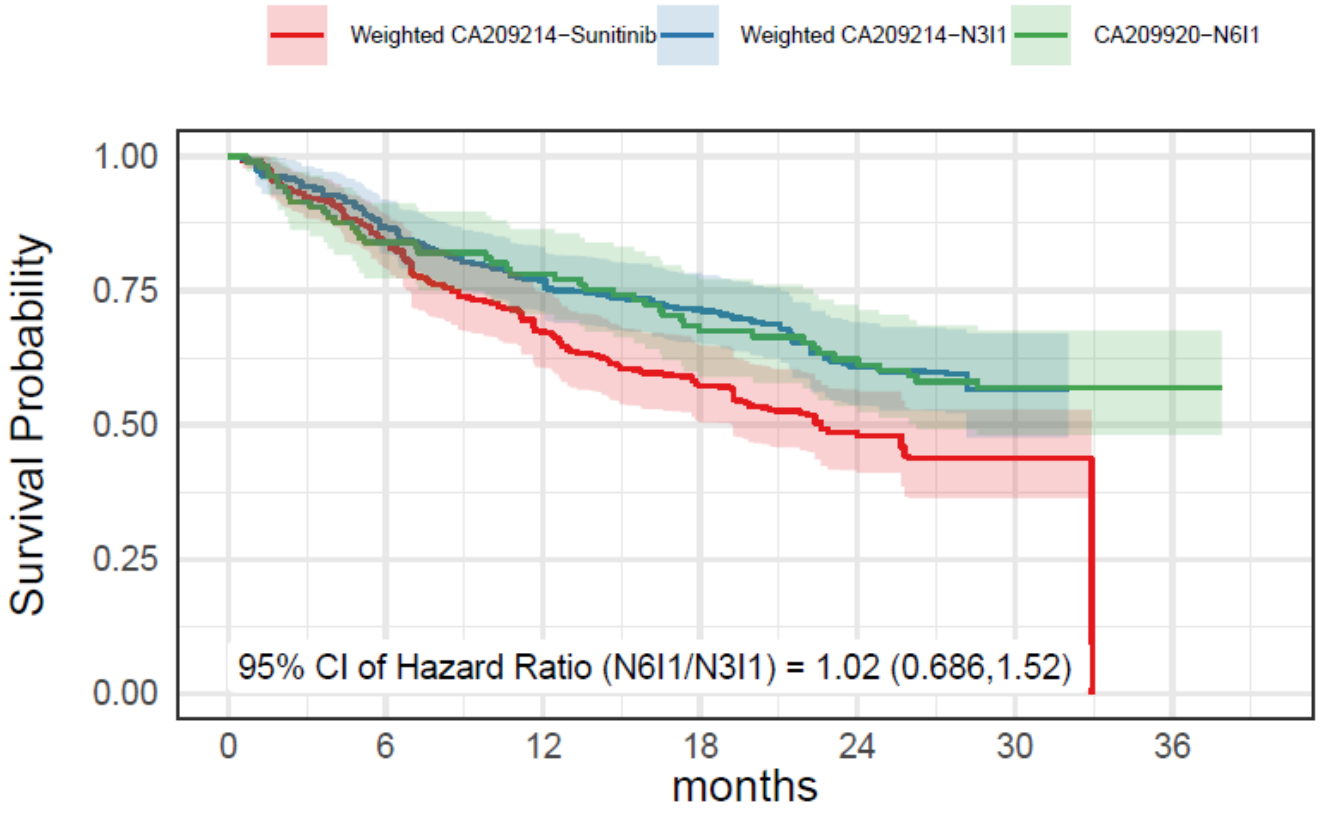
Weighted OS of CA209-214 reflects higher baseline severity in the CA209-920 population



Due to higher baseline disease severity in CA209920 population, overall survival of the weighted CA209214 N3I1 population is lower than when this same patient population is not weighted.

Weighting CA209214 N3I1 population decreases weight of the favorable risk subgroup which is very small in study 920. The weighting effect is stronger on the sunitinib arm as favorable risk patients have the best outcomes on Sunitinib.

