

Applications of Tumor Growth Inhibition- Overall Survival Models to Support Atezolizumab Combination Studies

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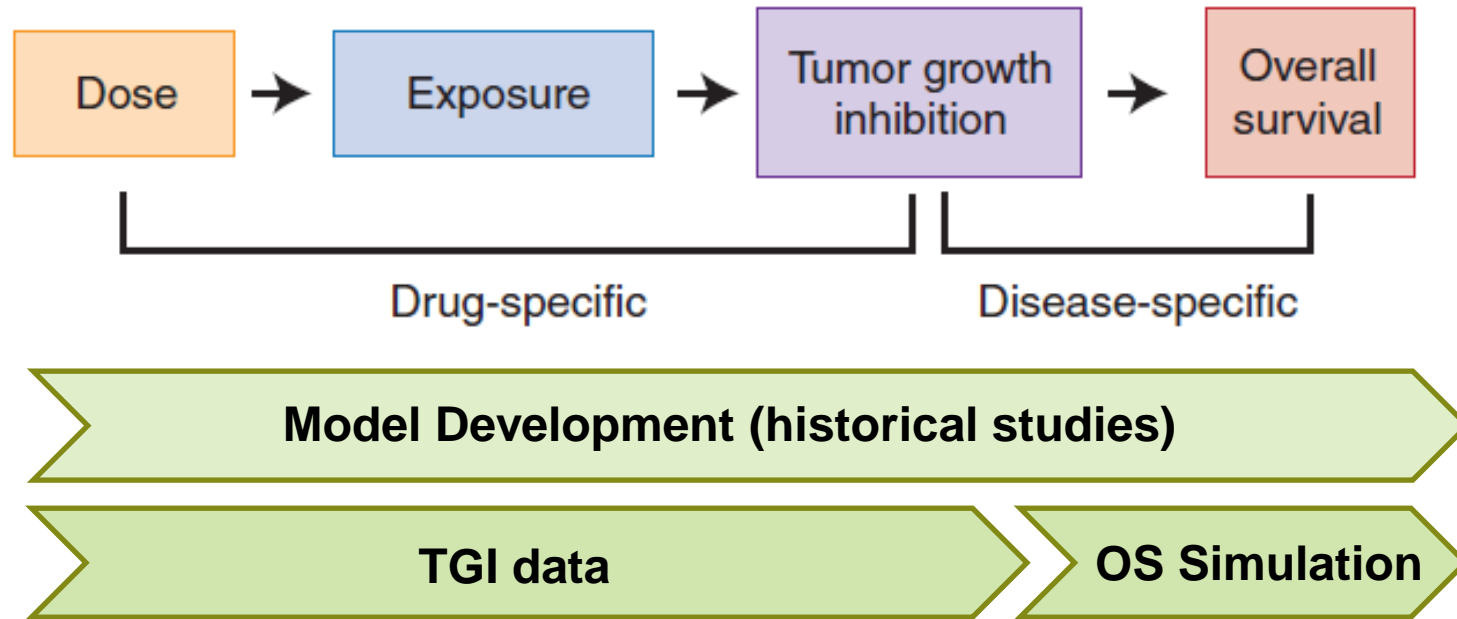
Genentech
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FDA-ISoP Workshop
Model-Informed Drug Development in Oncology
FDA White Oak Great Room
Silver Spring, MD
Feb 1st, 2018

Drug-disease modeling framework

Bruno et al. Clin Pharmacol Ther, 93:303-5, 2013

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Models-based tumor growth inhibition (TGI) metrics (tumor growth rate) as biomarkers to capture treatment effect and predict for OS benefit in 'drug-independent' TGI-OS models

To assess if this paradigm is working for cancer immunotherapy in NSCLC and mUC:
TGI-OS models based on Phase II data to predict Phase III studies



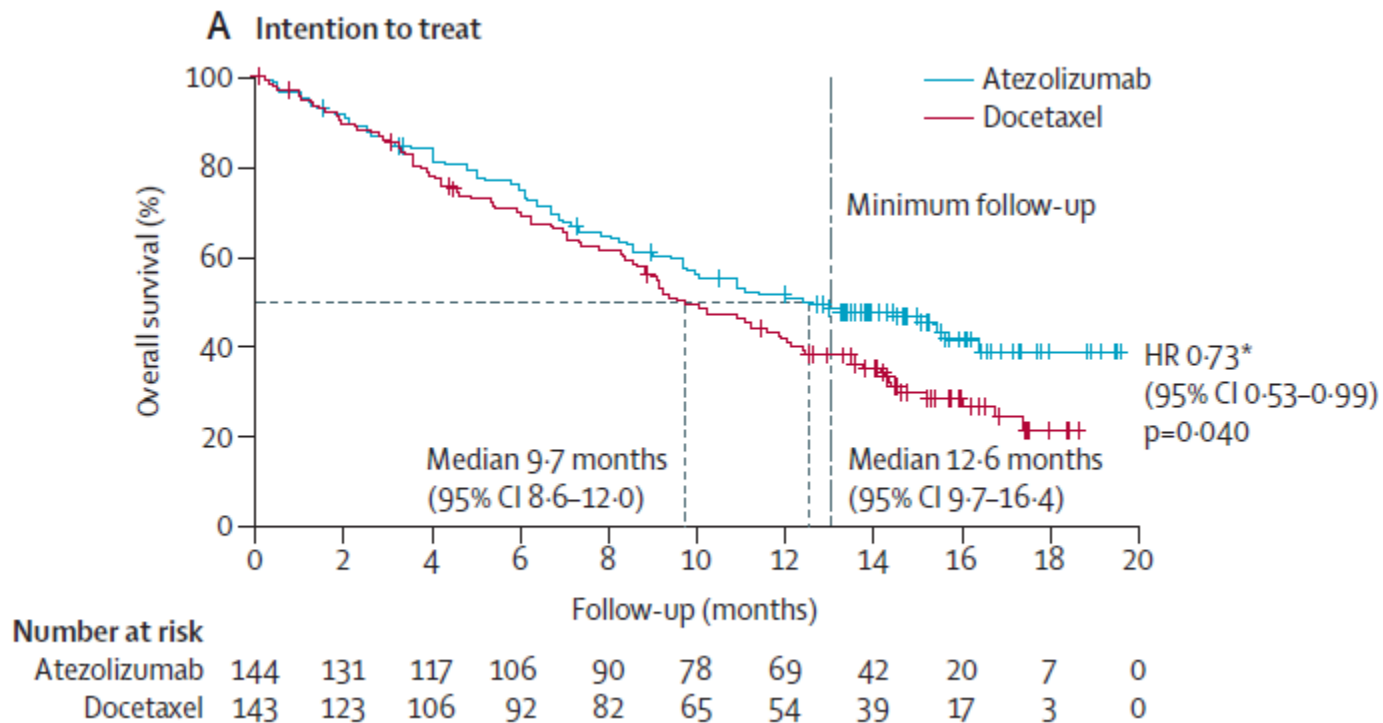
Non-Small Cell Lung Cancer: POPLAR and OAK

