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# Measuring the long-term “tail of curve” survival benefits in oncology trials: A comparison of the ASCO Value Framework and the ESMO Magnitude of Clinical Benefit Scale

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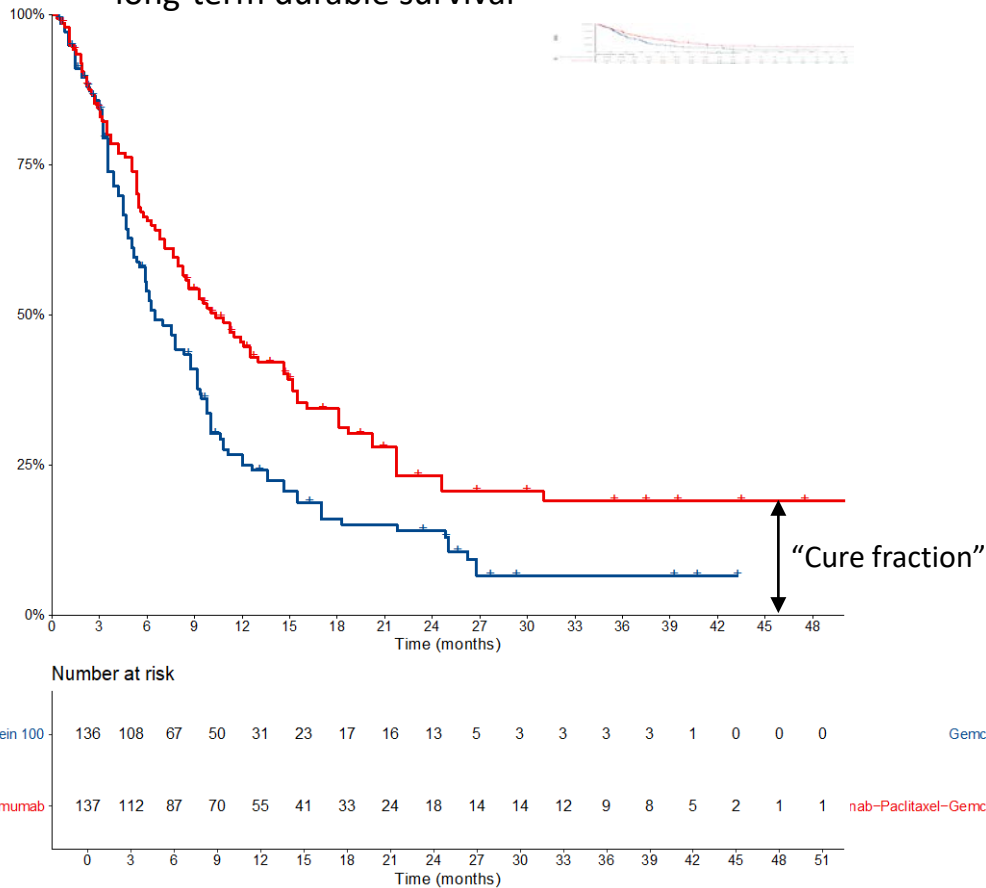
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# Background

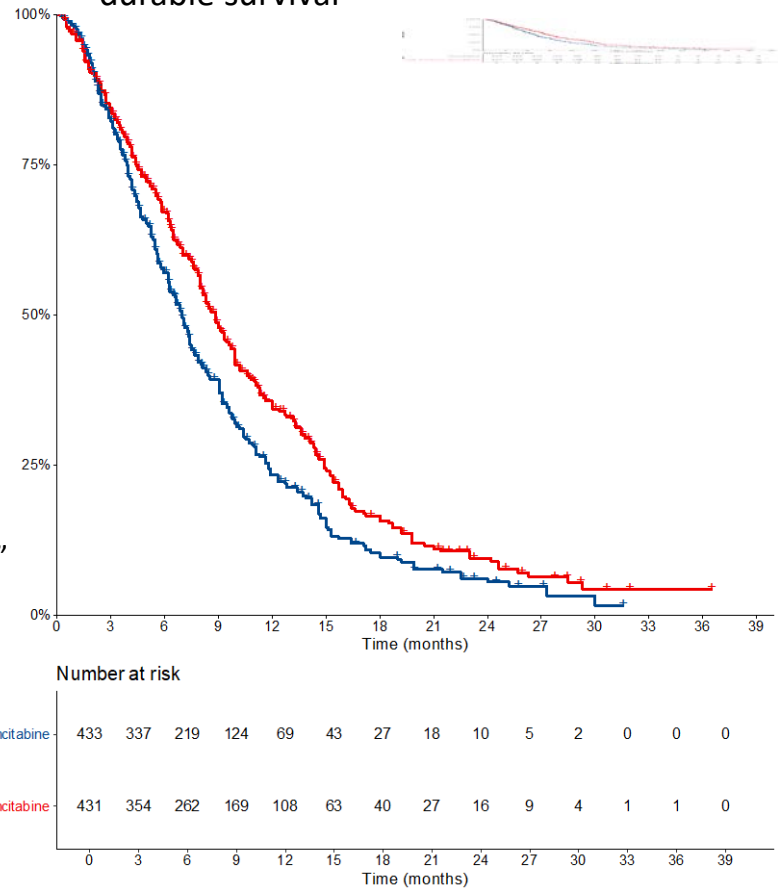
- Immune-checkpoint inhibitor agents have potential to preserve long-term survival in small patient populations
- Traditional measures of clinical benefit may not accurately capture long-term durable survival.
- Amendments to the American Society of Clinical Oncology *Value Framework* (ASCO-VF) and the European Society of Medical Oncology *Magnitude of Clinical Benefit Scale* (ESMO-MCBS) have been proposed to capture this benefit.

