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Quantifying Withdrawal of Consent, Loss to Follow-Up, Early Drug Discontinuation, and Censoring in Oncology Trials

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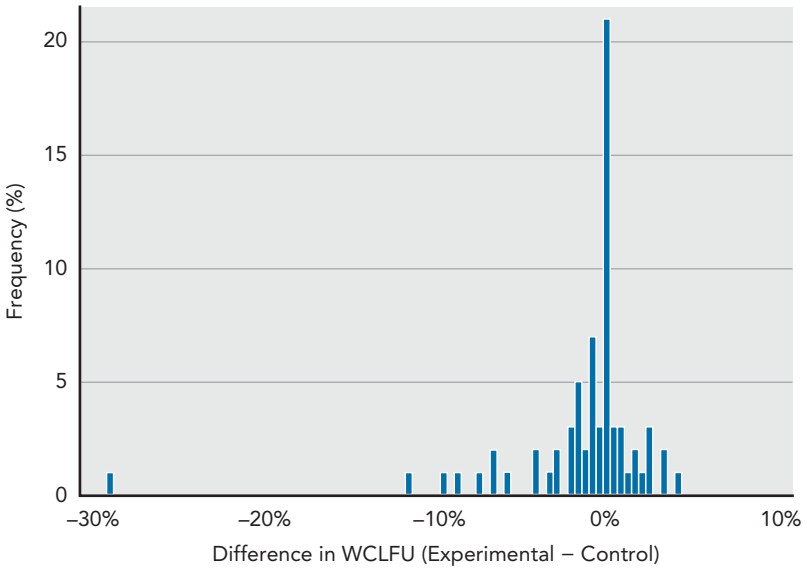

eFigure 1. Percentage differences in WCLFU between experimental and control arms (n=69).
Abbreviation: WCLFU, withdrawal of consent or loss to follow-up.

eTable 1. Characteristics of Trials Included (N=81)

Characteristic	n (%)
Primary endpoint	
PFS	42 (51.8)
OS	28 (34.6)
Other surrogate[a]	11 (13.6)
Year of approval	
2015	17 (21)
2016	10 (12.3)
2017	17 (21)
2018	21 (25.9)
2019	16 (19.7)
Study phase	
II	8 (9.9)
II/III	1 (1.2)
III	72 (88.9)
Drug class	
Immunotherapy	27 (33.3)
Chemotherapy	5 (6.2)
Monoclonal antibodies	5 (6.2)
ARB	6 (7.4)
TKI	17 (21)
Targeted	20 (24.7)
Other	1 (1.2)
Malignancy site	
Breast	15 (18.5)
Lung	20 (24.7)
Melanoma	11 (13.6)
Prostate	6 (7.4)
Other	29 (35.8)
Setting of approval	
Metastatic	72 (88.9)
Neoadjuvant/Adjuvant	9 (11.1)
Control group	
Active control	62 (76.5)
Placebo or BSC alone	19 (23.5)
Blinding	
Blinded	40 (58.0)
Open label	29 (42.0)

Abbreviations: ARB, androgen receptor blocker; BSC, best supportive care; OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.
[a]Disease-free survival, invasive disease-free survival, metastasis-free survival, relapse-free survival.

eTable 2. Differences in Reported Censoring Rates[a] Between Experimental and Control Arms (n=14)

Study	Proportion Censored in Experimental Arm	Proportion Censored in Control Arm	Difference in Censoring Rate
PFS/DFS or MFS analysis			
Impower 130	20.1%	12.1%	8%
REACH-2	12.7%	9.5%	3.2%
KEYNOTE 042	20.4%	20.9%	−0.5%
TAGS	13.9%	8.8%	5.1%
ARCHER 1050	38.3%	21.3%	17%
MONALEESA-7	27.8%	18.4%	9.4%
COLUMBUS	47.9%	42.4%	5.5%
ARIEL 3	37.6%	11.6%	26%
SOLO 2	60.7%	29.3%	31.4%
KEYNOTE 021	61.7%	47.6%	14.1%
METEOR 3	48.8%	34.8%	14%
RADIANT 4	44.9%	33%	11.9%
SQUIRE	20.9%	23.9%	−3%
Checkmate 069	54.7%	25.5%	29.2%
Average	35.5%	24.2%	12.2%
Overall survival analysis			
Impower 130	45.8%	39.2%	6.6%
REACH-2	25.4%	22.1%	3.3%
KEYNOTE 042	41.8%	31.2%	10.6%
TAGS	27.9%	17.6%	10.3%
KEYNOTE 021	78.3%	77.8%	0.5%
METEOR 3	57.6%	45.1%	12.5%
SQUIRE	23.3%	19.3%	4%
Checkmate 069	63.2%	53.2%	10%
Average	45.4%	38.2%	7.2%