Bruno et al, Am Conf Pharmacomet (ACoP7), Seattle, Oct 2016
FDA-AACR Workshop, Washington, July 20, 2017

POPLAR study

Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial

Louis Fehrenbacher, Alexander Spira, Marcus Ballinger, Marcin Kowanetz, Johan Vansteenkiste, Julien Mazieres, Keunchil Park, David Smith, Angel Artañ-Cortes, Conrad Lewanski, Fadi Braiteh, Daniel Waterkamp, Pei He, Wei Zou, Daniel S Chen, Jing Yi, Alan Sandler, Achim Rittmeyer, for the POPLAR Study Group*

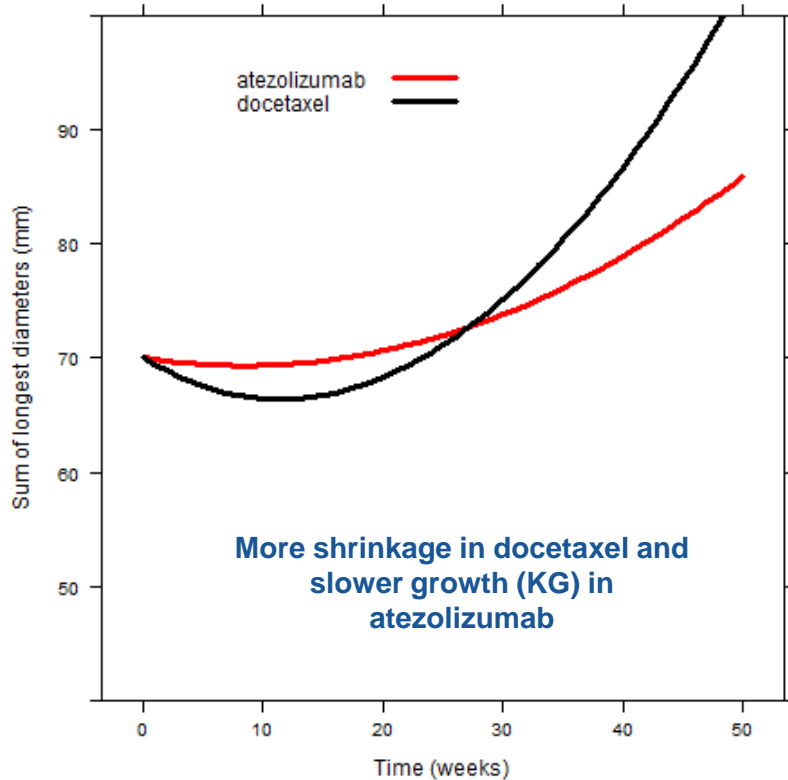


Lancet 2016; 387: 1837-46

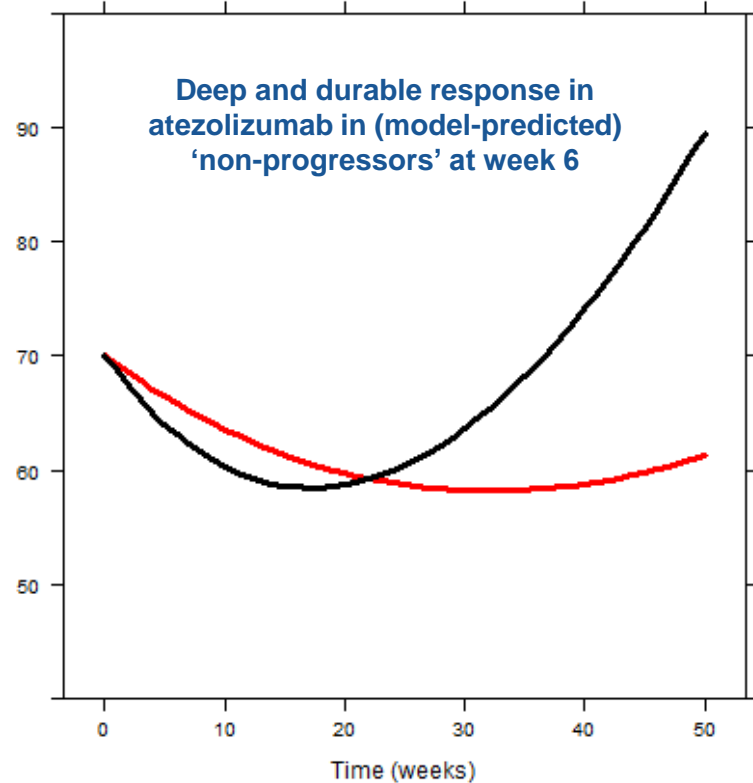
Typical TGI profiles in POPLAR

Bi-exponential model by Stein et al. CCR 17:907-17, 2011

Evaluable for TGI if at least one post-baseline tumor size measurement:
277 patients randomized (91.0%)



All patients



Patients with model-predicted SLD at week 6 < model-predicted SLD at time 0 (start of treatment)
83 patients (67.5%) in docetaxel, 73 patients (56.6%) in atezolizumab

