

## Supplementary Online Content

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**eTable 1.** List of RCTS with a control arm that is deemed optimal

**eTable 2.** Nature of sub-optimal control

This supplementary material has been provided by the authors to give readers additional information about their work.

**Abbreviations: SOC, standard of care; MFS, metastasis-free survival; PFS, progression-free survival; RFS, relapse-free survival; OS, overall survival; ORR, overall response rate; (i)DFS, (invasive) disease-free survival; EFS, event-free survival; CR, complete response; MMR, major molecular response**

**eTable 1. List of RCTs with a control arm that is deemed optimal**

#	Trial	Indication	Investigational Agent	Control	Primary Endpoint	Accrual Period	Scope/ Number of Sites	Date of Approval	Type of Approval	SOC Comments
1.	COLUMBUS	Metastatic melanoma with BRAF V600E or V600K mutation	Encorafenib + binimetinib	Encorafenib or Vemurafenib	PFS	December 2013 to April 2015	International/ 162	June, 2018	Regular	Vemurafenib single-agent SOC
2.	GOG-0218	Epithelial ovarian, fallopian tube or primary peritoneal cancer	Bevacizumab (+ carboplatin/ paclitaxel)	Carboplatin/ paclitaxel	PFS	October 2005 to June 2009	International/ 336	June, 2018	Regular	Carboplatin/ paclitaxel established SOC
3.	COMBI-AD	Adjuvant melanoma with BRAF V600E or V600K mutations after complete resection	Dabrafenib and trametinib	Placebo	RFS	January 2013 to December 2014	International/ 169	May, 2018	Regular	No established SOC for adjuvant therapy in BRAF mutant melanoma
4.	FLAURA	First-line metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R mutations	Osimertinib	Gefitinib or Erlotinib	PFS	December 2014 through March 2016	International/ 132	April, 2018	Regular	Gefitinib/erlotinib SOC in first-line setting
5.	CheckMate-214	First-line intermediate or poor-risk RCC	Nivolumab/ipilimumab	Sunitinib	PFS, OS, ORR	October 2014 through	International/ 175	April, 2018	Regular	Pazopanib shown to be "noninferior" to sunitinib in COMPARZ trial

						February 2016				
6.	ARIEL3	Maintenance of recurrent ovarian, fallopian tube, or primary peritoneal cancer, at least 2 prior lines	Rucaparib	Placebo	PFS	April 7, 2014, and July 19, 2016	International/87	March, 2018	Regular	Maintenance bevacizumab is not SOC. Major disagreement in NCCN (Category 3)
7.	ECHELO N-1	Stage III or IV Hodgkin lymphoma	BV (+ AVD)	ABVD	mPFS	November 19, 2012, through January 13, 2016	International/218	March, 2018	Regular	PET-adapted therapy after ECHELON-1 started accruing
8.	MONARCH-3	Postmenopausal HR-positive, HER-negative breast cancer	Abemaciclib (+ AI)	AI	PFS	November 18, 2014 and November 11, 2015	International/158	February, 2018	Regular	Started recruiting before approval of other CDK 4/6 inhibitors
9.	PACIFIC	Unresectable stage III NSCLC following chemoradiation	Durvalumab	Placebo	PFS, OS	May 2014 and April 2016	International / NR	February, 2018	Regular	No SOC in adjuvant setting of stage III NSCLC
10.	LATITUDE	Metastatic high-risk castration-sensitive prostate cancer	Abiraterone (with prednisone)	Placebo	PFS, OS	February 12, 2013, through December 11, 2014	International/235	February, 2018	Regular	
11.	NETTER-1	Somatostatin receptor-positive GEP-NETs	Lutetium dotatate (+ octreotide)	Octreotide	PFS	September 2012 through mid-January 2016	International/41	January, 2018	Regular	Everolimus approval came after start of recruitment on NETTER-1