PSM provided the benchmark distribution of OS on N3I1 and Sunitinib in a similar patient population in Cohort 1 of CA209-920 N6I1



Number at risk

233	192	152	123	45	2	0
162	139	122	109	43	0	0
106	89	80	69	60	53	10

Conclusion

- Using early endpoints, i.e. limited to radiographic tumor size measurements, of the CA209-920 patient population in 2018 and a joint TGD-OS model, this model was able to reliably predict future overall survival in 2020

- PSM generated a synthetic control arm from historical data by adjusting the baseline characteristics to more closely resemble the baseline characteristics of the CA209-920

- This work established the feasibility of predicting OS in advanced RCC with longitudinal TGD and immature OS data together with baseline covariates, and benchmarking the predicted OS with that of an established therapy using PSM weighting

Acknowledgement

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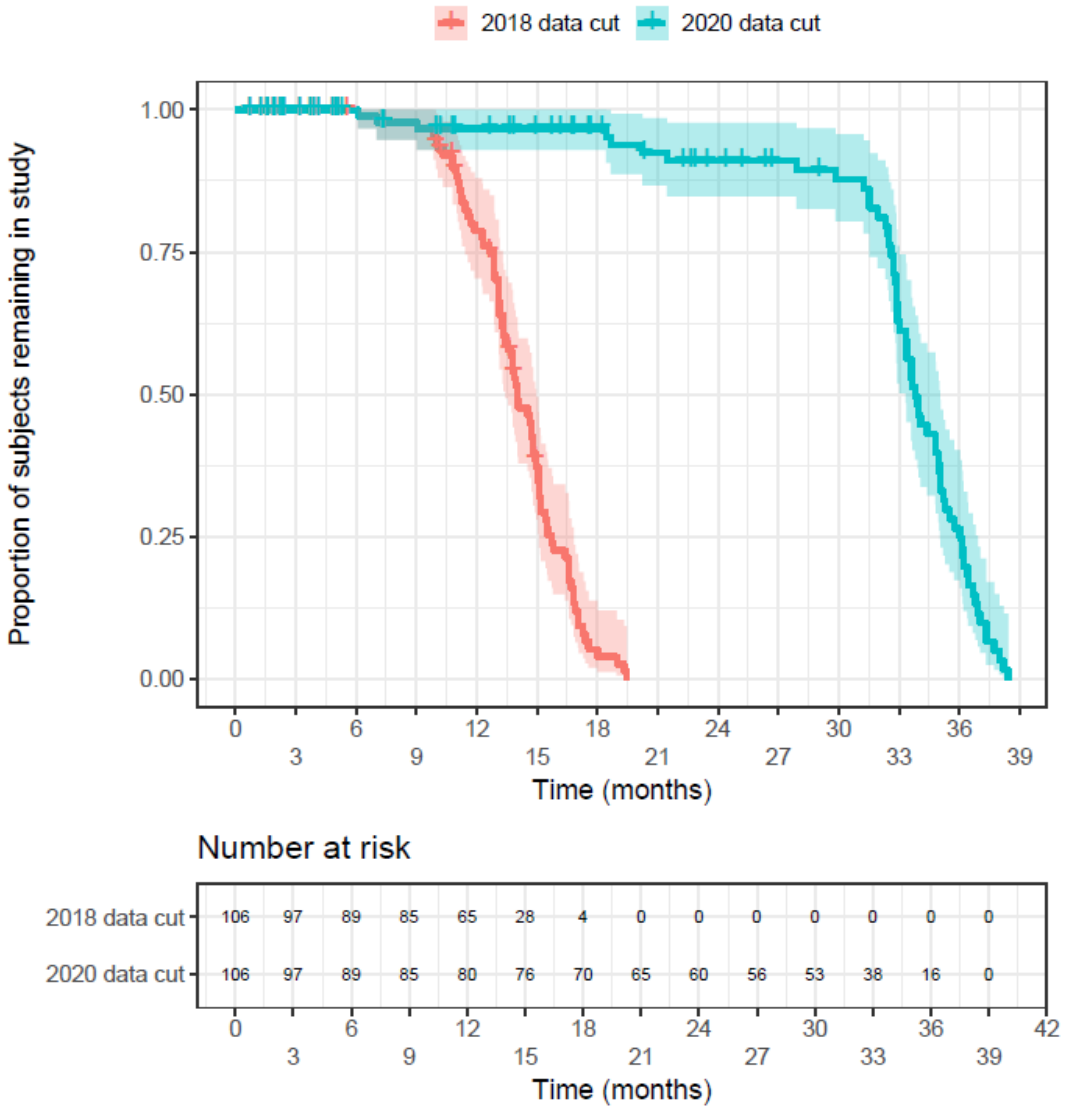
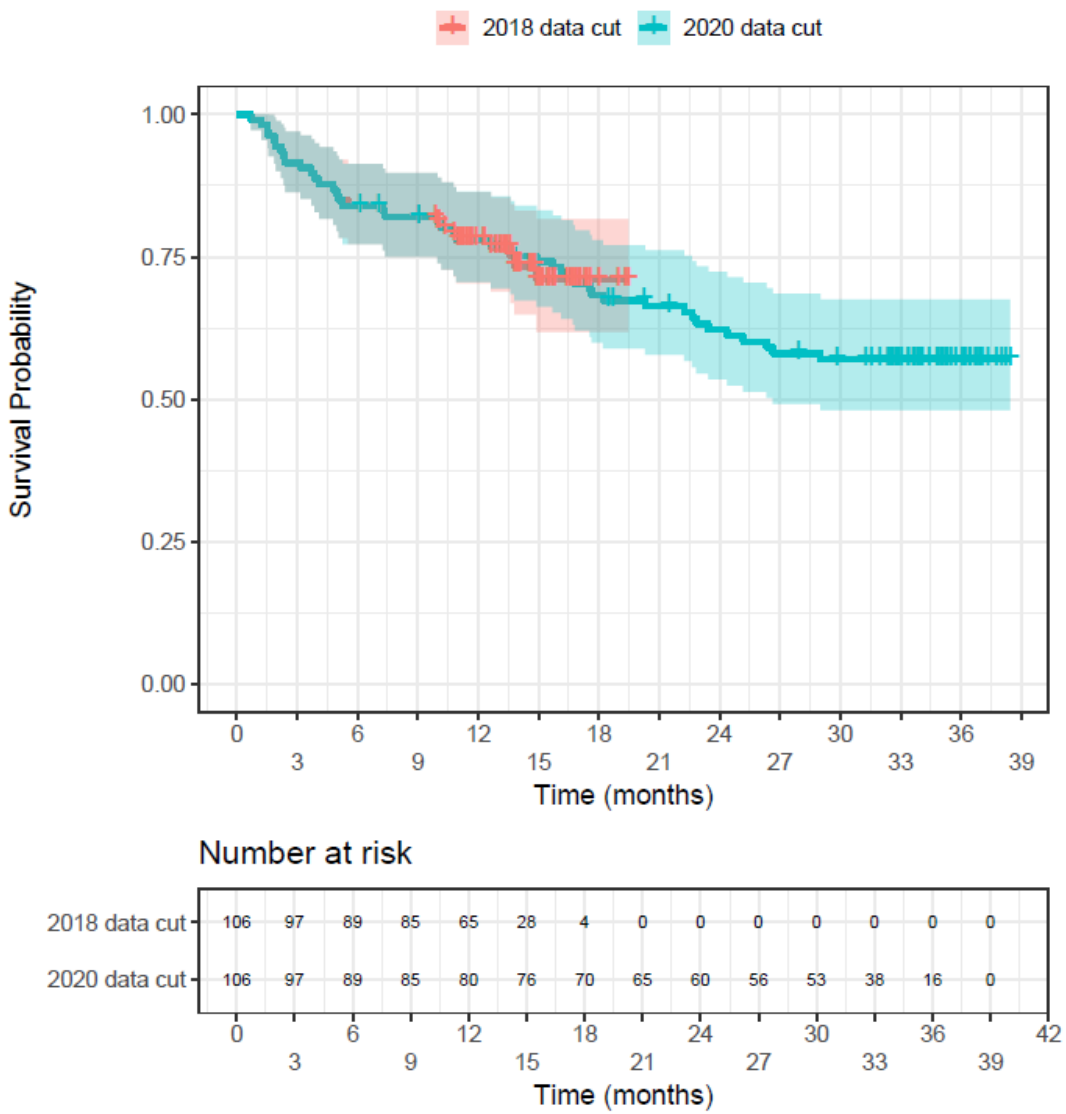
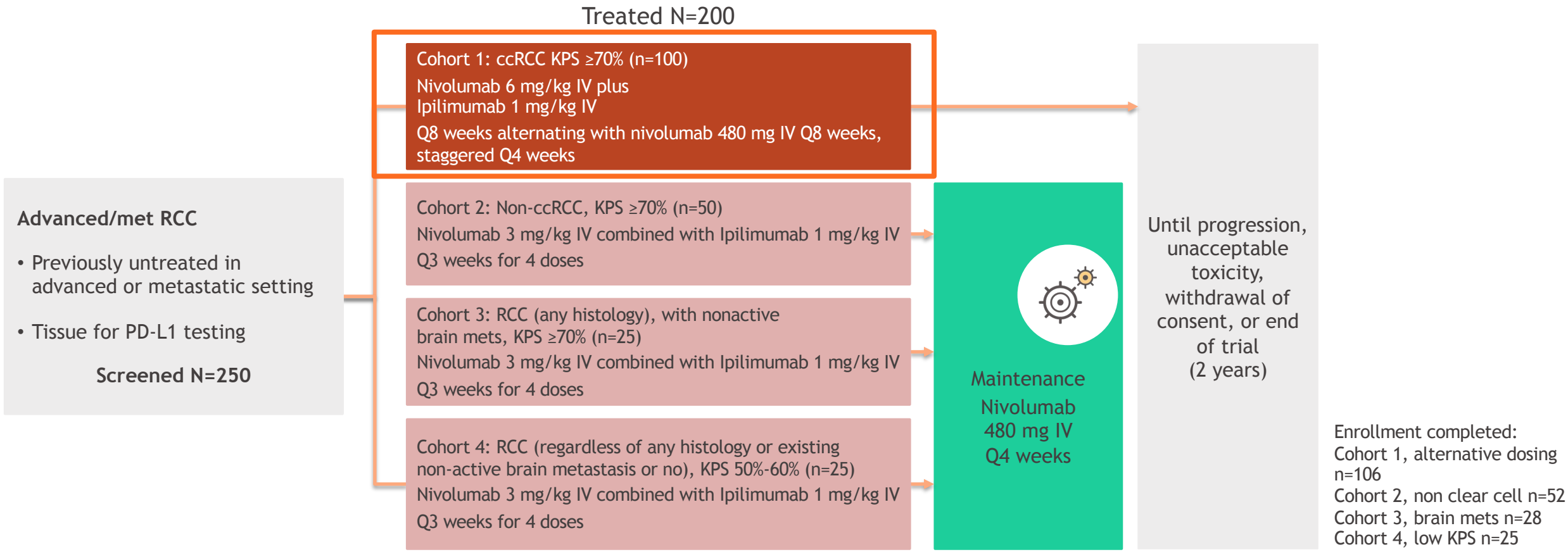
backups