Final OS lognormal model

	Value	SE	z	p
(Intercept)	1.224	0.600	2.04	0.041
# Met Sites	-0.163	0.0528	-3.09	0.002
Albumin	0.0519	0.0102	5.11	3.22e-07
logKG	-0.752	0.0875	-8.59	8.38e-18
Log(scale)	-0.338	0.0639	-5.29	1.23e-07

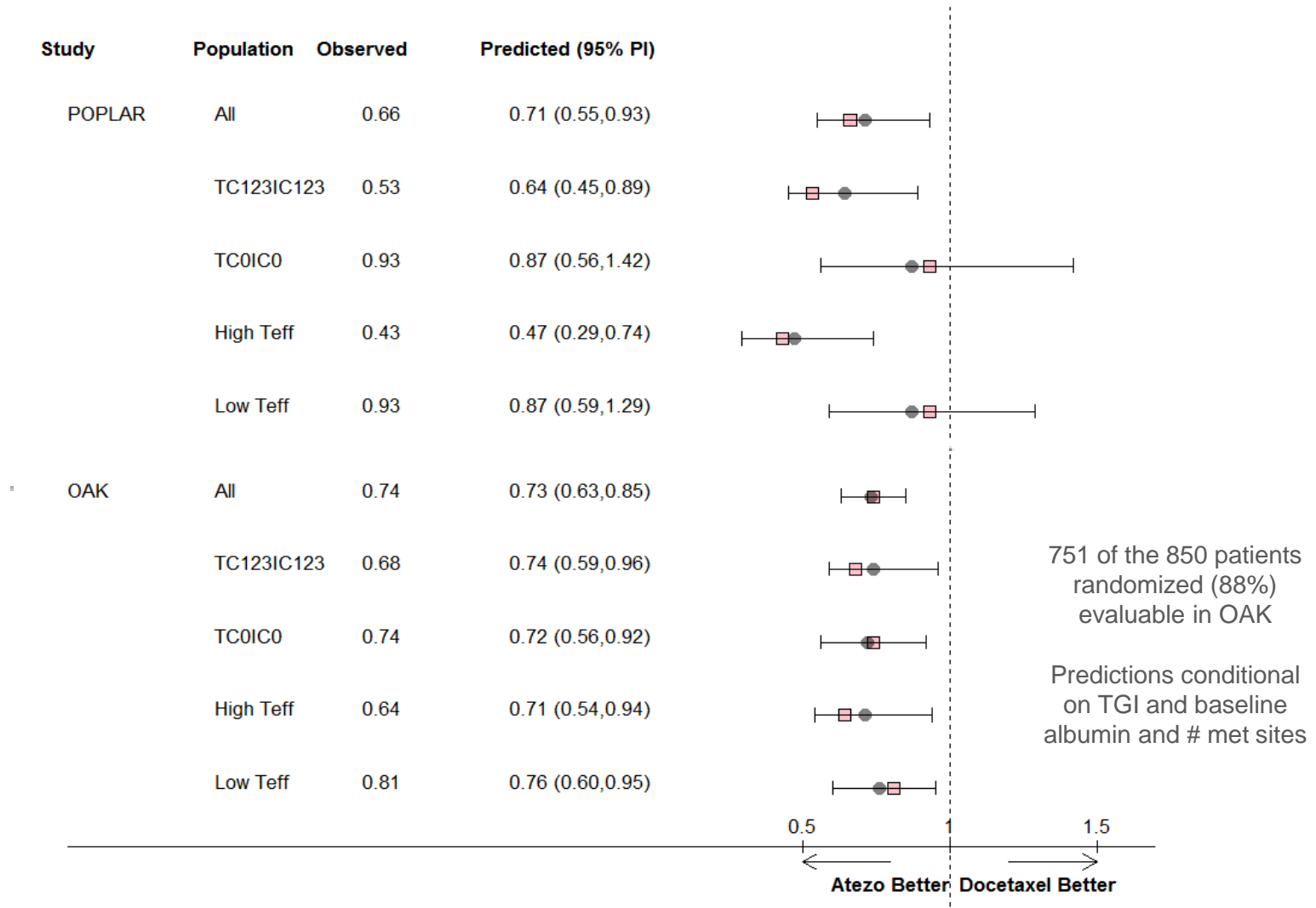
SE=standard error of parameter estimate; z=Wald statistic; p=Wald test (χ^2); Scale=standard deviation of log(OS)

Negative sign:
survival probability
decreases when
covariate increases

Survival probability decreases when log(KG)
increases

Treatment effect no longer in the multivariate model
Difference in logKG explains treatment effect

TGI-OS POPLAR model prediction of the atezolizumab to docetaxel hazard ratio in POPLAR and OAK





Metastatic Urothelial Carcinoma: IMvigor210, IMvigor211

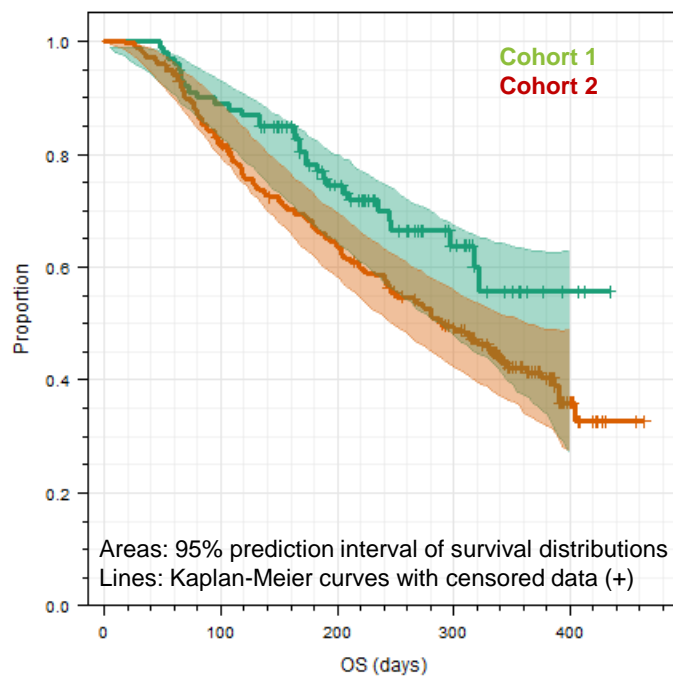
Bruno et al, ASCO-SITC, San Francisco, Jan 25, 2018