Abbreviations: DFS, disease-free survival; MFS, metastasis-free survival; PFS, progression-free survival.
[a]Censoring rates were provided in either the lifetables associated with the Kaplan-Meir curves or tables from the primary study publication. However, causes of censoring were not given. Therefore, patients may have been censored in the final analysis if they free of the primary endpoint and on study at the final data cut-off.

eTable 3. Trial Characteristics Associated With EDD

Characteristic	EDD Exp > Cont (n=42)	EDD Ctrl ≥ Exp (n=27)	OR (95% CI)	*P* Value
Primary endpoint				
PFS	23 (54.8%)	15 (55.6%)	Ref	
OS	12 (28.6%)	9 (33.3%)	1.15 (0.39–3.39)	.80
Other surrogate	7 (16.7%)	3 (11.1%)	0.66 (0.15–2.94)	.58
Year of approval				
2015	9 (21.4%)	6 (22.2%)	Ref	
2016	4 (9.5%)	3 (11.1%)	1.13 (0.18–6.93)	.90
2017	10 (23.8%)	7 (25.9%)	1.05 (0.26–4.31)	.95
2018	10 (23.8%)	6 (22.2%)	0.9 (0.21–3.82)	.89
2019	9 (21.4%)	5 (18.5%)	0.83 (0.18–3.75)	.81
Drug class				
Immunotherapy	11 (26.2%)	10 (37.0%)	Ref	
Chemotherapy	2 (4.8%)	3 (11.1%)	1.65 (0.23–12.0)	.62
Monoclonal antibodies	5 (11.9%)	0	—	—
ARB	1 (2.4%)	3 (11.1%)	3.3 (0.29–37.1)	.33
TKI	10 (23.8%)	5 (18.5%)	0.55 (0.14–2.17)	.39
Targeted	13 (20.9%)	6 (22.2%)	0.51 (0.14–1.85)	.30
Malignancy site				
Breast	11 (26.2%)	3 (11.1%)	Ref	
Lung	6 (14.3%)	9 (33.3%)	5.5 (1.06–28.4)	**.042**
Melanoma	6 (14.3%)	3 (11.1%)	1.83 (0.27–12.1)	.53
Prostate	1 (2.4%)	3 (11.1%)	11 (0.8–147.9)	**.07**
Other	18 (42.9%)	9 (33.3%)	1.8 (0.41–8.3)	.43
Setting of approval				
Metastatic	34 (80.9%)	26 (96.3%)	Ref	
Neoadjuvant/Adjuvant	8 (19.1%)	1 (3.7%)	0.16 (0.02–1.39)	.097
Control group				
Placebo or BSC alone	17 (40.5%)	2 (7.4%)	Ref	
Active control	25 (59.5%)	25 (92.6%)	8.5 (1.7–40.7)	**.007**
Reported HR, mean [SD]	0.58 [0.15]	0.56 [0.14]	0.38 (0.01–10.07)	.56
Total sample size, mean [SD]	767 [791]	603 [373]	0.99 (0.99–1.00)	.34
Blinding				
Blinded	10 (23.8%)	19 (70.4%)	Ref	
Open label	32 (76.2%)	8 (29.6%)	7.6 (2.56–22.59)	**<.001**

Bold indicates statistically significant *P* value.
Abbreviations: ARB, androgen receptor blocker; BSC, best supportive care; ctrl, control; exp, experimental; EDD, early drug discontinuation; HR, hazard ratio; OR, odds ratio; OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

eTable 4. Disposition at Time of Final Analysis: Proportion Discontinued From Study Due to WCLFU[a] (n=13)

Study	Proportion Excluded in Experimental Arm	Proportion Excluded in Control Arm	Differences in Exclusion Rate
Impower 130	6%	6.7%	−0.7%
Impower 133	11.4%	5%	6.4%
Impassion 130	5.3%	5.3%	0%
EMBRACA	4.9%	18.1%	−13.2%
COMBI-AD	10.7%	14.4%	−3.7%
Checkmate 238	3.3%	6.4%	−3.1%
ALEX	11.8%	19.2%	−7.4%
STUDY-19	5.1%	8.5%	−3.4%
POPLAR	4.2%	9.1%	−4.9%
OAK	6.6%	11.8%	−5.2%
NCT01327885	3.5%	3.6%	−0.1%
CheckMate 057	1.4%	1.4%	0%
RECOURSE	0.7%	1.1%	−0.4%
Average	**5.8%**	**8.5%**	**−2.7%**

The proportion of patients excluded from final analysis was greater than or equal to that in the control group compared with the experimental group in 12 of 13 studies and greater in the experimental group than in the control group in 1 of 13 studies.
Abbreviation: WCLFU, withdrawal of consent or loss to follow-up.
[a]This may not account for patients who have been censored for reasons other than WCLFU according to the protocol rules.