2018 data cut vs. 2022 data cut





CA209-920 (BMS-Sponsored NRDG) Phase 3b/4 Safety Trial of Nivolumab Combined with Ipilimumab in Subjects with Previously Untreated, Advanced or Metastatic RCC



George DJ et al., BMJ Open. 2022 Sep 14;12(9)

CA209-214 (Registrational Trial in 1L RCC)

- **Treatment-naïve advanced or metastatic clear-cell RCC**
- **Measurable disease**
- **KPS ≥70%**
- **Tumor tissue available for PD-L1 testing**

Randomize 1:1

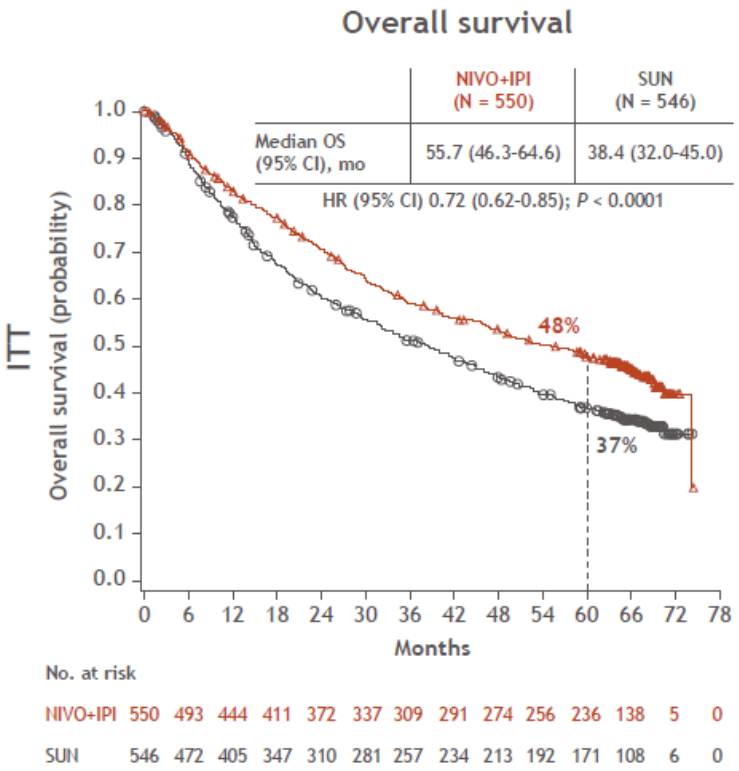
Stratified by
- IMDC prognostic score (0 vs 1–2 vs 3–6)
- Region (US vs Canada/Europe vs Rest of World)

Treatment

Arm A
3 mg/kg nivolumab IV + 1 mg/kg ipilimumab IV Q3W for four doses, then 3 mg/kg nivolumab IV Q2W

Arm B
50 mg sunitinib orally once daily for 4 weeks (6-week cycles)

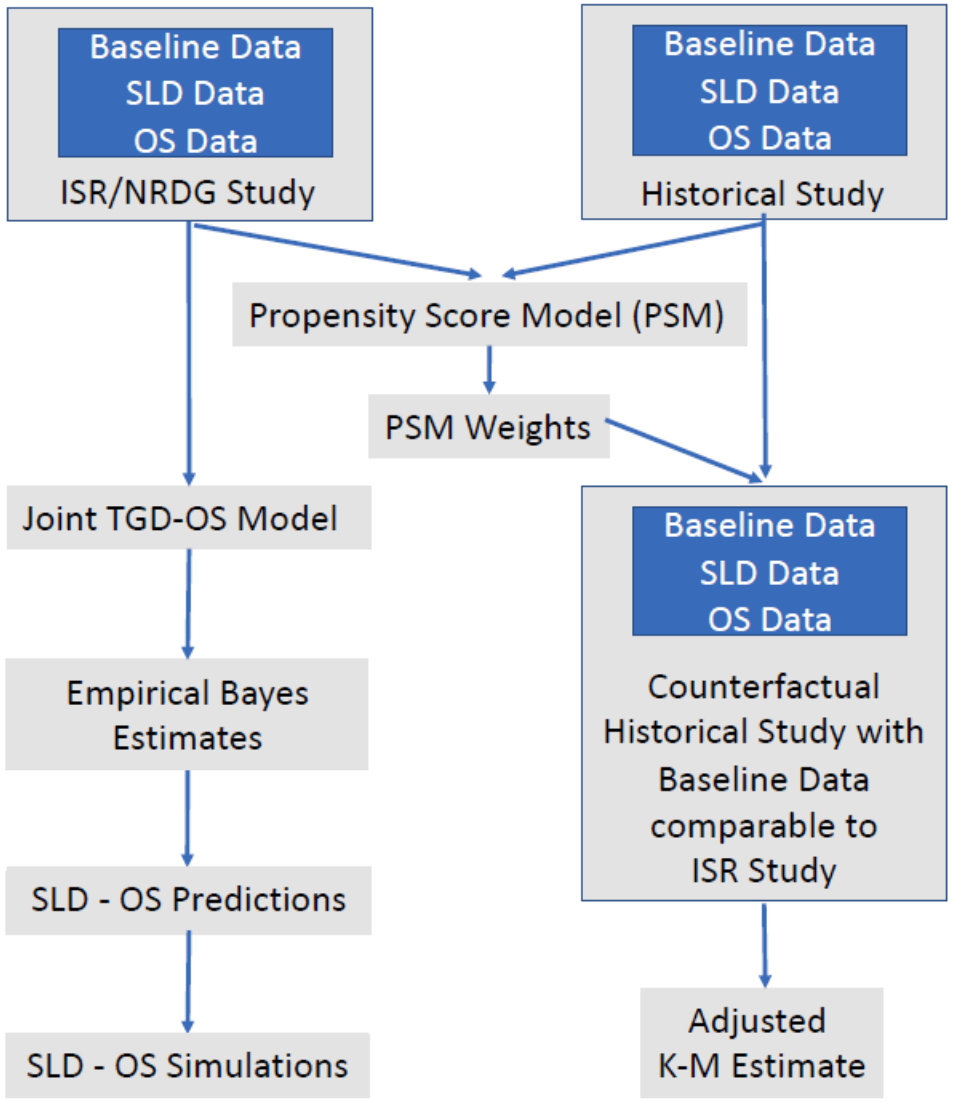
Treatment until progression or unacceptable toxicity



