Supplementary Online Content

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

eTable 1. Clinical trials with suboptimal control arms

Trial (Accrual Dates)	Indication	Investigational Agent	Control	Comment
ALCANZA (August 2012 – July 2015)	pcALCL, or CD30-expressing mycosis fungoides who received prior therapy	Brentuximab vedotin	Physician's choice (oral methotrexate or bexarotene)	Vorinostat and romidepsin used (in US). HDAC inhibitors not chosen because not EMA-approved in cutaneous T-cell lymphoma. Restricted choice.
ALCYONE (February 2015 – July 2016)	Newly diagnosed multiple myeloma that are transplant ineligible	Daratumumab (+ VMP)	VMP (bortezomib, melphalan, prednisone)	VMP is not used in the U.S. Immunomodulatory agent is SOC in newly diagnosed MM, but not utilized in this trial.
ASCEND-4 (August 2013 – May 2015)	Metastatic ALK-positive NSCLC, first-line	Ceritinib	Platinum-based therapy	Crizotinib is SOC and approved in 2011 by FDA prior to trial enrollment.
AUGMENT (February 2014 – January 2017)	Follicular lymphoma and marginal zone, previously treated (with rituximab)	Lenalidomide (+ rituximab)	Placebo (+ rituximab)	Single-agent rituximab not adequate. 85% previously exposed to rituximab. 60% received 1 line of chemoimmunotherapy before enrollment on trial. Chemotherapy with rituximab is SOC.
BFORE (July 2014 – August 2015)	First-line chronic phase CML	Bosutinib	Imatinib	Nilotinib and dasatinib have demonstrated better MMR compared to imatinib. Not allowed in control arm
CLARINET (June 2006 – April 2013)	Unresectable or metastatic GEP-NETs, nonfunctional	Lanreotide	Placebo	Compared to placebo; octreotide used with RCT data, everolimus sunitinib used in this setting to control tumor growth

CLL14 (August 2015 – August 2016)	Previously untreated CLL with comorbidities	Venetoclax (+ obinutuzumab)	Chlorambucil + obinutuzumab	Other SOC options not allowed (e.g. BR). Restricted choice in control arm.
COMPLEMENT 2 (March 2009 – January 2012)	Relapsed CLL	Ofatumumab (+ FC)	FC (fludarabine and cyclophosphamide)	Rituximab not allowed in control arm. Data from 2005 showed benefit of FCR in frontline and relapsed CLL.
EMBRACA (October 2013 – April 2017)	Germline BRCA-mutated HER2-negative metastatic breast cancer who have been treated with chemo	Talazoparib	Physician choice (capecitabine, eribulin, gemcitabine, vinorelbine)	Platinum not allowed in control arm as a physician choice.
iNNOVATE (July 2014 – January 2016)	Waldenstrom's macroglobulinemia	Ibrutinib (+ rituximab)	Rituximab	Single-agent rituximab is an option but other chemoimmunotherapy options are SOC based on phase 2 data that were not allowed.
MAIA (March 2015 – January 2017)	Newly diagnosed multiple myeloma that are transplant ineligible	Daratumumab (+ lenalidomide/dexamethasone)	Lenalidomide/dexamethasone	Rd is suboptimal font line therapy for transplant ineligible MM. RVD-lite was adopted as SOC for these patients in 2014/2015.
OlympiAD (April 2014 – November 2015)	Germline BRCA-mutated HER2-negative metastatic breast cancer who have been treated with chemo	Olaparib	Physicians' choice of chemotherapy (not platinum)	Platinum not allowed as SOC physician choice
PROSPER (November 2013 – June 2017)	Non-metastatic castration-resistant prostate cancer	Enzalutamide	Placebo	Bicalutamide used in this space. Patients on bicalutamide had to discontinue before enrollment.
SPARTAN (October 2013 – December 2016)	Non-metastatic castration-resistant prostate cancer	Apalutamide	Placebo	Bicalutamide used in this space. Patients on bicalutamide had to discontinue before enrollment.
TOURMALINE-MM1 (August 2012 – May 2014)	Myeloma after at least one prior therapy	Ixazomib (+ lenalidomide/dexamethasone)	Placebo (+ lenalidomide/dexamethasone)	Bortezomib-based therapy (doublet or triplet with alkylator) recommended for relapsed myeloma. Repeat induction therapy is also standard if >6 months remission.