IMvigor210 TGI-OS model (lognormal distribution)

	Estimate	SE	z	p
(Intercept)	3.609	0.286	12.6	1.25e-36
logKG	-0.676	0.0598	-11.3	1.44e-29
Alk Phos	-0.00199	0.00063	-3.16	0.00158
Ecog>0	-0.377	0.101	-3.74	0.00018
# Met Sites	-0.138	0.0454	-3.04	0.00234
Log(scale)	-0.315	0.0555	-5.67	1.39e-08

SE=standard error of parameter estimate; z=Wald statistic; p=Wald test (χ^2); Scale=standard deviation of log(OS)

Negative sign:
survival probability
decreases when
covariate increases



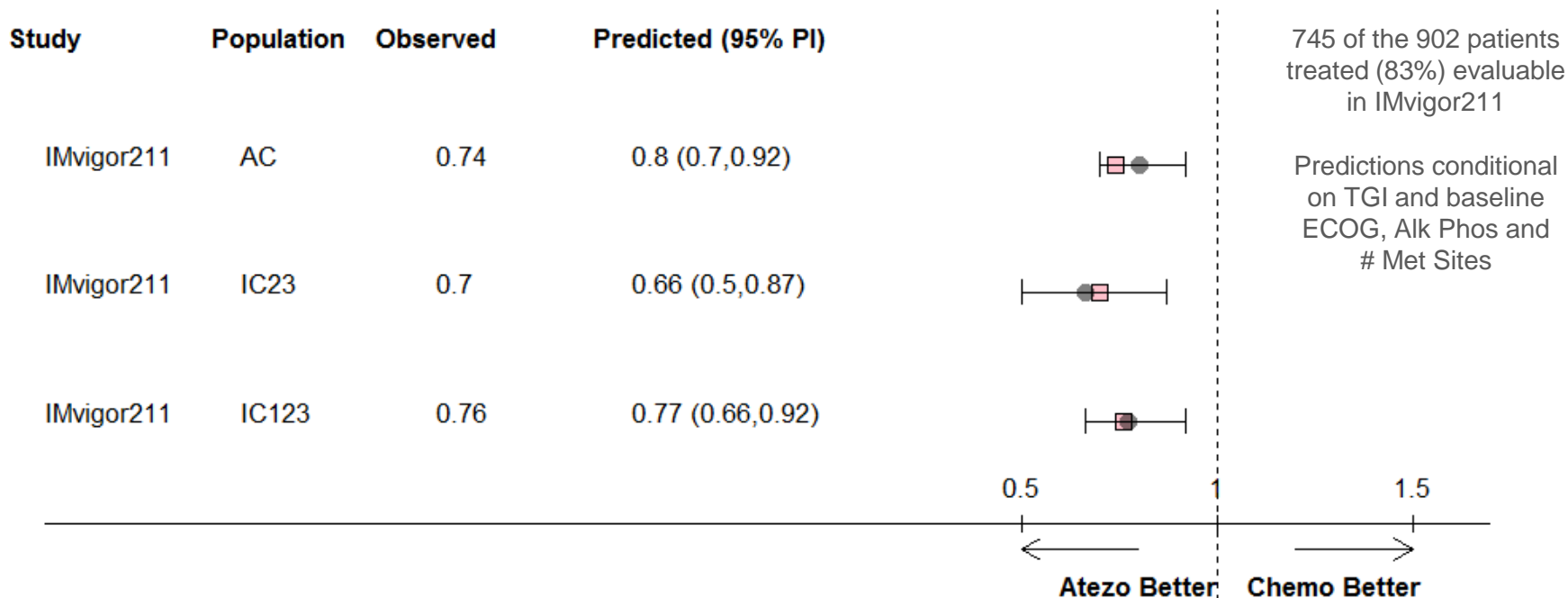
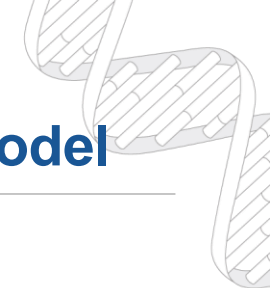
Cohort 1
cisplatin-ineligible patients with locally
advanced and metastatic UC

Lancet 2017; 389: 67-76

Cohort 2
patients with locally advanced and
metastatic UC who have progressed
following treatment with platinum-
based chemotherapy