12.	APHINITY	Adjuvant treatment of HER2-positive early breast cancer with chemo and trastuzumab	Pertuzumab (+ chemo/ trastuzumab)	Placebo (+ chemo/ trastuzumab)	iDFS	November 2011 through August 2013	International/ 549	December, 2017	Regular	
13.	CheckMate-238	Adjuvant melanoma with lymph nodes	Nivolumab	Ipilimumab	RFS	March 30, 2015, to November 30, 2015	International/ 130	December, 2017	Regular	Ipilimumab is SOC
14.	CABOSUN	First line RCC, intermediate and poor risk	Cabozantinib	Sunitinib	PFS	From July 9, 2013, to April 6, 2015	National/ NA	December, 2017	Regular	Sunitinib shown to be "noninferior" to pazopanib in COMPARZ trial
15.	S-TRAC	Adjuvant RCC	Sunitinib	Placebo	DFS	September 19, 2007, to April 7, 2011	International/ 99	November, 2017	Regular	No SOC for RCC in the adjuvant setting
16.	GALLIUM	Previously untreated stage II bulky, III, or IV follicular lymphoma	Obinutuzumab (with chemo)	Rituximab (with chemo)	PFS	July 6, 2011, and February 4, 2014	International/ NA	November, 2017	Regular	Rituximab + chemo is SOC
17.	ALEX	ALK-positive metastatic NSCLC	Alectinib	Crizotinib	PFS	August 18, 2014, and January 20, 2016	International/ 98	November, 2017	Regular	
18.	MONARCH-2	HR-positive, HER2-negative metastatic breast cancer with disease prog on endocrine tx	Abemaciclib (with fulvestrant)	Placebo (with fulvestrant)	PFS	August 2014 and December 2015	International/ 142	September, 2017	Regular	Fulvestrant is SOC
19.	ALFA-0701	Previously untreated AML	Gemtuzumab (with 7 + 3)	Placebo (with 7+3)	EFS	January, 2008, and	National/ 26	September, 2017	Regular	

						November, 2010				
20.	SOLO2	Maintenance for BRCA-mutated ovarian cancer in CR or PR after platinum-based chemo	Olaparib	Placebo	PFS	Sept 3, 2013, and Nov 21, 2014	International/123	August, 2017	Regular	No approved standard. Maintenance bevacizumab is controversial.
21.	INO-VATE ALL	Relapsed/ref B-ALL	Inotuzumab	Standard chemotherapy	CR, OS	August 27, 2012, and October 2, 2014	International/NA	August, 2017	Regular	Physician choice of second-line induction
22.	CLTR03 10-301	t-AML or AML-MRC	CPX-351	7 + 3 (cytarabine + daunorubicin 60 mg)	OS	December 2012 and November 2014	U.S. and Canada / 39	August, 2017	Regular	
23.	ExteNET	Adjuvant HER-2-positive breast cancer	Neratinib	Placebo	iDFS	Between July 9, 2009, and Oct 24, 2011	International/NA	July, 2017	Regular	
24.	TOWER	Relapsed/ref B-ALL	Blinatumomab	FLAG + anthracycline, HiDAC-based, high-dose MTR-based, clofarabine-based	OS	Between January 2014, and September 2015	International/101	July, 2017	Regular	
25.	Keynote-021	Previously untreated metastatic NSCLC	Pembrolizumab (+ carbo/pem)	Platinum-based doublet	ORR	Between November 25, 2014 and Jan 25, 2016	International/26	May, 2017	Accelerated	

26.	RATIFY	FLT3+ AML	Midostaurin (with 7+ 3)	7 + 3	OS	Between May 2008 to March 7, 2016	International/ 225	April, 2017	Regular	
27.	RESORCE	HCC in pts previously treated with sorafenib	Regorafenib	Placebo	OS	Between May 14, 2013 and Dec 31, 2015	International/ 152	April, 2017	Regular	
28.	PALOMA-2	Postmenopausal HR-positive, HER-negative breast cancer	Palbociclib (+AI)	Placebo +letrozole	PFS	Between February 2013 through July 2014	International/ 186	March, 2017	Regular	
29.	AURA-3	Metastatic EGFR T790M-mutated NSCLC after progression	Osimertinib	Platinum + pemetrexed	PFS	Between August 2014 through September 2015	International/ 126	March, 2017	Regular	
30.	NOVA	Maintenance for recurrent ovarian cancer in CR or PR after platinum-based chemo	Niraparib	Placebo	PFS	Between August 26, 2013 through June 20, 2016	International/ 107	March, 2017	Regular	Other PARP inhibitors approved in first remission or third remission
31.	MONALEESA-2	Postmenopausal HR-positive, HER-negative breast cancer	Ribociclib (+AI)	AI	PFS	Between January 24, 2014 through March 24, 2015	International/ NA	March, 2017	Regular	
32.	CALGB 100104	Maintenance for myeloma following ASCT	Lenalidomide	Placebo	PFS	Between April 14, 2005 through July 2, 2009	National/ 47	February, 2017	Regular	Thalidomide maintenance data available with data showing improved outcomes, but not chosen as control because of toxicity