Study 0761-010 (December 2012 – January 2016)	Relapsed or refractory mycosis fungoides (MF) or Sézary syndrome (SS) after at least one prior systemic therapy	Mogamulizumab-kpkc	Vorinostat	Other systemic therapies not allowed (including bexarotene, methotrexate).
IMpassion130 (June 2015 – May 2017)	First-line metastatic TNBC	Atezolizumab (+ nab-paclitaxel)	Placebo (+ nab-paclitaxel)	No established SOC. Many single agent chemo.
iLLUMINATE (October 2014 – October 2015)	Treatment naïve CLL, >65 years or younger with coexisting conditions	Ibrutinib (+ obinutuzumab)	Chlorambucil (+obinutuzumab)	BR (bendamustine + rituximab) not allowed in control arm, more commonly used for older patients. Restricting choice of control therapy.
DUO (January 2014 – December 2015)	Relapsed/refractory CLL or SLL after 2 prior therapies	Duvelisib	Ofatumomab	No previous BTK inhibitor allowed. Ofatumumab not standard therapy in third or fourth line treatment of CLL (especially del 17p who were 22% of pts)
RADIANT-4 (April 2012 – August 2013)	Progressive, nonfunctional GI and lung NET	Everolimus	Placebo + BSC	SOC is octreotide; patients were randomized to placebo and were not able to receive octreotide with placebo
Keynote-054 (July 2015 – January 2018)	Adjuvant melanoma after complete resection	Pembrolizumab	Placebo	Ipilimumab approved in 2015, likely after the protocol was written, but CheckMate-238 comparing nivolumab to ipilimumab accrued during same time period.
ARAMIS (September 2014 – March 2018)	Nonmetastatic castration-resistant prostate cancer	Darolutamide	Placebo	Bicalutamide and other AR antagonists used in this space. Standard bicalutamide was discontinued before trial enrollment in both arms.
BRIGHT AML 1003 (January 2014 – January 2017)	Newly diagnosed AML in 75 or older or who have comorbidities	Glasdegib (+ LDAC)	LDAC	LDAC is viewed as inferior to HMAs in the US. HMAs were not allowed in control arm
JGDG (October 2010 – January 2013)	Soft tissue sarcoma for which anthracycline is appropriate	Olaratumab (+ doxorubicin)	Doxorubicin	Doublet chemo is commonly used (anthracycline with ifosfamide) and shown to be superior in terms of PFS to single-agent doxorubicin. Primary endpoint of this trial was PFS
METEOR (August 2013 – November 2014)	Advanced RCC in following one line of therapy	Cabozantinib	Everolimus	Axitinib superior to sorafenib in second line setting. Everolimus not proven to be

				superior to active agent in second-lilne setting.
POLLUX (June 2014 – July 2015)	Myeloma after at least one prior therapy	Daratumumab (+ lenalidomide/dexamethasone)	Lenalidomide/dexamethasone	Only 15% previously received combination of bortezomib/ lenalidomide. 55% previously received IMiD. Re-using VRD in control arm would be optimal.
MURANO (March 2014 – September 2015)	CLL with or without 17p deletion, who have received at least 1 line of therapy	Venetoclax	Bendamustine/rituximab	Most patients (95%) previously treated with alkylating agent. 78% previously treated with anti-CD20 antibody. Obinutuzumab/ chlorambucil not allowed. Restricted choice.
RESONATE (June 2012 – April 2013)	Previously treated CLL	Ibrutinib	Ofatumumab	Many options considered SOC. Single-agent ofatumumab in relapsed disease is sub-optimal.
RESONATE-2 (March 2013 – March 2015)	First-line CLL	Ibrutinib	Chlorambucil	Chemoimmunotherapy is standard of care for first-line CLL 1 year prior to trial enrollment.
Keynote-045 (November 2014 – November 2015)	Metastatic urothelial carcinoma who progress on platinum therapy	Pembrolizumab	Paclitaxel/docetaxel/vinflunine	Phase 2 data for nab-paclitaxel or pemetrexed, NCCN listing. Not allowed as physician choice. Restricted choice.
GADOLIN (April 2010 – September 2014)	Follicular lymphoma who relapsed after/refractory to rituximab	Obinutuzumab (+ bendamustine)	Bendamustine	50% of patients received 1 previous line of therapy. 30% received 2 lines of therapy. Single-agent bendamustine in control arm is not standard for those patients, even if progressed within 6 months.

eTable 2. Clinical trials with crossover errors

Trial (Accrual Dates)	Indication	Investigational Agent	Control	Protocol Specified Crossover?	Crossover Comment
AUGMENT (February 2014 – January 2017)	Follicular lymphoma and marginal zone, previously treated (with rituximab)	Lenalidomide (+ rituximab)	Placebo (+ rituximab)	No	There is data on established efficacy of lenalidomide in second-line setting (Leonard. CALGB 50401. JCO 2012)
BFORE (July 2014 – August 2015)	First-line chronic phase CML	Bosutinib	Imatinib	No	Bosutinib approved in second-line for imatinib resistant CML.
MAIA (March 2015 – January 2017)	Newly diagnosed multiple myeloma that are transplant ineligible	Daratumumab (+ lenalidomide/dexamethasone)	Lenalidomide/dexamethasone	No	Daratumumab showed efficacy in relapsed myeloma in 2015 and POLLUX published in 2016 showed DRd better than Rd in relapsed MM.
ALEX (August 2014 – January 2016)	ALK-positive metastatic NSCLC, first-line	Alectinib	Crizotinib	No	Alectinib FDA approved in 2015 for second-line NSCLC after crizotinib. In some countries, patients may receive alectinib in second-line setting, but off-protocol (no mention of numbers).