Lancet 2016; 387: 1909-20

Imvigor211 HR predictions based on IMvigor210 TGI-OS model



Bullets and segments: HR predictions; red squares: observed HR

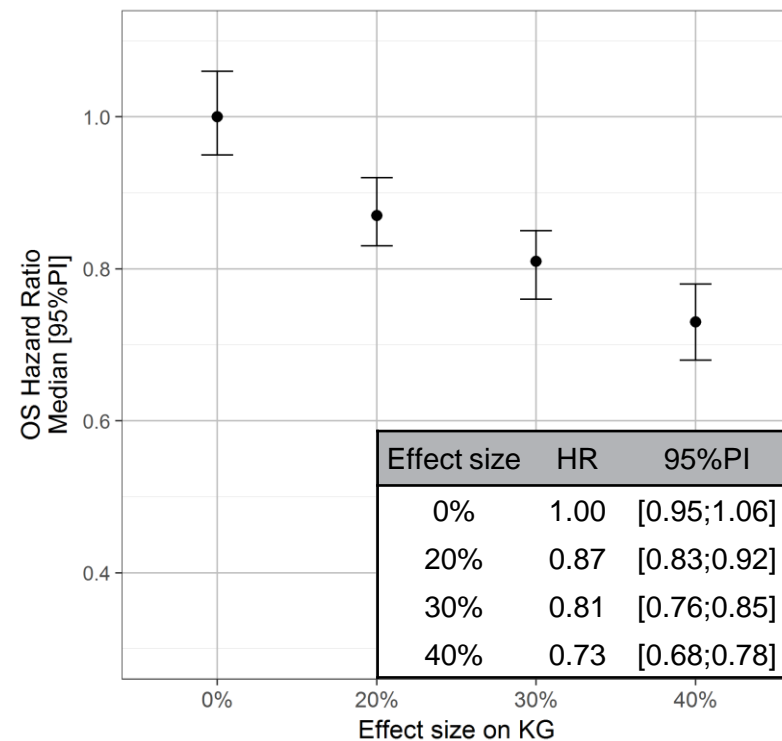
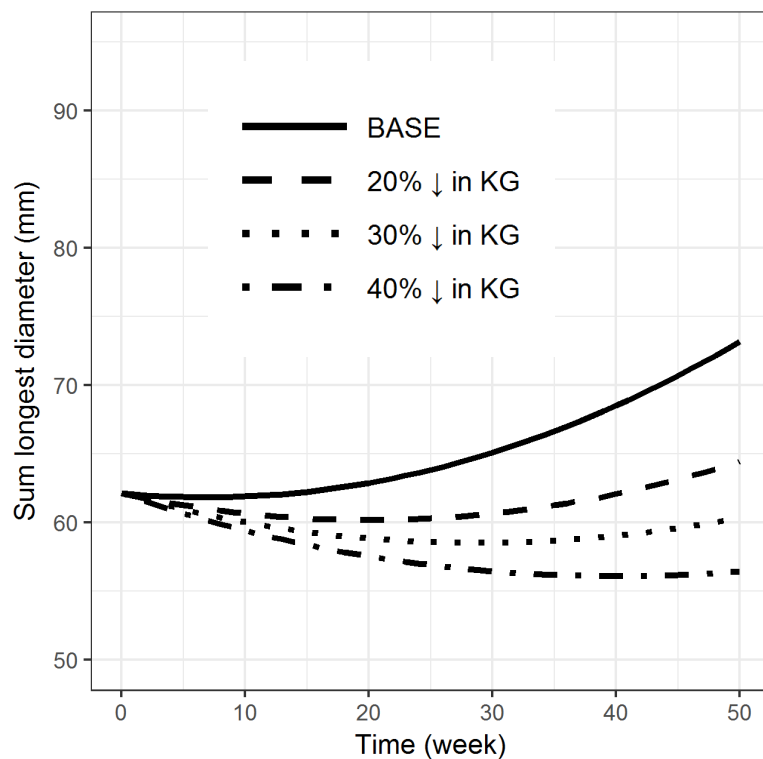
- Predictions using IMvigor210 TGI-OS model conditional on IMvigor211 baseline characteristics and estimated KG
- Observed HR are within the 95% prediction intervals



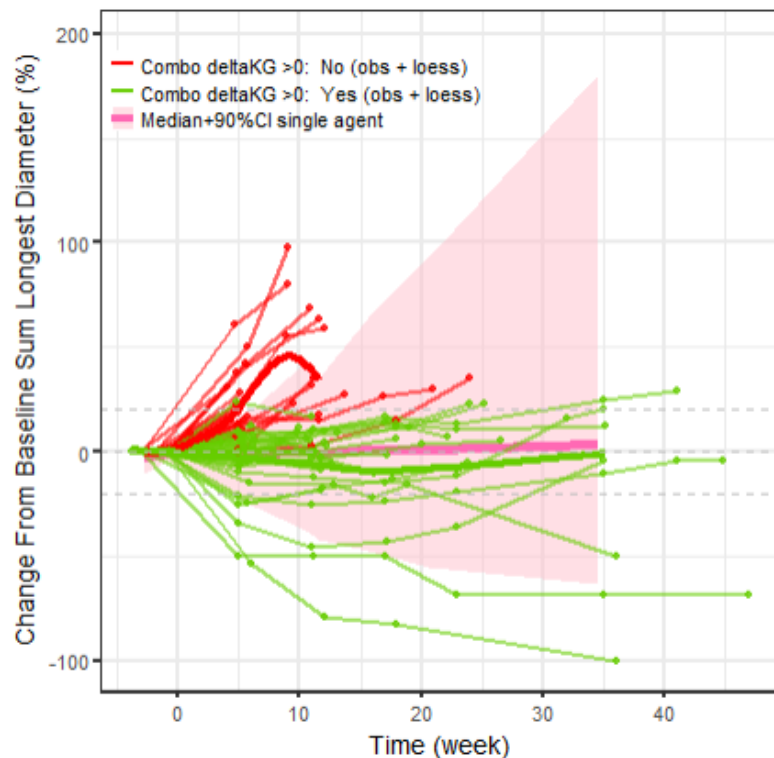
A framework to help decisions in early Phase Ib combination studies

Marchand et al, ACoP 8, Fort Lauderdale, Oct 16, 2017

Expected impact of combinations on TGI profile and HR

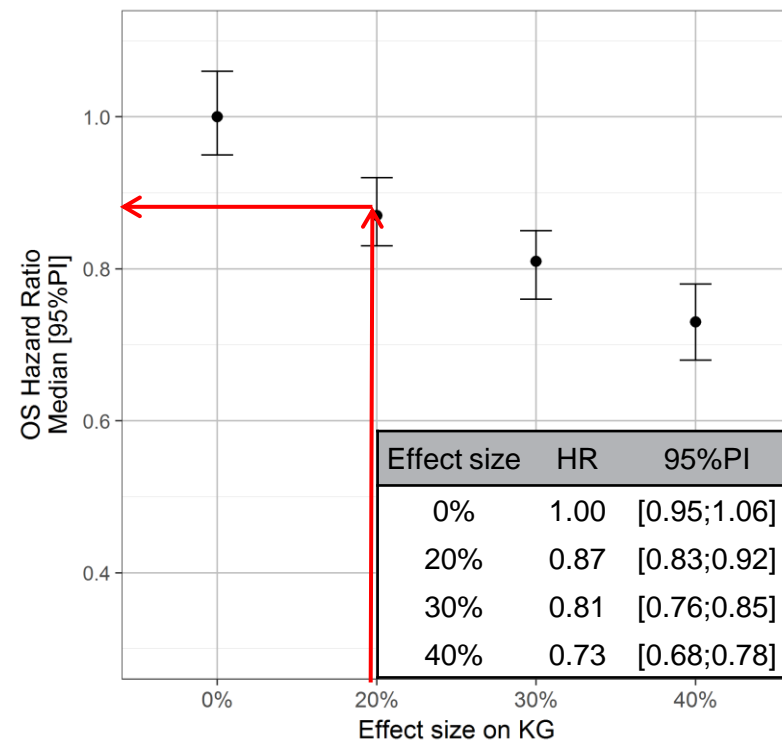


Expected impact of combinations on TGI profile and HR



A Phase Ib study of drug X in combination with atezolizumab:

