
Supplementary information

Should the control arms of randomized trials have an expiry date?

In the format provided by the
authors and unedited

Table 1. First-line phase III immunotherapy RCTs in non-small cell lung cancer with chemotherapy as the control group

	Trial Name (NCT Number)	Experimental Treatment vs. Control Treatment	Number of Patients in the Control group (all; PDL1≥50%)	First Enrollment Date	Last Enrollment Date	Primary Completion Date	Initial Publication Date	Status and Last Update Posted on clinicaltrials.gov	Country Involved in Patient Accrual	Protocol/Consent Form Amendment Based on Benchmark Trials	Crossover Allowed
Benchmark trials	Keynote-024 (NCT02142738)	Pembrolizumab vs. Chemo	N/A	Sep 19, 2014	Oct 29, 2015	May 9, 2016	Nov 10, 2016	Completed (Jun 14, 2021)	N/A	N/A	N/A
	Keynote-042 (NCT02220894)	Pembrolizumab vs. Chemo	637 (300)	Dec 19, 2014	Mar 6, 2017	Feb 26, 2018	May 4, 2019	Active, not recruiting (Aug 5, 2020)	N/A	N/A	N/A
First Enrollment Date after Pembrolizumab FDA Full Approval	EMPOWER-Lung 1 (NCT03088540)	Cemiplimab vs. Chemo	354 (280)	Jun 27, 2017	Feb 27, 2020	Nov 1, 2022 (estimated)	Feb 13, 2021	Active, not recruiting (Aug 17, 2021)	Australia, Belarus, Brazil, Bulgaria, Chile, China, Colombia, Czech Republic, Georgia, Greece, Hungary, Jordan, Lebanon, Malaysia, Mexico, Philippines, Poland, Romania, Russia, Spain, Taiwan, Thailand, Turkey, Ukraine	No	Yes

	Checkmate-9LA (NCT03215706)	Nivolumab + Ipilimumab + Chemo vs. Chemo	358 (98)	Aug 24, 2017	Jan 30 2019	Aug 16, 2019	Feb 1, 2021	Active, not recruiting (Apr 8, 2021)	Romania, Spain, Poland, Brazil, Argentina, France, Spain, Japan, Argentina, Chile, Germany, Mexico, United States, Italy, Russian Federation, Belgium, Japan, China, Australia, United Kingdom, Ireland, Canada	No Did not mention Keynote-024; protocol dated May 10 2017	No
	EMPOWER-lung-3 (NCT03409614)	Cemiplimab + Chemo vs. Placebo + Chemo	154 (Unknown ^)	Mar 6, 2018	Unknown	May 1, 2023 (estimated)	Pending	Active, not recruiting (Oct 8, 2020)	United States, Austria, China, Czechia, France, Georgia, Greece, Ireland, Italy, Republic of Korea, Lithuania, Malaysia, Poland, Romania, Russian Federation, Slovakia, Thailand, Turkey, Ukraine	No available information	Unknown

	POSEIDON (NCT03164616)	Durvalumab +Tremelimumab +Chemo vs. Durvalumab +Chemo vs. Chemo	398 (133)*	Jun 1, 2017	Unknown	Mar 12, 2021	Pending	Recruiting (Oct 29, 2021)	United States, Brazil, Bulgaria, China, Germany, Hong Kong, Hungary, Japan, Korea, Mexico, Peru, Poland, Russian Federation, South Africa, Taiwan, Thailand, Ukraine, United Kingdom, Vietnam	No available information	Unknown
	AK105 (Non-Squamous) (NCT03866980)	Penpulimab +Chemo vs. Placebo+ Chemo	Unknown [Estimated 360 total patients to be enrolled in the trial]	Nov 27, 2018	Unknown	Nov 30, 2020 (estimated)	Unknown	Recruiting (Mar 7, 2019)	China	No available information	Unknown
	AK105 (Squamous) (NCT03722147)	Penpulimab +Chemo vs. Placebo+ Chemo	Unknown [Estimated 338 total patients to be enrolled in the trial]	Dec 20, 2018	Unknown	Dec 31, 2020 (estimated)	Unknown	Recruiting (Mar 7, 2019)	China	No available information	Unknown
	IPSOS (NCT03191786)	Atezolizumab vs. single-agent chemotherapy (Vinorelbine or Gemcitabine)	Unknown [Estimated 453 total patients to be enrolled in the trial]	Sep 11, 2017	Unknown	Dec 24, 2021 (estimated)	Unknown	Active, not recruiting (Nov 18, 2021)	Argentina, Belgium, Brazil, Bulgaria, Canada, China, Colombia, Czechia, Denmark, Germany,	No available information	Unknown

