Supplementary Online Content

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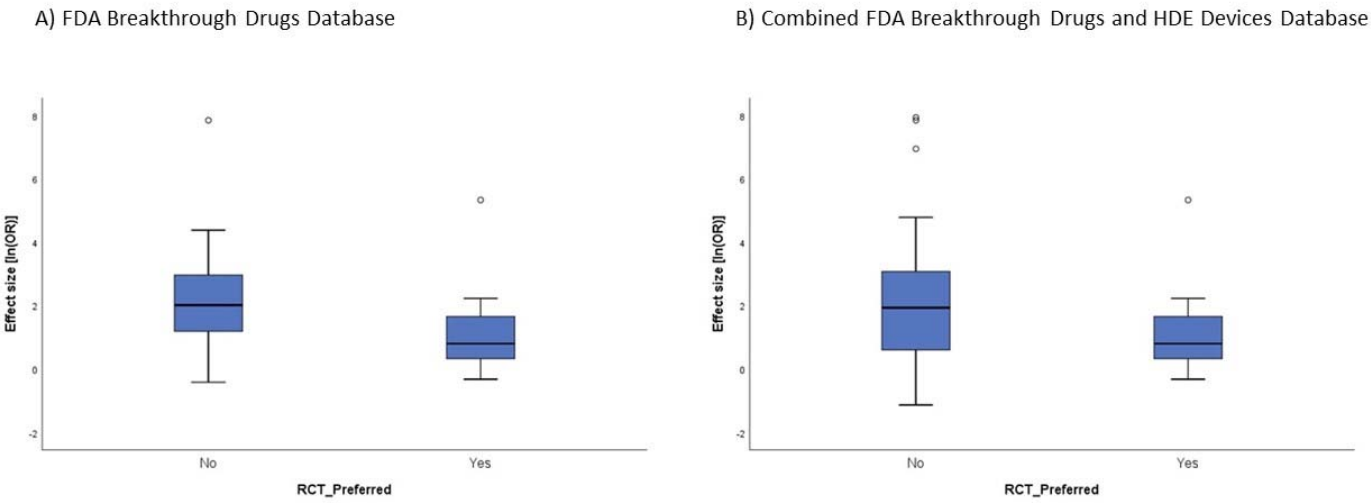
This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure. Distribution of Magnitude of Treatment Effects as a Function of FDA Preference for Testing of Approved Treatments in Further Randomized Controlled Trials (RCTs)

The treatment effects expressed as natural logarithms of odds ratio [ln(OR)] were significantly larger among drugs and devices authorized without further requests for RCTs than for those for which FDA would have preferred additional testing in RCTs.
Figure S1A; Drugs only (p=0.02); Figure S1B: combined drugs and devices (p=0.03).



eTable 1. Characteristics of Included Drugs

Active substance (FDA name) Year of approval	Condition	Primary outcome	Experimental Favorable Results % n/N	Control	Control Favorable Results % n/N	Comment	RCT desired
Alectinib (Alencensa) 2015	Anaplastic lymphoma kinase (ALK) positive metastatic non-small cell lung cancer, who have progressed on or are intolerant to crizotinib	Objective response rate	42% 94/225	Active treatment with chemotherapy (docetaxel or pemetrexed)	20% 34/174	Comparator was cited in approval document under current treatment options.	Yes
Brigatinib (Alunbrig) 2017	Locally advanced or metastatic ALK-positive non-small cell lung cancer (NSCLC) who had progressed on crizotinib	Overall response rate	50% 112/222	Active treatment with ceritinib	58% 75/130	Comparator was cited in main study used for approval.	Yes
Ofatumumab (Arzerra) 2014	Chronic lymphocytic leukemia refractory to fludarabine-containing treatment and failed or are inappropriate for alemtuzumab-containing treatment	Overall response rate	49% 67/138	Standard treatment	15% 21/138	Comparator data was extracted from sample size calculation in FDA summary review.	Yes
Avelumab (Bavencio) 2017	Metastatic Merkel cell carcinoma	Overall response rate	33% 29/88	Second line chemotherapy (e.g. topotecan, paclitaxel, etc.)	23% 7/30	Comparator data was referenced in the discussion section of FDA document.	No