33.	IFM 2005-02	Maintenance for myeloma following ASCT	Lenalidomide	Placebo	PFS	Between July 2006 through August 2008	Europe / 77	February, 2017	Regular	Thalidomide maintenance data available with data showing improved outcomes, but not chosen as control because of toxicity
34.	CASTOR	Myeloma after at least one prior therapy	Daratumumab (+ bortezomib/dex amethasone)	Bortezomib/ dexamethasone	PFS	September 4, 2014, to September 24, 2015,	International/ 115	November, 2016	Regular	
35.	POLLUX	Myeloma after at least one prior therapy	Daratumumab (+ len/dex)	Lenalidomide /dexamethasone	PFS	June 16, 2014, and July 14, 2015	International/ 135	November, 2016	Regular	
36.	CheckMate-141	Recurrent or metastatic SCC of HN progress on or after platinum (refractory <6 months)	Nivolumab	Single-agent (MTX, docetaxel, cetuximab)	OS	Between June 2014 through August 2015	International/ NA	November, 2016	Regular	
37.	KEYNOTE-024	Metastatic NSCLC who express PD-L1	Pembrolizumab	Investigator's choice (carboplatin/ pemetrexed, cisplatin/ pemetrexed, carboplatin/ gemcitabine, cisplatin/ gemcitabine, or carboplatin/ paclitaxel)	PFS	June 2014 through August 2015	International/ 142	October, 2016	Regular	
38.	OAK	Metastatic NSCLC who progress	Atezolizumab	Docetaxel	OS	March 11, 2014, and	International/ 194	October, 2016	Regular	

		during or following platinum chemotherapy				Nov 28, 2014				
39.	Motzer, 2015	Advanced RCC following one line of therapy	Lenvatinib + Everolimus	Everolimus	PFS	March 16, 2012, to June 19, 2013	International/ 37	May, 2016	Regular	Nivolumab not approved yet
40.	PALOMA-3	HR-positive, HER2-negative metastatic breast cancer with disease prog on endocrine tx	Palbociclib (+ fulvestrant)	Fulvestrant + placebo	PFS	Oct 7, 2013, and Aug 26, 2014	International/ 144	February, 2016	Regular	
41.	Schöffski, 2016	Metastatic liposarcoma who received anthracycline	Eribulin	Dacarbazine	OS	March 10, 2011 and May 22, 2013	International/ 110	January, 2016	Regular	
42.	PROLONG	Extended therapy (maintenance) in Recurrent/progressive CLL in PR or CR	Ofatumumab	Observation	PFS	May 6, 2010, and June 19, 201	International/ 130	January, 2016	Regular	Rituximab maintenance. No data prior to 2010
43.	KEYNOTE-006	Unresectable or metastatic melanoma	Pembrolizumab	Ipilimumab	PFS and OS	September 18, 2013, to March 3, 2014,	International/ NR	December, 2015	Regular	
44.	ELOQUENT-2	Myeloma after at least one prior therapy	Elotuzumab (+ len/ dex)	Len/ dexamethasone	Copriary, PFS and OS	June 2011 and November 2012	International/ 168	November, 2015	Regular	Triplet therapy is standard as of 2011.
45.	SQUIRE	Metastatic squamous lung cancer	Necitumumab (+ gem + cis)	GEM+CIS	OS	Jan 7, 2010, and Feb 22, 2012	International/ 184	November, 2015	Regular	



46.	CHECKMATE-025	Advanced RCC following one line of therapy	Nivolumab	Everolimus	OS	October 2012 through March 2014	International/146	November, 2015	Regular	
47.	Long, 2015	Unresectable or metastatic melanoma with BRAF V600E mutations	Dabrafenib and trametinib	Dabrafenib + placebo	PFS	May 4, 2012, and Nov 30, 2012,	International/113	November, 2015	Regular	
48.	Larkin, 2014	Unresectable or metastatic melanoma with BRAF V600E mutations	Cobimetinib (with vemurafenib)	Vemurafenib + placebo	PFS	January 2013 through January 2014	International/135	November, 2015	Regular	
49.	Eggermont, 2016	Adjuvant melanoma with lymph nodes	Ipilimumab	Placebo	RFS	From July 2008 through August 2011	International/99	October, 2015	Regular	IFN was category 2B as improved RFS but not OS: observation or clinical trials were the other recommendations by NCCN
50.	Demetri, 2016	Unresectable or metastatic liposarcoma or leiomyosarcoma who received prior anthracycline	Trabectedin	Decarbazine	OS	May 27, 2011, and the September 16, 2013	International/85	October, 2015	Regular	
51.	Wang-Gillam, 2015	Metastatic adenocarcinoma of pancreas after gemcitabine-based therapy	Liposomal irinotecan (with 5-FU)	5-FU	OS	Jan 11, 2012, and Sept 11, 2013,	International/76	October, 2015	Regular	
52.	Borghaei, 2015	Metastatic NSCLC after progression of	Nivolumab	Docetaxel	OS	November 2012 through	International/NR	October, 2015	Regular	