59 patients with median follow up:
11 weeks (1-47 weeks)



Δ KG vs. covariate adjusted single agent:
-18% (effect size)

Expected HR vs. single agent:
0.905 (0.745-1.12)

TGI-OS modeling frameworks based on Phase II studies are validated to predict atezolizumab vs. chemotherapy HRs in Phase III studies in both NSCLC and mUC

- Survival probability decreases when growth rate increases
- Treatment effect no longer in the multivariate models
- Difference in growth rates across arms predicts atezolizumab OS benefit compared with chemotherapy
 - In both all comers and by diagnostic subgroups

On-treatment growth rate has potential:

- To be an early exploratory endpoints in CIT combination studies
- To support interim analysis of Phase III studies

Clinical studies patients and investigators

M&S and Clinical Pharmacology

- Wan-Ting (Alyse) Lin, Rui Zhu, Kari Morrissey, Ben Wu, Helen Winter, Mark Stroh, Sandhya Girish, Amita Joshi
- Mathilde Marchand (Certara)

Biomarkers, Biostatistics and Clinical

- Marcin Kowanetz, Priti Hegde, Wei Zou, Pei He, Marcus Ballinger, Dan Chen

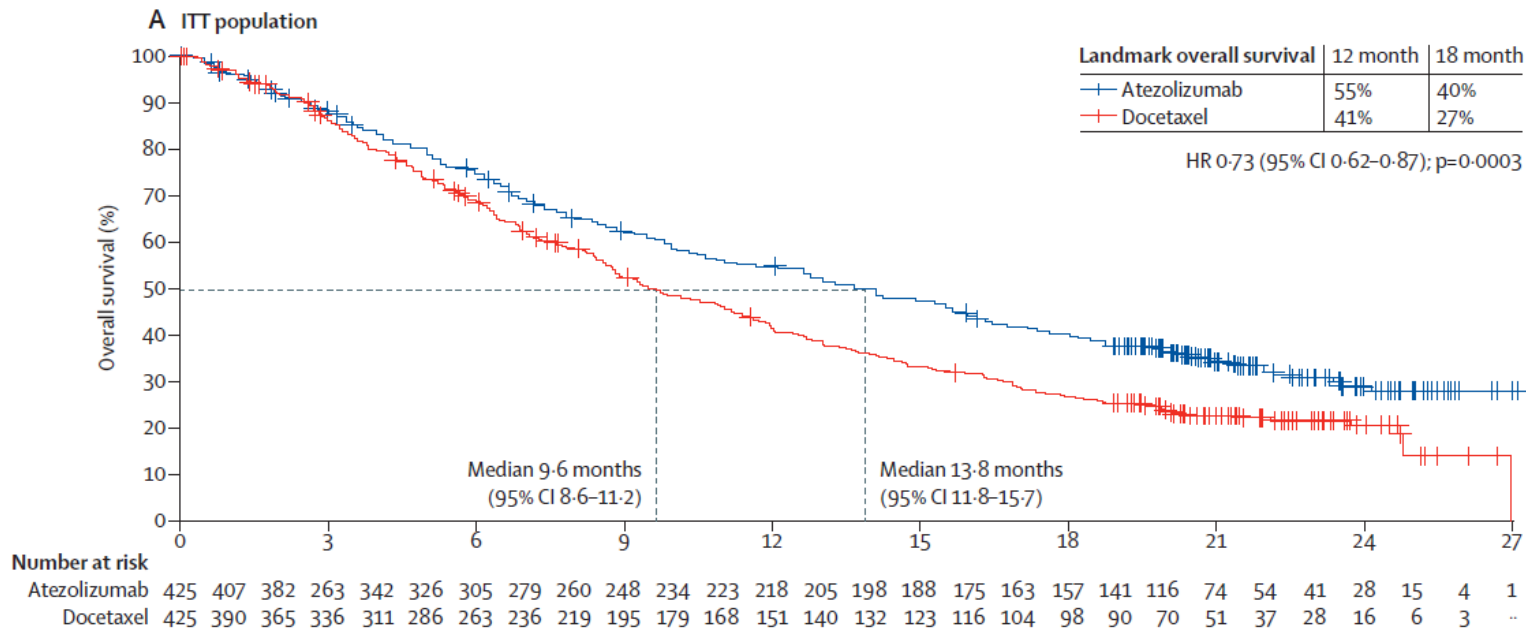
Atezolizumab Global Development Teams



Backups

Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial

Achim Rittmeyer, Fabrice Barlesi, Daniel Waterkamp, Keunchil Park, Fortunato Ciardiello, Joachim von Pawel, Shirish M Gadgeel, Toyooki Hida, Dariusz M Kowalski, Manuel Cobo Dols, Diego L Cortinovis, Joseph Leach, Jonathan Polikoff, Carlos Barrios, Fairooz Kabbavar, Osvaldo Arén Frontera, Filippo De Marinis, Hande Turna, Jong-Seok Lee, Marcus Ballinger, Marcin Kowanetz, Pei He, Daniel S Chen, Alan Sandler, David R Gandara, for the OAK Study Group*