SOLO1 (September 2013 – March 2015)	First-line maintenance for BRCA-mutated ovarian cancer in CR or PR after platinum	Olaparib	Placebo	No	Crossover desirable. Olaparib proven benefit and approved by FDA in December 2014 for advanced BRCA-mutated ovarian cancer.
CheckMate-238 (March 2015 – October 2015)	Adjuvant melanoma with lymph nodes	Nivolumab	Ipilimumab	No	Crossover to nivolumab upon progression of disease should be allowed. Nivolumab approved for metastatic melanoma in front-line
Keynote-006 (September 2013 – March 2014)	Unresectable or metastatic melanoma	Pembrolizumab	Ipilimumab	No	Crossover desirable. Pembrolizumab approved for second-line advanced melanoma in September 2014. Double crossover would have been appropriate as well.
Keynote-042 (October 2014 – February 2018)	First-line NSCLC (PD-L1 >=1%)	Pembrolizumab	Platinum-doublet	No	Crossover desirable. Pembrolizumab proven benefit in later line, approved in October 2015
CLARINET (June 2006 – April 2013)	Unresectable or metastatic GEP-NETs, nonfunctional	Lanreotide	Placebo	Yes	Crossover not desirable. Lanreotide approved for acromegaly. No FDA approval. Octreotide was used and patients could receive octreotide.

Study 0761-010 (December 2012 – January 2016)	Relapsed or refractory mycosis fungoides (MF) or Sézary syndrome (SS) after at least one prior systemic therapy	Mogamulizumab-kpkc	Vorinostat	Yes	73% (136/186) crossed over to mogamulizumab. No randomized data to establish mogamulizumab efficacy or FDA approval based on single-arm data.
AETHERA (April 2010 – September 2012)	cHL after ASCT consolidation treatment	Brentuximab vedotin	Placebo	Yes	Crossover not desirable. Brentuximab vedotin approved for progressive disease after ASCT in August 2011, more than 1 year after trial enrollment, based on single-arm data.
AURELIA (October 2009 – April 2011)	Platinum-resistant, recurrent ovarian cancer	Bevacizumab (+ paclitaxel or pegylated liposomal doxorubicin)	Chemotherapy (pegylated liposomal doxorubicin, weekly paclitaxel, or topotecan)	Yes	Crossover not desirable. No proven benefit of bevacizumab in platinum-resistant ovarian cancer during trial period. No RCT or FDA approval in second or third-line. There is a phase II trial showing efficacy (PMID: 18024865).
SELECT (August 2011 – October 2012)	Metastatic differentiated thyroid cancer	Lenvatinib	Placebo	Yes	Crossover not desirable. Lenvatinib not approved in radioiodine-refractory disease. No RCT prior SELECT showing efficacy in later line therapy.
RESPONSE (November 2010 – February 2013)	PV who had inadequate response to hydroxyurea	Ruxolitinib	Hydroxyurea, interferon or pegylated interferon, pipobroman, anagrelide, immunomodulators such as lenalidomide or thalidomide, or no medication	Yes	Crossover not desirable. Ruxolitinib not FDA approved, but positive phase 2 data. 86% crossed over to ruxolitinib around week 32.

SPARTAN (October 2013 – December 2016)	Non-metastatic castration-resistant prostate cancer	Apalutamide	Placebo	Yes	No approval of apalutamide in early CSPR. 19% crossed over to apalutamide.
CheckMate-214 (October 2014 – February 2016)	First-line intermediate or poor-risk RCC	Nivolumab/ipilimumab	Sunitinib	No (but amendment after primary endpoint met)	Nivolumab approved in second line setting in November 2015 based on phase 3 RCT. Should have allowed crossover from the start. No mention of post progression therapy in appendix in control arm.
DUO (January 2014 – December 2015)	Relapsed/refractory CLL or SLL after 2 prior therapies	Duvelisib	Ofatumumab	Yes (double)	Duvelisib efficacy not confirmed and crossing patients in control arm to duvelisib exposed them to therapy that was not proven to be superior to other standards.