Blinatumomab (Blincyto) 2014	Ph-relapsed or refractory B-precursor acute lymphocytic leukemia (ALL)	Complete remission + complete remission with partial hematological recovery	42% 77/185	Standard treatment	30% 56/185	Comparator data was extracted from FDA document as the pre-specified efficacy threshold.	Yes
Cerliponase alfa (Brineura) 2017	Symptomatic pediatric patients with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2) disease	Decline in the motor domain of the CLN2 clinical rating scale	95% 21/22	No active treatment (natural history of disease)	50% 21/42	Comparator data was extracted from FDA document (historical control).	No
Acalabrutinib (Calquence) 2017	Mantle-cell lymphoma in adults who have received at least one prior therapy	Overall response rate	81% 100/124	Active treatment with bortezomib	31% 48/155	Comparator was cited in FDA document under current treatment options.	Yes
Daratumumab (Darzalex) 2015	Multiple myeloma (received at least three prior lines of therapy including a proteasome inhibitor and an immunomodulatory agent or who are double refractory to a proteasome inhibitor and an immunomodulatory agent)	Overall response rate	29% 31/106	Active treatment with dexamethasone	19% 201/1056	Dexamethasone was mentioned in FDA document as a possible comparator. Comparator study was found through a PICO search.	No

Ibrutinib (Imbruvica-1) 2013	Relapsed or refractory mantle-cell lymphoma	Overall response rate	66% 73/111	Active treatment with bortezomib (velcade)	31% 48/155	Comparator was cited in approval document under current treatment options.	Yes
Ibrutinib (Imbruvica-2) 2015	Waldenstrom's macroglobulinemia-received at least one previous treatment	Overall response rate	62% 39/63	Standard treatment	19% 12/63	Comparator data was extracted from sample size calculation in main study used for FDA approval.	No
Ibrutinib (Imbruvica-3) 2017	Chronic graft versus host disease after failure of one or more lines of systemic therapy	Overall response rate	67% 28/42	Active treatment with extracorporeal photopheresis	64% 27/42	Comparator was cited in main study used for approval.	Yes

Durvalumab (Imfinzi) 2017	Locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum containing chemotherapy	Overall response rate	17% 31/182	Active treatment with atezolizumab	15% 45/310	Comparator was cited in main study used for approval.	Yes
Sebelipase alfa (Kanuma) 2015	Lysosomal acid lipase deficiency (Wolman disease patient population)-infantile onset	Number of patients alive at 12 months of age	67% 6/9	No active treatment (natural history of disease)	0% 0/21	Comparator data was extracted from FDA document (historical control).	No
Pembrolizumab (Keytruda-1) 2014	Unresectable or metastatic melanoma and disease progression following ipilimumab, and if BRAF V600 mutation positive, a BRAF inhibitor	Overall response rate	24% 21/89	Active treatment with investigator-choice chemotherapy (paclitaxel + carboplatin, paclitaxel, carboplatin, dacarbazine, or oral temozolomide)	4% 8/179	Comparator data was extracted from RCT of pemrolizumab versus investigator-choice chemotherapy published after the date of approval.	Yes
Pembrolizumab (Keytruda-2) 2015	Metastatic, PD-L1 positive, non-small cell lung cancer with disease progression on or after platinum-containing chemotherapy (tumor proportion score of 50% or greater)	Overall response rate	41% 25/61	Active treatment with docetaxel	8% 12/152	Comparator data was extracted from RCT of pemrolizumab versus docetaxel published after the date of approval.	No