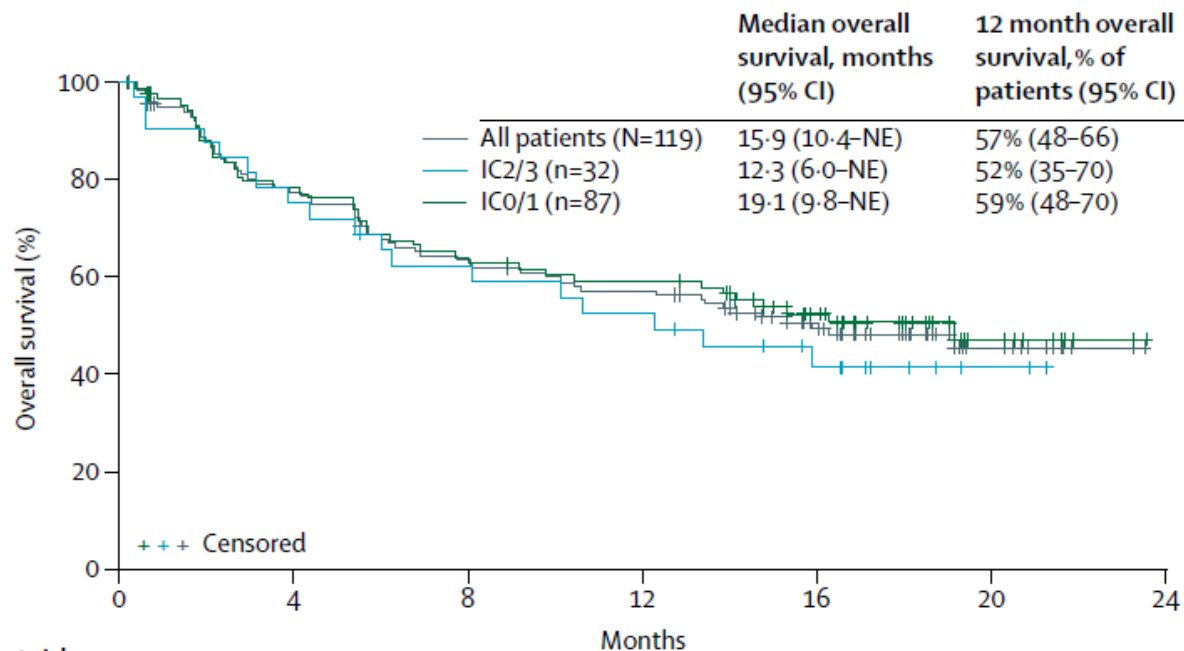


www.thelancet.com Published online December 12, 2016 [http://dx.doi.org/10.1016/S0140-6736\(16\)32517-X](http://dx.doi.org/10.1016/S0140-6736(16)32517-X)

IMvigor210, Cohort 1

Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial

Arjun V Balar, Matthew D Galsky, Jonathan E Rosenberg, Thomas Powles, Daniel P Petrylak, Joaquim Bellmunt, Yohann Loriot, Andrea Necchi, Jean Hoffman-Censits, Jose Luis Perez-Gracia, Nancy A Dawson, Michiel S van der Heijden, Robert Dreicer, Sandy Srinivas, Margitta M Retz, Richard W Joseph, Alexandra Drakaki, Ulka N Vaishampayan, Srikala S Sridhar, David I Quinn, Ignacio Durán, David R Shaffer, Bernhard J Egl, Petros D Grivas, Evan Y Yu, Shi Li, Edward E Kadel III, Zachary Boyd, Richard Bourgon, Priti S Hegde, Sanjeev Mariathasan, AnnChristine Thåström, Oyewale O Abidoye, Gregg D Fine, Dean F Bajorin, for the IMvigor210 Study Group*