		platinum therapy				December 2013				
53.	Postow, 2015	Unresectable or metastatic melanoma with BRAF V600E wild-type	Nivolumab (+ipilimumab)	Ipilimumab + Placebo	ORR	September 16, 2013, to February 6, 2014	International/ NR	September, 2015	Accelerated	
54.	Mayer, 2015	Metastatic colorectal cancer, third-line	TAS-102	Placebo	OS	June 17, 2012, and October 8, 2013	International/ NR	September, 2015	Regular	
55.	Moskowitz, 2015	cHL after ASCT consolidation treatment	BV	Placebo	PFS	April 6, 2010, and Sept 21, 2012	International/ 78	August, 2015	Regular	
56.	ASPIRE	Myeloma after at least one prior therapy	Carfilzomib (+ len/ dex)	Len/ dex	PFS	July 2010 and March 2012	International/ NR	July, 2015	Regular	Triplet regimen is standard as of 2011.
57.	Tabernero, 2015	Metastatic colorectal cancer who progress on bev- oxali- 5-FU regimen	Ramucirumab (+FOLFIRI)	FOLFIRI + Placebo	OS	Dec 14, 2010, and Aug 23, 2013	International/ 224	April, 2015	Regular	
58.	Brahmer, 2015	Metastatic squamous lung cancer with progression after platinum therapy	Nivolumab	Docetaxel	OS	October 2012 through December 2013	International/ NR	March, 2015	Regular	
59.	PANORAMA1	Myeloma after at least 2 lines of therapy	Panobinostat (+ bortezomib/ dexamethasone)	Placebo (+ bortezomib/ dexamethasone)	PFS	January, 2010 through February, 2012	International/ 215	February, 2015	Regular	
60.	Schlumberger, 2015	Metastatic differentiated thyroid cancer	Lenvatinib	Placebo	PFS	August 5, 2011, through	International/ NR	February, 2015	Regular	

						October 4, 2012				
61.	PALOMA-1	Postmenopausal HR-positive, HER-negative breast cancer	Palbociclib (+ AI)	Letrozole	PFS	Dec 22, 2009, and May 12, 2012,	International/50	February, 2015	Accelerated	
62.	Weber, 2015	Unresectable or metastatic melanoma and disease progression following ipi	Nivolumab	Chemotherapy (decarbazine OR carboplatin/paclitaxel)	ORR, OS	Dec 21, 2012, to Jan 10, 2014	International/90	December, 2014	Accelerated	
63.	CLARINET	Unresectable or metastatic GEP-NETs	Lanreotide	Placebo	PFS	June 2006 and April 2013	International/48	December, 2014	Regular	
64.	REVEL	Metastatic NSCLC after progression of platinum therapy	Ramucirumab (+ docetaxel)	Docetaxel+ Placebo	OS	Dec 3, 2010, and Jan 24, 2013	International/NR	December, 2014	Regular	
65.	Vannucci, 2015	PV who had inadequate response to hydroxyurea	Ruxolitinib	Hydroxyurea, interferon or pegylated interferon, pipobroman, anagrelide, immunomodulators (lenalidomide or thalidomide), no medication	Hematologic control, spleen size reduction	November 29, 2010, to February 13, 2013	International/NR	December, 2014	Regular	
66.	AURELIA	Platinum-resistant, recurrent ovarian cancer	Bevacizumab (+ paclitaxel or Doxil)	Chemotherapy (pegylated liposomal doxorubicin, weekly	PFS	October 2009 and April 2011	International/NR	November, 2014	Regular	