# Tail of the Survival Curve

Immune checkpoint-inhibitor agent with long-term durable survival



Chemotherapy agent without long-term durable survival



Hodi SF, O'Day SJ, McDermott DF, et al. Improved Survival with Ipilimumab in Patients with Metastatic Melanoma. *N Engl J Med.* 2010;363:711-23

Von Hoff DD, Ervin T, Arena FP, et al. Increased Survival in Pancreatic Cancer with nab-Paclitaxel plus Gemcitabine. *N Engl J Med.* 2013;369:1691-703.

# Study Aims

- We aimed to determine how frequently immune checkpoint inhibitor vs. non-immune checkpoint inhibitor anti-cancer agents, displayed trends of long-term durable survival, as defined by the ASCO-VF and ESMO-MCBS.
- Compare the degree of agreement between ASCO and ESMO frameworks.

# Methods

## *Selection of Studies*

- RCTs cited for clinical efficacy evidence in drug approval by the Food and Drug Administration between Jan-2011/Mar-2018 were identified.
- Inclusion criteria: phase II/III, double/triple-arm RCTs, primary endpoint of overall survival (OS) or progression-free survival (PFS).

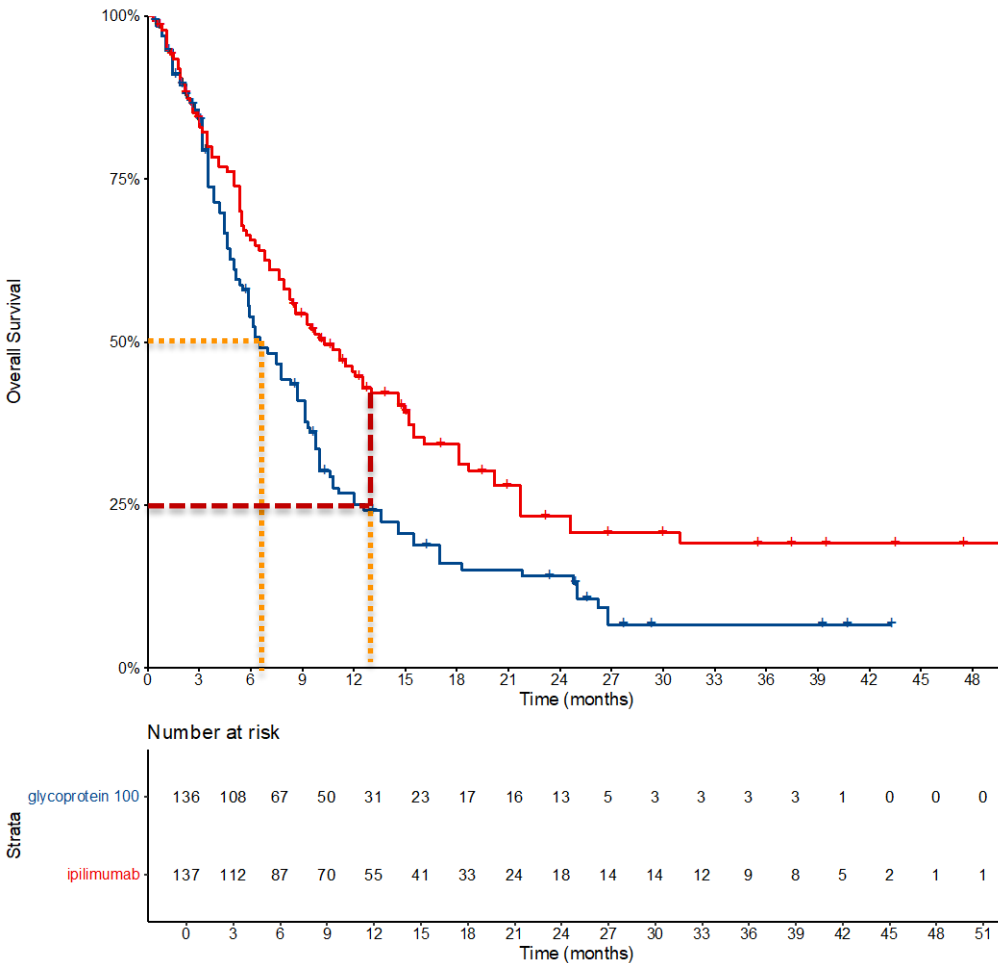
# Methods

## *Study Scoring*

- ASCO-VF “tail of the curve” bonus and ESMO-MCBS “immunotherapy triggered” long-term plateau adjustment were assessed by two independent reviewers
- When available, field testing scores from the framework developers were used in preference to reviewer scores.

# Methods: ASCO-VF

## “Tail of the curve” bonus



### Bonuses Awarded

- Overall survival: 20 points
- Progression-free survival: 16 points

### Criteria

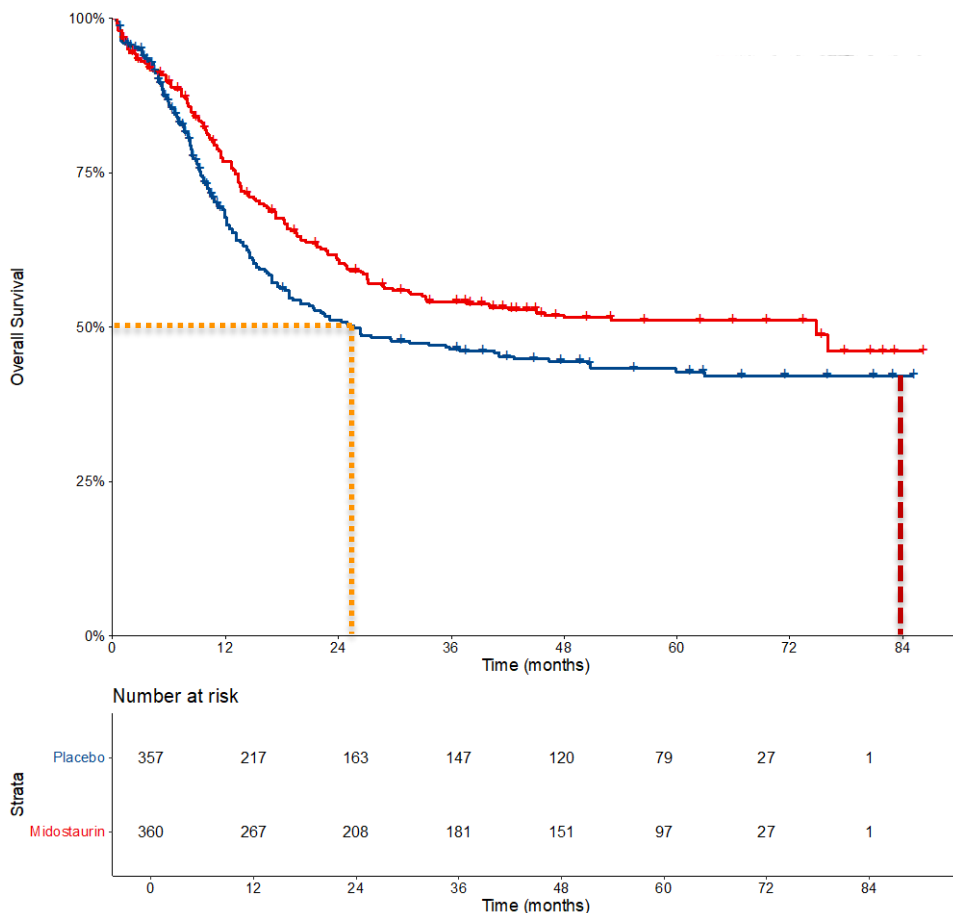
1. 50% or greater improvement in proportion of patients alive with the test regimen
2. Patients surviving  $\geq 20\%$  with standard regimen

### Times Evaluated

*Overall survival and progression-free survival*

- Twice the median survival time of the control group

# Methods: ESMO-MCBS “immunotherapy-triggered” long-term plateau adjustments



Stone RM, Mandrekar SJ, Sanford BL, et al. Midostaurin plus Chemotherapy for Acute Myeloid Leukemia with FLT3 Mutation. *N Engl J Med.* 2017;377:454-64.