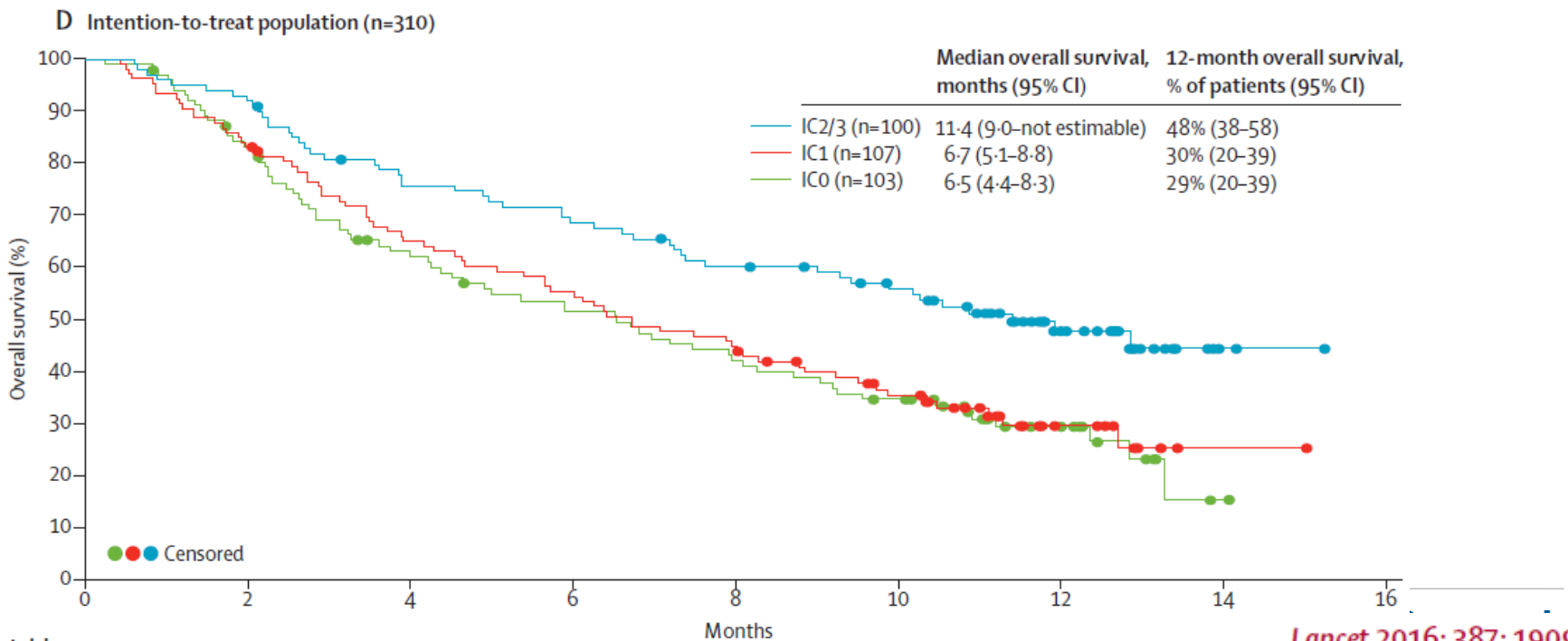
Number at risk

	0	4	8	12	16	20	24
All patients	119	101	89	78	72	67	64
IC2/3	32	28	24	21	19	18	16
IC0/1	87	73	65	57	53	49	48

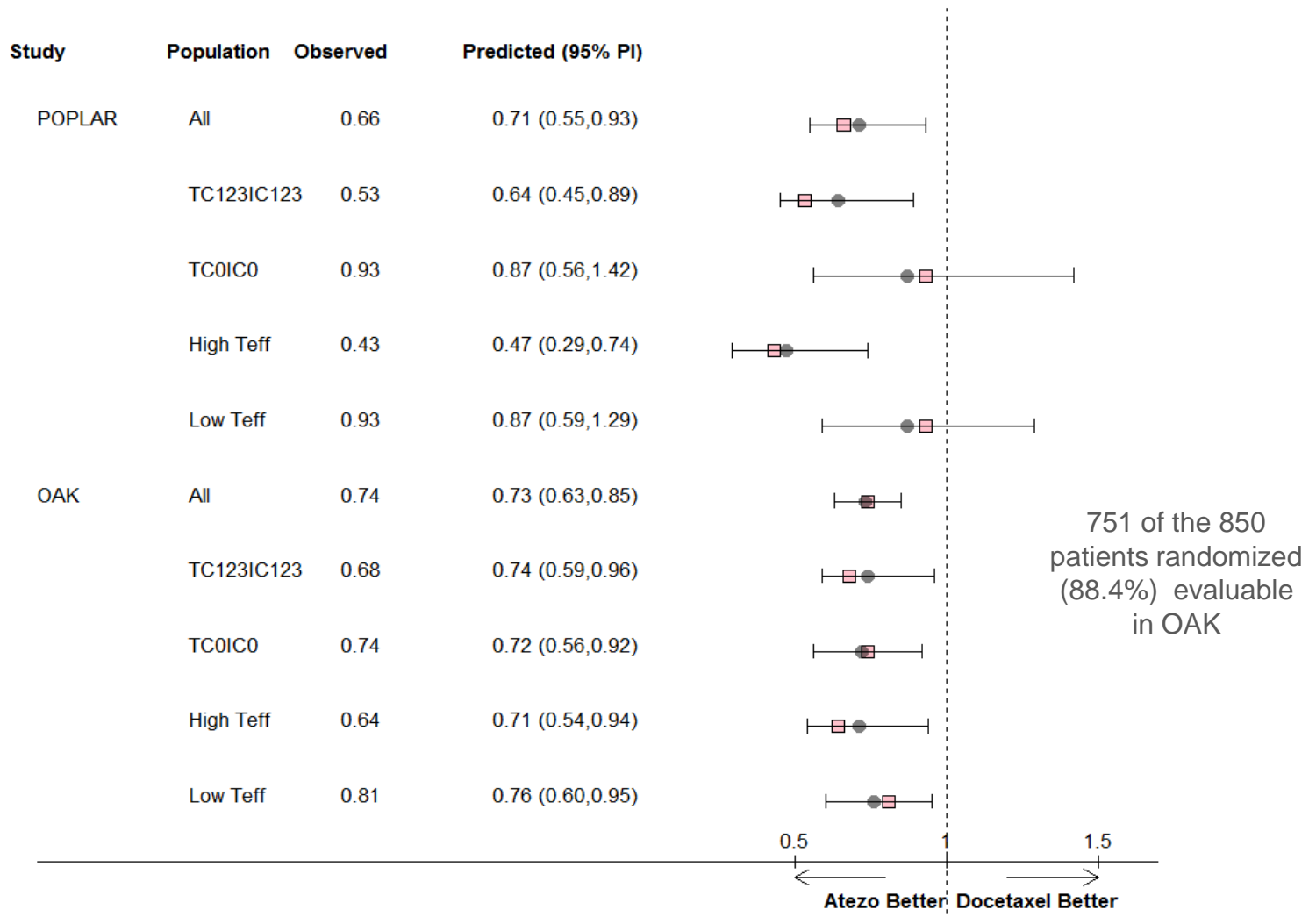
IMvigor210, Cohort 2

Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial

Jonathan E Rosenberg, Jean Hoffman-Censits, Tom Powles, Michiel S van der Heijden, Arjun V Balar, Andrea Necchi, Nancy Dawson, Peter H O'Donnell, Ani Balmanoukian, Yohann Loriot, Sandy Srinivas, Margitta M Retz, Petros Grivas, Richard W Joseph, Matthew D Galsky, Mark T Fleming, Daniel P Petrylak, Jose Luis Perez-Gracia, Howard A Burris, Daniel Castellano, Christina Canil, Joaquim Bellmunt, Dean Bajorin, Dorothee Nickles, Richard Bourgon, Garrett M Frampton, Na Cui, Sanjeev Mariathasan, Oyewale Abidoye, Gregg D Fine, Robert Dreicer



TGI-OS POPLAR model prediction of the atezolizumab to docetaxel hazard ratio in POPLAR and OAK



Model predictions (dots) and 95% prediction interval (1000 replicates, bars) with observed (squares)

TC/IC: PD-L1 expression in tumor/tumor-infiltrating immune cells

Teff: T-effector and interferon- γ gene signature (courtesy Marcin Kowanetz)