Motzer RJ et al., Cancer. 2022 Jun 1;128(11):2085-2097.

Schematic of Modeling Strategy

CA209-920 (NRDG)



CA209-214 Registrational in 1L RCC)

Ref: Metrum Research Group

Mixture Wang Model

Subpopulation 1 (fast TG):

$$TB_i(t) = TB_0 \times e^{-TS_i t} + TG_i \times t$$

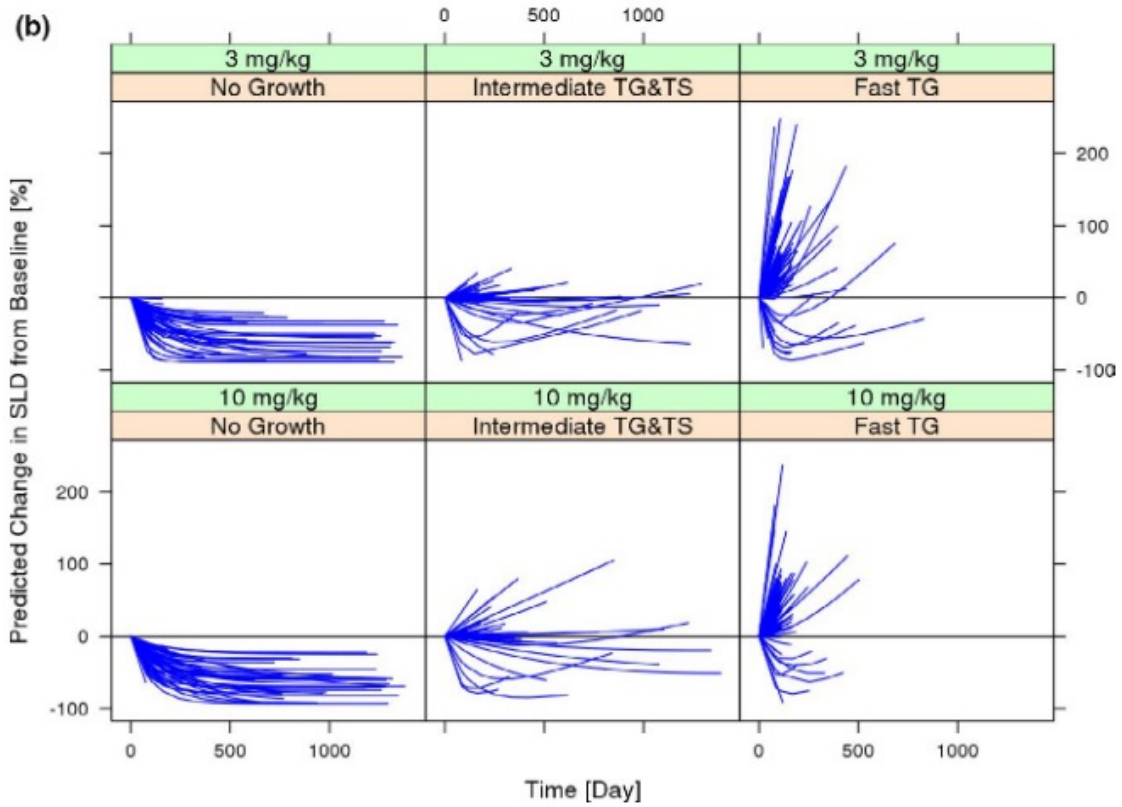
Subpopulation 2 (no-growth):