				paclitaxel, or topotecan)						
67.	RAINBOW	Advanced gastric or GEJ adenocarcinoma	Ramucirumab (+ paclitaxel)	Paclitaxel	OS	Dec 23, 2010, and Sept 23, 2011	International/170	November, 2014	Regular	
68.	Tewari, 2014	Recurrent cervical cancer	Bevacizumab (+ paclitaxel/cisplatin or paclitaxel/topotecan)	Chemotherapy (paclitaxel/cisplatin or paclitaxel/topotecan)	OS	April 2009 and January 2012	National/11	August, 2014	Regular	
69.	Furman, 2014	Relapsed CLL	Idelalisib (+ rituximab)	Placebo + rituximab	PFS	May 2012 and August 2013	International/90	July, 2014	Regular	
70.	COMPLEMENT1	Previously untreated CLL who are not candidates for fludarabine	Ofatumumab (+ chlorambucil)	Chlorambucil	PFS	Dec 22, 2008, and May 26, 2011	International/109	April, 2014	Regular	Chlorambucil is used as single-agent but most would use BR if fludarabine cannot be given.
71.	Flaherty, 2012	Unresectable or metastatic melanoma with BRAF V600E mutations	Dabrafenib and trametinib	Dabrafenib monotherapy	ORR	March 26, 2010, to July 7, 2011	International/16	January, 2014	Accelerated	
72.	DECISION	Metastatic differentiated thyroid cancer	Sorafenib	Placebo	PFS	October 2009 to August 2011	International/77	November, 2013	Regular	
73.	Shaw, 2013	ALK-positive metastatic NSCLC	Crizotinib	Chemotherapy (pemetrexed OR docetaxel)	PFS	February 2010 through February 2012	International	November, 2013	Regular	
74.	NeoSphere	Neoadjuvant HER2-positive locally advanced breast cancer	Pertuzumab combination	Trastuzumab / docetaxel OR Pertuzumab/trastuzumab	pCR	Dec 17, 2007, to Dec 22, 2009	International/59	September, 2013	Accelerated	

				/docetaxel (group B) OR pertuzumab/trastuzumab (group C) OR pertuzumab/docetaxel (group D)						
75.	IMPACT	First-line pancreatic cancer	Nab-paclitaxel (+ gemcitabine)	Gemcitabine	OS	May 2009 through April 2012	International/151	September, 2013	Regular	
76.	Flaherty, 2012	Unresectable or metastatic melanoma with BRAF V600E mutations	Trametinib	Chemotherapy (decarbazine OR paclitaxel)	PFS	December 2010 through July 2011	International/103	June, 2013	Regular	
77.	Hauschild, 2012	Unresectable or metastatic melanoma with BRAF V600E mutations	Dabrafenib	decarbazine	PFS	Dec 23, 2010, and Sept 1, 2011	International/70	June, 2013	Regular	
78.	ALSYMP CA	Castration resistant prostate cancer, symptomatic brain mets	Radium 223	Placebo + SOC (included local radiotherapy, corticosteroids, anti-androgens, estrogens, estramustine or ketoconazole)	OS	June 2008 through February 2011	International/136	May, 2013	Regular	Patients were not eligible to or declined docetaxel
79.	EURTAC	First-line metastatic NSCLC with EGFR exon 19 deletions or	Erlotinib	Platinum-based chemotherapy	PFS	Feb 15, 2007, and Jan 4, 2011	Europe / NR	May, 2013	Regular	Trial conducted in Europe only.

		exon 21 L858R mutations								
80.	EMILIA	HER-2 positive metastatic breast cancer who previously received trastuzumab and taxane	TDM-1	Capecitabine + lapatinib	PFS, OS, and safety	February 2009 through October 2011	International/ 213	February, 2013	Regular	
81.	ML18147	Metastatic colorectal cancer after progression on first-line bev regimen	Bevacizumab (+ FOLFIRI or FOLFOX)	FOLFIRI/FOLFOX	OS	Feb 1, 2006, until June 9, 2010	International/ 220	January, 2013	Regular	

**eTable 2. Nature of sub-optimal control**

<b>Category of Sub-Optimal Control</b>	<b>Trials</b>
Omitting active treatment in control arm by limiting investigator's choice	OlympiAD, ALCANZA, Keynote-045, GADOLIN
Omitting active treatment in control arm by using control known to be inferior to other available agents or not allowing combinations	PROSPER, SPARTAN, BFORE, ASCEND-4, Tap et al, METEOR, RADIANT-4, TOURMALIN, REGARD, CLL11, LUX-Lung 3
Using previously used treatment in control arm with known lack of benefit upon re-exposure	MURANO