Pembrolizumab (Keytruda-3) 2017	Microsatellite instability-high cancer	Overall response rate	40% 59/149	Active treatment with opdivo	31% 23/74	Comparator data was found by literature search using PICO.	No
Pembrolizumab (Keytruda-4) 2017	Locally advanced or metastatic urothelial carcinoma who were not eligible for cisplatin-containing chemotherapy	Overall response rate	29% 107/370	Active treatment with atezolizumab	23% 27/119	Comparator was cited in main study used for approval.	Yes
Pembrolizumab (Keytruda-5) 2017	Refractory Hodgkin's lymphoma (3 or more prior lines)	Overall response rate	69% 145/210	Active treatment with brentuximab vedotin	75% 77/102	Comparator was cited in main study used for approval.	Yes
Axicabtagene ciloleucel (Kymriah) 2017	Relapsed or refractory aggressive B-cell non-Hodgkin lymphoma	Overall response rate	72% 73/101	Standard treatment	20% 20/101	Comparator data was listed in main study used for approval as a historical control rate.	No
Nivolumab (Opdivo-1) 2016	Classical Hodgkin's lymphoma-after failure of autologous HSCT and post-transplantation brentuximab vedotin	Objective response rate	65% 62/95	Standard treatment	20% 19/95	Comparator data was extracted from sample size calculation in main study used for FDA approval.	No
Nivolumab (Opdivo-2) 2017	Locally advanced or metastatic urothelial carcinoma who had disease progression during or following platinum-containing chemotherapy or who had	Overall response rate	20% 53/270	Standard treatment	10% 27/270	Comparator data was extracted from sample size calculation in	Yes

	disease progression within 12 months of treatment					main study used for FDA approval	
Idarucizumab (Praxbind) 2015	Reversal of anticoagulation effects of dabigatran in patients who presented with serious bleeding or who required urgent surgery or intervention	Normalization of dilute thrombin time	96% 65/68	No active treatment	0% 0/68	Comparator data was extracted from main study used for FDA approval.	No
Eltrombopag (Promacta) 2014	Severe aplastic anemia refractory to immunosuppressive therapy	Overall response rate (hematologic response)	40% 17/43	Standard treatment	9% 4/43	Comparator data was extracted from sample size calculation in main study used for FDA approval.	No
Rucaparib (Rubraca) 2016	Advanced BRCA-mutant ovarian cancer who had progressed after 2 or more chemotherapies	Objective response rate	54% 57/106	Active treatment with olaparib	34% 47/137	Comparator was cited in FDA document under current treatment options.	Yes
Sofosbuvir + ribavirin + peg interferon alfa-2a (Sovaldi) 2013	Hepatitis C infection-genotype 1, 4, 5, or 6 (treatment-naïve)	Overall sustained virologic response	90% 295/327	Standard treatment	60% 196/327	Comparator data was mentioned in FDA document as a historical control rate.	No

Asfotase alfa (Strensiq-1) 2015	Perinatal/infantile onset hypophosphatasia	Overall survival	91% 62/68	No active treatment (natural history of disease)	27% 13/48	Comparator data was extracted from FDA document (historical control).	No
Asfotase alfa (Strensiq-2) 2015	Juvenile-onset hypophosphatasia	Radiographic global impression of change scores of +2	100% 8/8	No active treatment (natural history of disease)	6% 2/32	Comparator data was extracted from FDA document (historical control).	Yes
Dabrafenib+Trametinib (Tafinlar+Mekinist) 2017	Metastatic non-small cell lung cancer with BRAF V600E mutation	Overall response rate	62% 58/93	Standard treatment (e.g. taxane, pemetrexed, erlotinib, crizotinib, etc.)	8% 5/59	Comparator was cited in main study used for approval.	No
Osimertinib (Tagrisso) 2015	Non-small cell lung cancer (with metastatic EGFR T790M mutation positive)-relapsed/refractory	Objective response rate	59% 241/411	Active treatment with platinum-pemetrexed	31% 44/140	Comparator data was extracted from RCT of osimertinib versus platinum-pemetrexed published after the date of approval.	Yes
Atezolizumab (Tecentriq) 2015	Locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum containing	Objective response rate	15% 46/310	Standard treatment	10% 31/310	Comparator data was extracted from FDA document as a	Yes

	chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum containing chemotherapy					historical response rate.	
Venetoclax (Venclexta) 2016	Chronic lymphocytic leukemia with 17p deletion, as detected by an FDA approved test, who have received at least one prior therapy	Overall response rate	79% 85/107	Standard treatment	40% 43/107	Comparator data was extracted from sample size calculation in main study used for FDA approval.	Yes
Abemaciclib (Verzenio) 2017	HR-positive, HER2-negative advanced or metastatic breast cancer with disease progession following endocrine therapy and prior chemotherapy in the metastatic setting	Overall response rate	17% 23/132	Active treatment with palbociclib and fulvestrant	24% 32/132	Comparator was cited in FDA document under current treatment options.	No
Crizotinib (Xalkori) 2016	Advanced non-small cell lung cancer with a ROS1 rearrangement	Overall response rate	72% 36/50	Standard treatment	10% 5/50	Comparator data was extracted from sample size calculation in main study used for FDA approval.	No
Tisagenlecleuel (Yescarta) 2017	Relapsed or refractory B-cell acute lymphoblastic leukemia (ALL)	Overall response rate	83% 52/63	Standard treatment	20% 13/63	Comparator data was extracted from sample size calculation in main study used for FDA approval.	No

Ceritinib (Zykadia) 2014	Anaplastic lymphoma kinase-positive metastatic non-small cell lung cancer who have progressed on or are intolerant to crizotinib (prior ALK inhibitors)	Overall response rate	55% 89/163	Active treatment with docetaxel	5% 3/55	Comparator data was listed in FDA document under current treatment options.	No

eTable 2. Characteristics of Included Devices

FDA name Year of approval	Condition	Primary outcome	Experimental Favorable Results % n/N	Control	Control Favorable Results % n/N	Comment	RCT desired
Abiocor Replacement Heart (2006)	Severe biventricular end stage heart disease	Survival beyond 60 days	71% 10/14	No active treatment	0% 0/14	Comparator data is natural history data.	No
Amplatzer Post Infarct Muscular VSD Occluder (2017)	Post myocardial infarct muscular ventricular septal defects in patients who are not satisfactory surgical candidates	One-month survival	49% 19/39	Medical therapy (intravenous inotropic medications and intravenous diuretics and mechanical respiratory support)	10% 4/39	Comparator was reported in approval document.	No
Argus II retinal prosthesis system (2013)	Severe to profound retinitis pigmentosa	Object localization	96% 27/28	Self-control: device on vs device off	0% 0/28	Comparator was reported in approval document.	No
Barostim neo legacy system (2014)	Resistant hypertension (previously had bilateral implantation of the Rheos carotid sinus leads and were deemed responders in the Rheos pivotal clinical study)	Systolic blood pressure	Mean (SD) 142.8 (26.4)	Self-control: baseline vs 6 months	Mean (SD) 176.8 (21.3)	Comparator data is baseline data.	No

CentriMag Right Ventricular Assist System (2008)	Acute cardiogenic shock due to acute right ventricular failure	Survival to 30 days after device removal	50% 12/24	Extracorporeal membrane oxygenation	50% 14/28	Comparator was reported and cited in the approval document.	No
CoAxia NeuroFlo Catheter (2005)	Symptomatic cerebral vasospasm following aneurismal subarachnoid hemorrhage	Clinical improvement (decrease of greater than or equal to 3 points in NIHSS from baseline to 24 hours after)	50% 8/16	Standard medical management	37% 92/249	Comparator was found in an outside search (RCT published after approval)	No
Contegra Pulmonary Valved Conduit (2003)	Correction or reconstruction of the right ventricular outflow tract (RVOT)	Survival at one year	88% 209/237	Homograft	84% 187/223	Comparator was cited in approval document.	No
CPAX aneurysm treatment system (2011)	Wide-necked large and giant-sized cerebral aneurysms (>10 mm) that require use of adjunctive assist devices such as stents or balloons	Percent of aneurysms ≥90% occluded at 90-day follow up	67% 8/12	Success criteria	58% 7/12	Comparator is reported in the FDA document as "success criteria"	No