## Bonuses Awarded

- Overall survival: Also score with form 1 (receipt of additional letter grade representing curative potential).
- Progression-free survival: Upgrade 1 clinical benefit grade level

## Criteria

1. “Long-term plateau” of the curve
- 2a. PFS Improvement  $\geq 10\%$
- 2b. OS “advantage” in the test regimen

## Times Evaluated

	Control median (months)	Time point evaluated (months)
Progression-free survival	$\leq 6$	12
	$> 6$	24
Overall Survival	$\leq 12$	60
	$> 12$	84

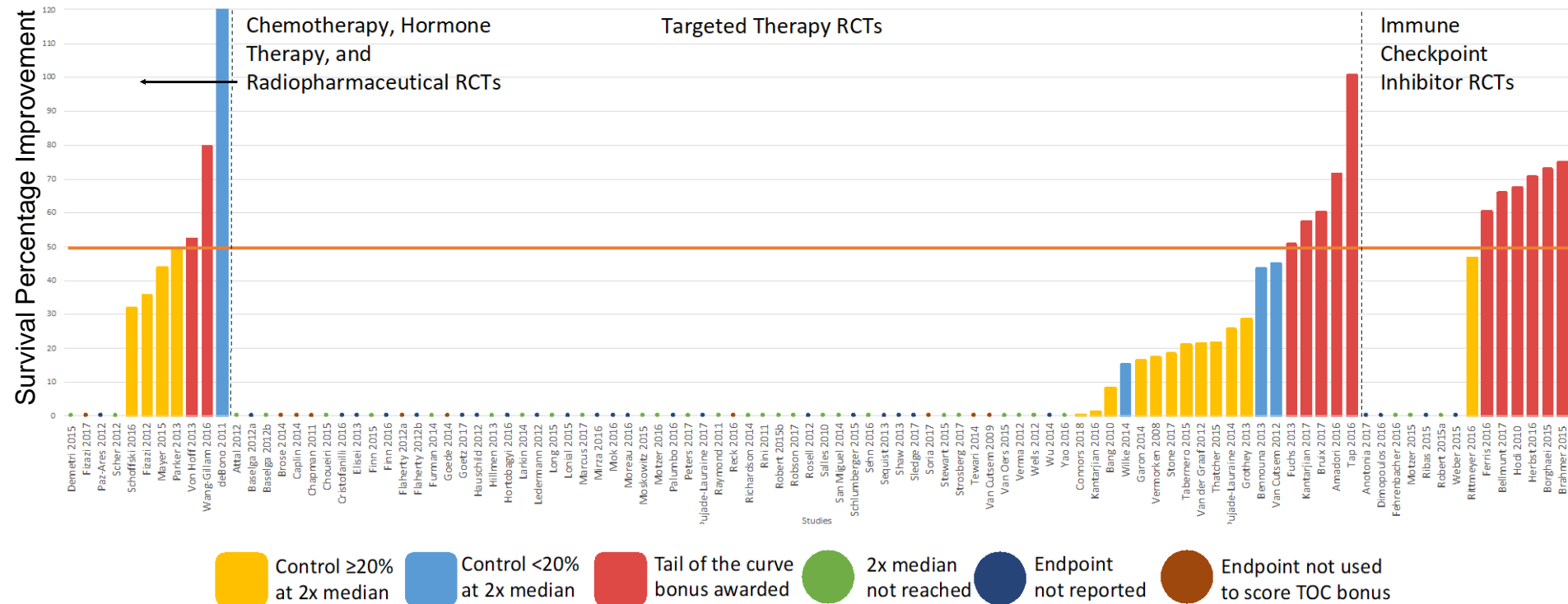


# Methods

## *Statistical Analysis*

- Risk differences were used to calculate how frequently immune checkpoint inhibitor and non-immune checkpoint inhibitor RCTs qualified for these bonuses/adjustments.
- Cohen's Kappa Statistic was used to calculate agreement between ASCO-VF and ESMO-MCBS long-term survival bonuses and adjustments.