$$TB_i(t) = TB_0 \times e^{-TS_i t} + TB_{SS_i}$$

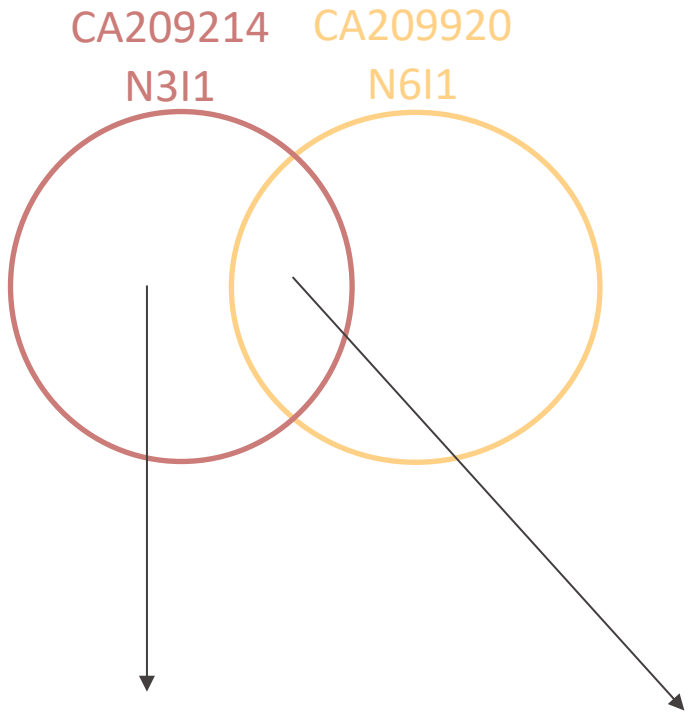
Subpopulation 3 (intermediate TG and tumor shrinkage (TS)):

$$TB_i(t) = TB_0 \times e^{-TS_i t} + TG_i \times t$$

where $TB_i(t)$ is the TB at time t for the i^{th} patient, and $TB0_i$, TS_i, and TG_i represent baseline TB, TS rate constant, and linear TG rate for the ith patient, respectively.

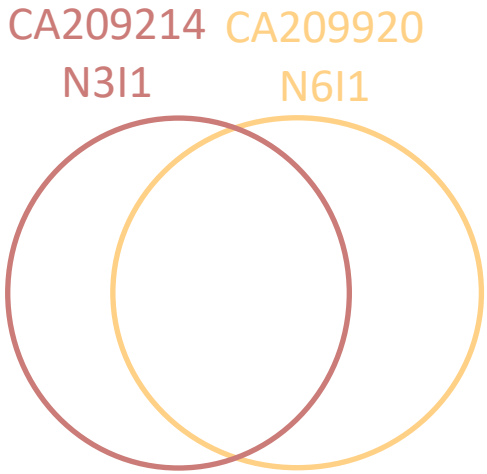


Before PSM ATT Weighting



- Propensity Score model
- ATT weighting

After PSM ATT Weighting



Subjects in CA209214 with dissimilar BL disease severity given lower ATT weights

Subjects in CA209214 with similar BL disease severity given higher ATT weights

After PSM ATT weighting, weighted CA209214 population is more similar to CA209920 with respect to BL disease severity

2018 data cut vs. 2022 data cut (Tumor size)