DeBakey VAD Child system for humanitarian use in pediatric patients (2004)	NYHA Class IV end-stage heart failure, refractory to medical therapy	Survival to 30 days post-transplant	63% 19/30	Heartmate vented electric left ventricular assist system	62% 173/280	FDA document cited main study used for approval, which then cited a comparator.	No
Elana surgical Kit HUD (arteriotomy system) (2011)	Aneurysm or a skull base tumor affecting a large [>2.5 mm], intracranial artery that failed balloon test occlusion, cannot be sacrificed, or cannot be treated with conventional means due to local anatomy or complexity	Bypass patent at 0-7 days post-op	77% 277/361	Long saphenous vein bypass grafts	86% 173/201	Comparator reported in the approval document.	No
Enterprise Vascular Reconstruction Device and Delivery System (2007)	Wide-neck, intracranial, saccular or fusiform aneurysms arising from a parent vessel with a diameter of ≥3mm and ≤4mm	≥ 95% occlusion	57% 16/28	Self-control: baseline vs 6 months	0% 0/28	Comparator data is baseline data.	No

EXCOR pediatric ventricular assist device (2011)	Severe isolated left ventricular or biventricular dysfunction who are candidates for cardiac transplant and require circulatory support-pediatric patients	Survival to transplant/successful recovery	90% 43/48	Extracorporeal membrane oxygenation	66% 63/96	Comparator data is reported in the FDA document as a historical control (active treatment)	No
Excorim immunoadsorption system (1998)	Hemophilia A and B with factor VIII or IX inhibitor titers above 10 bethesda units	Bleeding resolved	91% 20/22	Prothrombin complex concentrates	50% 11/22	Comparator was cited in the approval document	No
FENIX continence restoration system (2015)	Fecal incontinence in patients who are not candidates for or have previously failed conservative treatment and less invasive therapy options	Fecal incontinence episodes per week	Mean (SD) 3.4 (4.3)	Self-control: baseline vs 36 months	Mean (SD) 13.9 (6.7)	Comparator data is baseline data.	No
Flourish pediatric esophageal atresia device (2017)	Esophageal atresia without a tracheoesophageal fistula (TEF) or a TEF that has been closed as a result of a prior procedure	Successful creation of an anastomosis	100% 16/16	Thoracoscopic repair	95% 58/61	FDA document cited main study, which then cited a comparator.	No

Impella RP System (2015)	Acute right heart failure or decompensation following left ventricular assist device implantation, myocardial infarction heart transplant, or open heart surgery (pediatric or adult)	Survival to 30 days/discharge/next therapy	73% 22/30	Active treatment with CentriMag Right Ventricular Assist System	58% 7/12	Comparator cited in main study used for approval.	No
Jostent coronary stent graft (2001)	Coronary artery perforation	Perforation closed/vessel sealed	100% 41/41	Intracoronary stenting	58% 3750/3815	FDA document cited main study, which then cited a comparator.	No
Liposorber LA-15 system (2013)	Nephrotic syndrome	Remission of nephrotic syndrome	63% 25/40	Spontaneous remission	5% 2/40	FDA document cited main study, which then cited a comparator.	No
LVIS and LVIS Jr Device (low profile visualized intraluminal support) (2014)	Unruptured, wide neck, intracranial, saccular aneurysms	Aneurysm angiographic occlusion of >90% at 6 months	84% 26/31	Self-control: baseline vs 6 month	65% 20/31	Comparator data is baseline data.	No
Melody Transcatheter Pulmonary Valve (2010)	Right ventricular outflow valve dysfunction	Reoperation in 0-14 months	99% 88/89	Valve conduit stenting: a bovine jugular venous valve mounted into a platinum stent	84% 49/58	We proposed to study an effect for which the results were included in the comparator historical references.	No