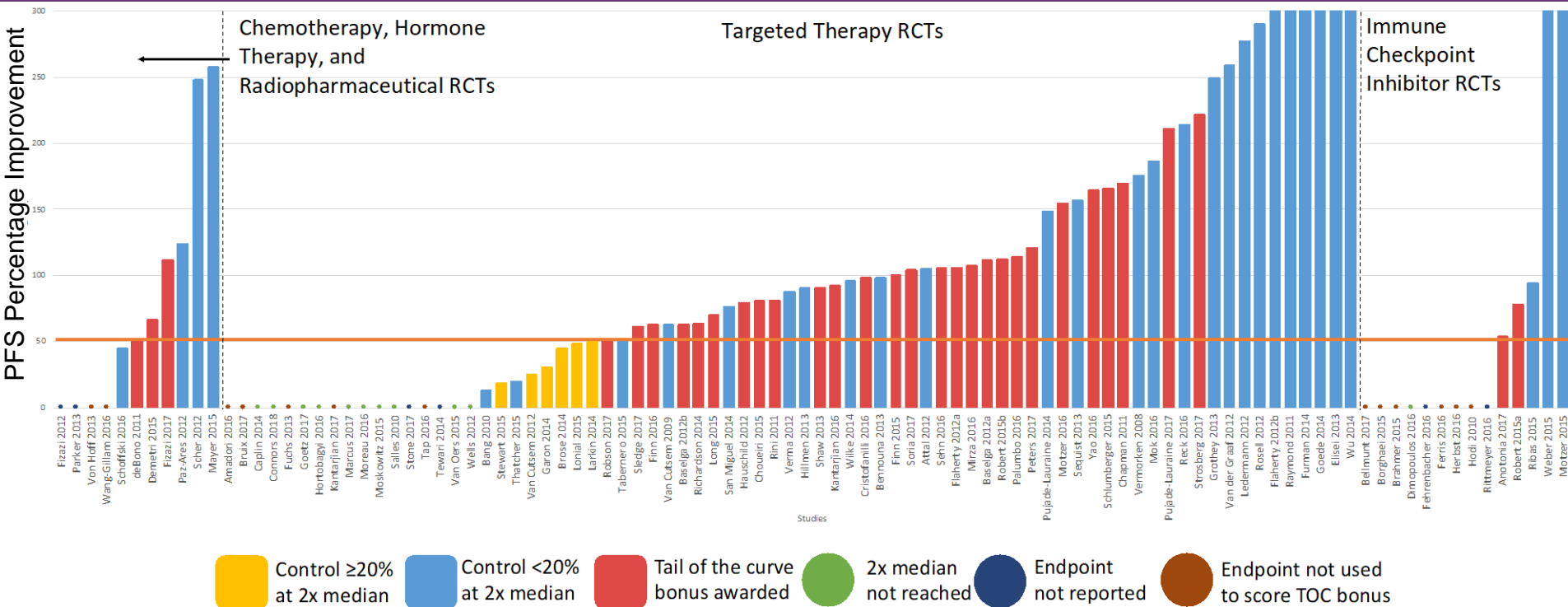
# Results: ASCO-VF “tail of the curve” bonus overall survival



- Immune-checkpoint inhibitor RCTs *did* receive ASCO-VF “tail of the curve” bonuses more often than non-immune checkpoint inhibitor RCTs based on OS.

Risk difference 0.66 (95% CI 0.38, 0.94 p-value: <0.001)

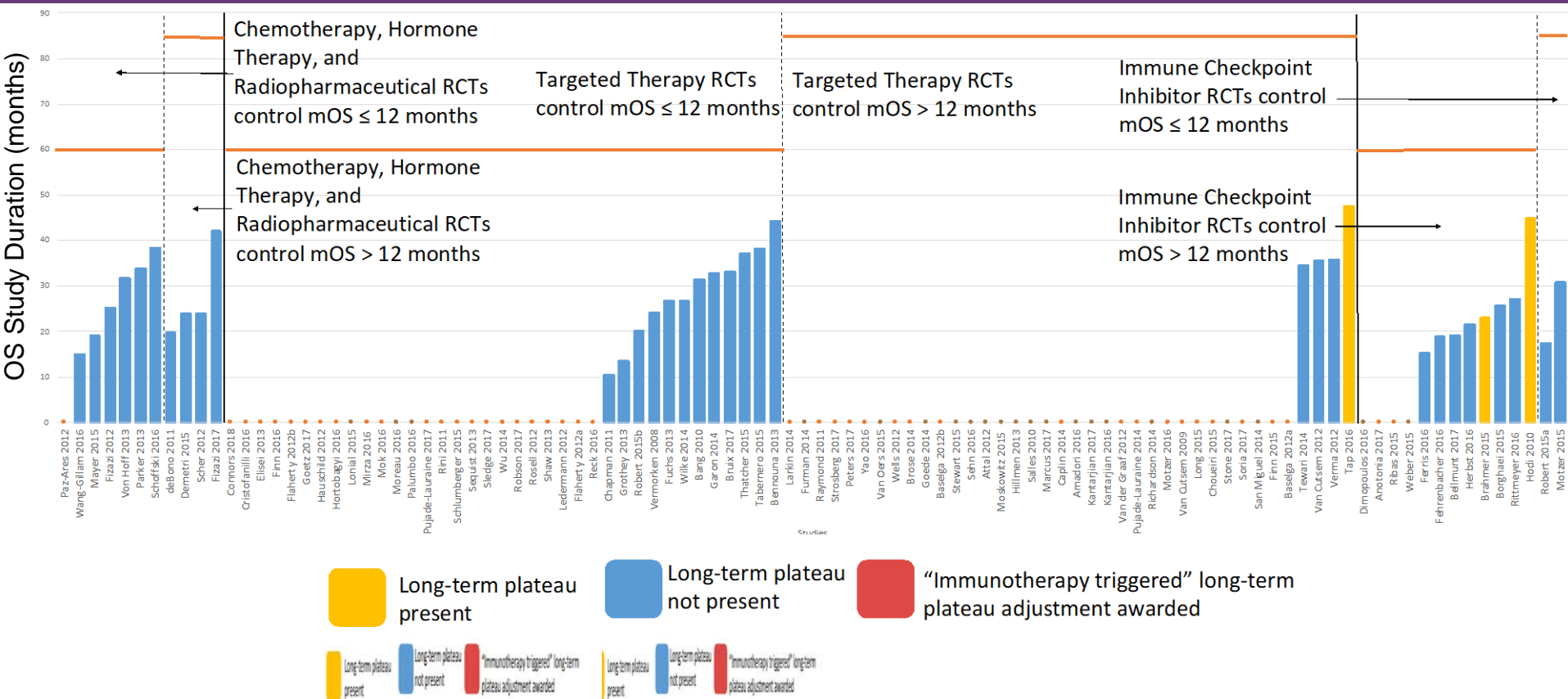
# Results: ASCO-VF “tail of the curve” bonus progression-free survival



- Immune-checkpoint inhibitor RCTs *did not* receive ASCO-VF “tail of the curve” bonuses more often than non-immune checkpoint inhibitor RCTs based on PFS.

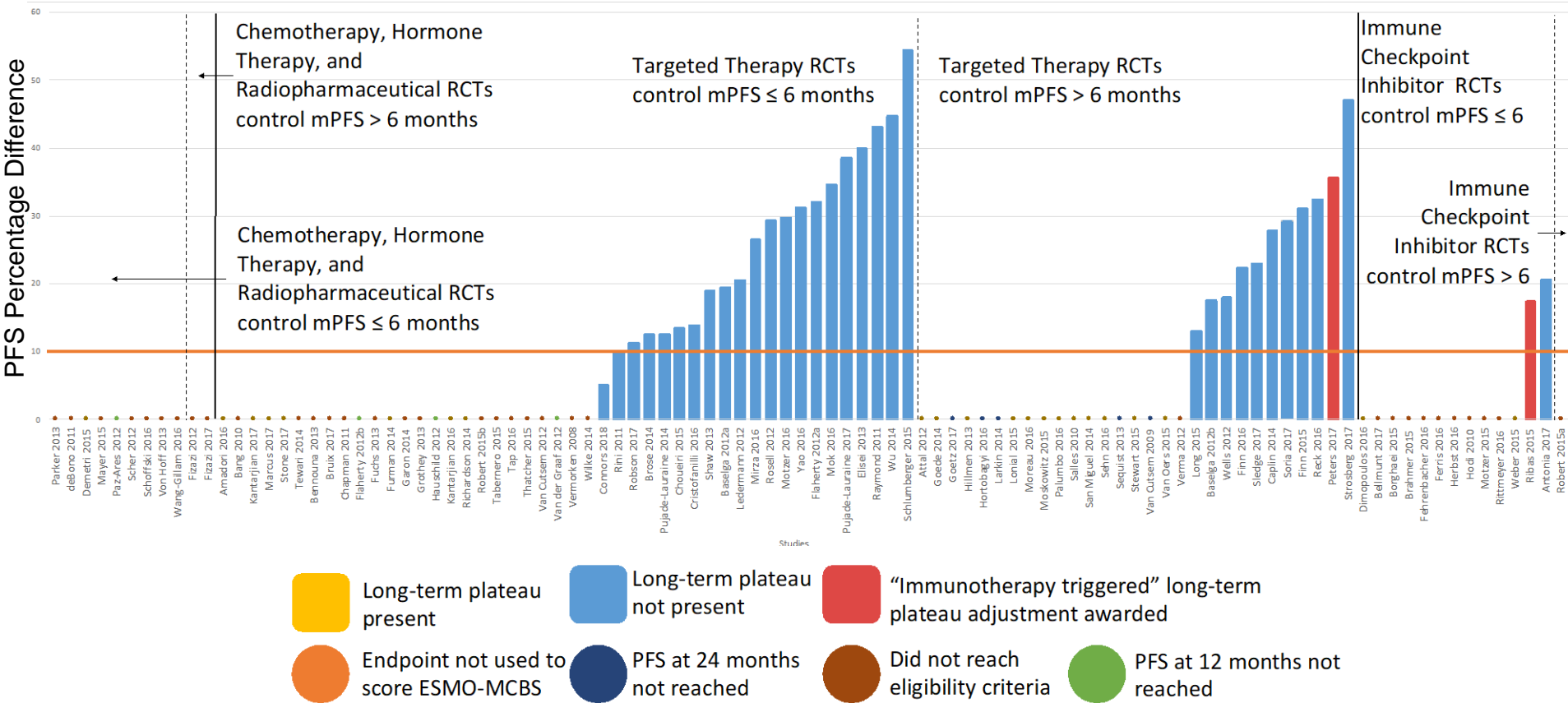
Risk difference 0.05 (95% CI -0.10, 0.21 p-value: 0.5)