Neuroform Microdelivery Stent System (2002)	Wide-neck, intracranial, saccular aneurysms	≥95% occlusion	100% 26/26	Natural history	0% 0/26	Comparator data is natural history data.	No
Neurolink System (2002)	Atherosclerotic disease in the neurovasculature refractory to medical therapy	One-year survival	87% 53/61	Traditional medical therapy	72% 21/29	Comparator data was reported and cited in approval document.	No
NeuRx DPS RA/4 Respiratory Stimulation System (2008)	Ventilator-dependent spinal cord injury	Survival	92% 46/50	Mechanical ventilation via tracheostomy	34% 17/50	Comparator was cited in the main study used for approval.	No
OPRA (Osseoanchored prostheses for the rehabilitation of amputees) (2015)	Transfemoral amputation due to trauma or cancer in patients who have rehabilitation problems with, or cannot use, a conventional socket prosthesis	Mean prosthetic use score (higher is better)	Mean (SD) 79.9 (27.1)	Self-control: baseline vs 24 months	Mean (SD) 46.7 (36.7)	Comparator is baseline data.	No
Possis Perma-Flow Coronary Bypass Graft (1998)	Single or multiple vessel coronary artery bypass in patients who are receiving coronary bypass grafting but who have inadequate autologous conduit to complete the required revascularization	Proportion of patients with NYHA classes I and II	72% 23/32	Self-control: baseline vs 6 months	28% 9/32	Comparator was reported in approval document.	No

Reclaim DBS therapy for OCD (2009)	Chronic, severe, treatment-resistant obsessive-compulsive disorder (failed at least three selective serotonin reuptake inhibitors)	Yale Brown Obsessive Compulsive Scale score (lower is better)	Mean (SD) 20.2 (9.0)	Self-control: baseline vs 12 months	Mean (SD) 34 (2.5)	Comparator is baseline data.	No
Shelhigh pulmonic valve conduit with "no-react" treatment (1999)	Diseased, damaged, or absent pulmonic artery (in children less than 4 years old)	Survival to 14 months	94% 44/47	Pulmonary allografts	78% 31/40	Comparator was cited in the approval document.	No
Therasphere (1999)	Unresectable hepatocellular carcinoma	Objective response	20% 4/20	Cisplatin	14% 4/28	Comparator was cited in main study used for approval.	No
Urostim Bladder Stimulator (1997)	Neurogenic bladder disease secondary to spina bifida	Increase in bladder capacity of 20%	53% 316/597	No active treatment	17% 100/597	Comparator based on clinical information included in FDA/HDE report.	No
VOCARE bladder system (1998)	Complete spinal cord lesions with intact parasympathetic innervation of the bladder	Voided > 200 mL in < 5 minutes (at 12 months)	86% 18/21	Self-control: device ON vs OFF	5% 1/21	Comparator data was given in the approval document.	No
Wingspan Stent System with Gateway PTA Balloon Catheter (2005)	High-grade, intracranial, atherosclerotic lesions	Survival at 6 months	90% 38/42	Neurolink system	83 % 40/48	Comparator data was reported and cited in the approval document.	No

XVIVO perfusion system with STEEN solution perfusate (2014)	As an aid for ex vivo evaluation and perfusion of potential donor lungs prior to possible transplantation	30-day survival	97% 30/31	Standard cold storage lung transplant	100% 31/31	Comparator was reported in approval document.	No