# Results: ESMO-MCBS “immunotherapy-triggered” long-term plateau adjustments overall survival



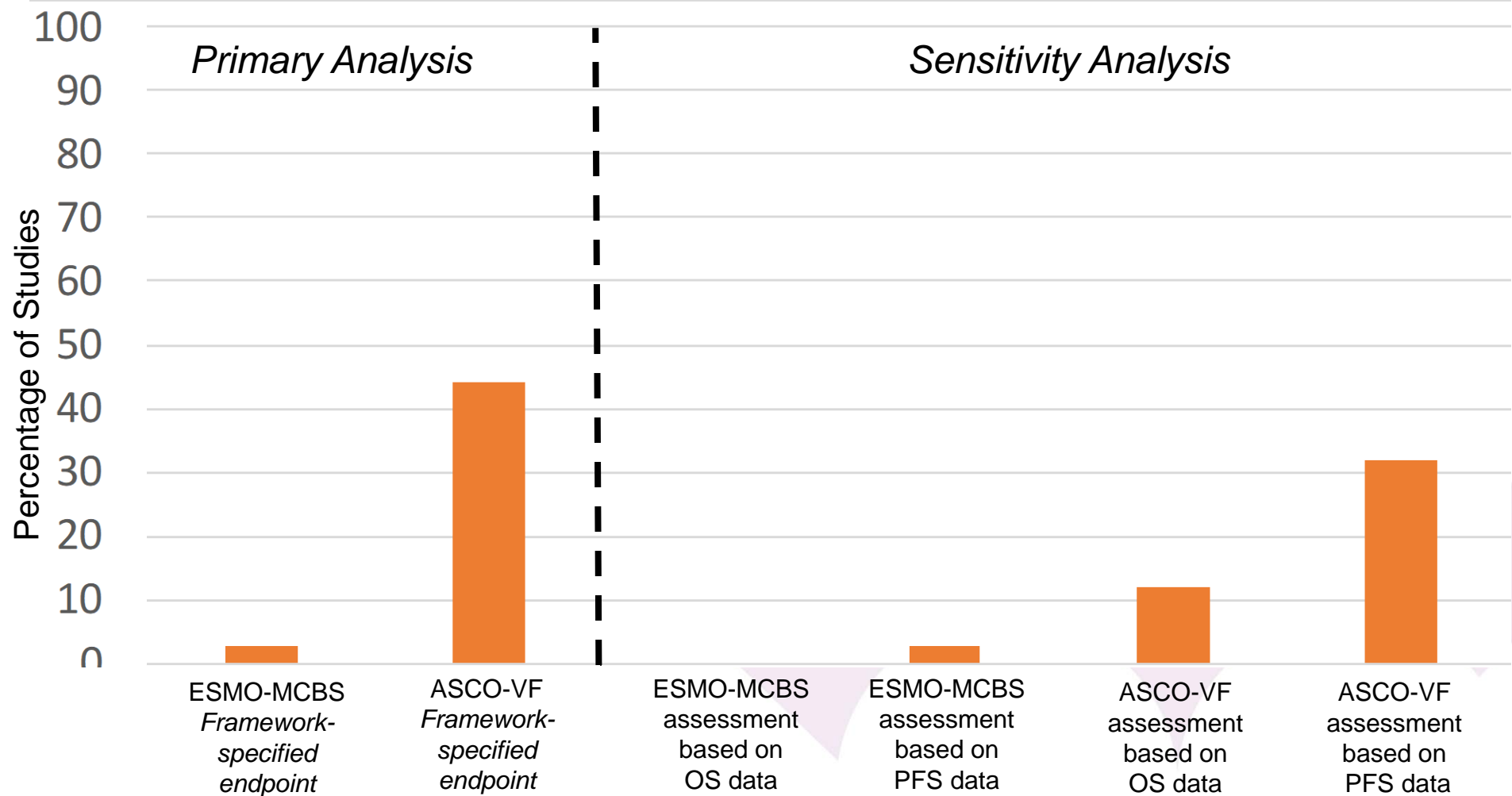
- Immune-checkpoint inhibitors *did not* receive ESMO-MCBS “immunotherapy triggered” long-term plateau adjustments more often than non-immune checkpoint inhibitor RCTs based on OS. Risk difference 0 (95% CI 0, 0 p-value: NA)

# Results: ESMO-MCBS “immunotherapy-triggered” long-term plateau adjustments progression-free survival



- Immune-checkpoint inhibitors *did not* receive ESMO-MCBS “immunotherapy triggered” long-term plateau adjustments more often than non-immune checkpoint inhibitor RCTs based on PFS. Risk difference 0.48 (95% CI -0.22, 1.17 p-value: 0.18)

# Summary of ASCO-VF “tail of the curve” bonuses and EMSO-MCBS “immunotherapy triggered” long-term plateau adjustments



# Results: Risk Differences

Immune checkpoint inhibitor vs non-immune checkpoint inhibitor agents risk differences

Endpoint	Framework	Therapy	Subgroup	Risk Difference	95% CI	p-value
Framework-specified endpoint	ASCO-VF v2	Non-immune Checkpoint Inhibitor		0.14	-0.14, 0.42	0.32
			Chemotherapy, Hormone Therapy, Radiopharmaceutical	0.12	-0.27, 0.51	0.56
			Targeted Therapy	0.15	-0.14, 0.43	0.32
	ESMO-MCBS v1.1	Non-immune Checkpoint Inhibitor		0.07	-0.09, 0.23	0.40
			Chemotherapy, Hormone Therapy, Radiopharmaceutical	0.08	-0.07, 0.24	0.30
			Targeted Therapy	0.07	-0.09, 0.23	0.42

# Results: ASCO and ESMO framework agreement

		Cohen's Kappa Statistics			McNemar's chi-squared test		
Analysis	Endpoint Comparison	Kappa's Correlation Statistic	95% CI	p-value	McNemar's chi-squared	p-value	Number of comparisons
<b>Primary Analysis</b>	<i>Framework-specified endpoint</i>	0.01	-0.23, 0.22	0.50	32.24	<0.001	78
<b>Sensitivity Analysis</b>	Overall survival	0	-0.47, 0.47	0.50	9.09	0.003	35
	Progression free survival	0	-0.30, 0.30	0.50	16.41	<0.001	43
	Immune Checkpoint Inhibitor	-0.17	-0.56, 0.21	0.79	4.00	0.045	12
	Non-immune Checkpoint Inhibitor	0.04	-0.23, 0.30	0.39	27.03	<0.001	66



# Discussion

- Immune checkpoint inhibitor agents did not qualify for ASCO-VF v2 “tail of the curve” bonus or ESMO-MCBS v1.1 “immunotherapy-triggered” long-term plateau adjustments more often than non-immune checkpoint inhibitor agents using the framework-specified endpoint.
- Our results showed low agreement between ASCO-VF v2 “tail of curve” bonus and ESMO-MCBS v1.1 “immunotherapy triggered” long-term plateau adjustments.

# Discussion

- Discrepancies between the present analysis and published literature highlights the need for updated clear, easy-to-follow framework instructions.
- Restricted mean survival time and milestone survival have been proposed as alternative measures that may capture long-term survival benefits.

# Conclusion

- Immune checkpoint inhibitor agents may not preserve long-term survival as conventionally thought
- or*
- ASCO-VF v2 and ESMO-MCBS v1.1 may require additional refinement to accurately capture the benefit of long-term durable survival

# Acknowledgements

This study was supported by ARCC, funding for ARCC is provided by the Canadian Cancer Society grant #2015-703549



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