									India, Ireland, Italy, Kazakhstan, Luxembourg, Mexico, Poland, Portugal, Romania, Slovakia, Spain, Swaziland, Switzerland, United Kingdom, Vietnam		
Last Enrollment Date After Pembrolizumab FDA Full Approval	Impower150 (NCT02366143)	Atezolizumab +Chemo vs. Atezolizumab +Chemo + Bevacizumab vs. Chemo + Bevacizumab	400 (73)	Mar 2015	Dec 2016	Sep 13, 2019	June 14, 2018	Completed (Sep 23, 2021)	Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Canada, Chile, France, Germany, Italy, Japan, Latvia, Lithuania, Mexico, Netherlands, Portugal, Russia, Singapore, Spain, Sweden, Switzerland, Taiwan, Ukraine, United States	No The protocol mentioned Keynote-024 having OS benefit for high PDL1 group, and pembrolizumab was approved on this basis.	No
	Keynote-189 (NCT02578680)	Pembrolizumab +Chemo vs. Placebo + Chemo	206 (70)	Feb 26, 2016	Mar 6, 2017	Nov 8, 2017	May 31, 2018	Active, not recruiting (Oct 23, 2020)	Australia, Austria, Belgium, Canada, Denmark,	No Mentioned Keynote-024 as	Yes

									Finland, France, Germany, Ireland, Israel, Italy, Japan, Netherlands, Spain, United Kingdom, United States	'ongoing trial with results expected in 2015-2016'. The protocol was dated November 6 2017	
	Keynote-407 (NCT02775435)	Pembrolizumab +Chemo vs. Placebo + Chemo	281 (73)	Aug 19, 2016	Dec 28, 2017	Apr 3, 2018	Nov 22, 2018	Active, not recruiting (Sep 30, 2020)	Australia, Canada, China, France, Germany, Hungary, Italy, Japan, Mexico, Netherlands, Poland, Russia, South Korea, Spain, Thailand, Turkey, United States	No Mentioned Keynote-024 as 'ongoing trial with results expected in 2015-2016'. The protocol was dated June 25 2018	Yes
	Impower132 (NCT02657434)	Atezolizumab +Chemo vs. Chemo	286 (20)	Apr 7, 2016	May 31, 2017	Jul 18, 2019	Apr 2021	Active, not recruiting (Sep 29, 2021)	Argentina, Australia, Austria, Belgium, Bulgaria, Chile, France, Hungary, Ireland, Israel, Italy, Japan, Latvia, Lithuania, Malaysia, Netherlands, Peru, Portugal,	No Did not mention Keynote-024	Unknown

									Republic of Korea, Romania, Russia, Spain, Taiwan, Ukraine, United Kingdom, United States		
	NEPTUNE (NCT02542293)	Durvalumab +Trametinumab vs. Chemo	477 (143)**	Nov 3, 2015	Unknown	Sep 21, 2020	Pending	Active, not recruiting (Jul 7, 2021)	United States, Argentina, Brazil, Bulgaria, Chile, China, Denmark, Finland, Greece, Hong Kong, India, Israel, Japan, Republic of Korea, Malaysia, Mexico, Peru, Philippines, Poland, Portugal, Qatar, Romania, Russian Federation, Saudi Arabia, Singapore, Sweden, Turkey, Ukraine, United Kingdom	No available information	Unknown
	Impower130	Atezolizumab +Chemo vs. Chemo	240 (43)	Apr 16, 2015	Feb 13, 2017	Mar 15, 2018	July 1, 2019	Completed (Aug 9, 2021)	United States,	No	Yes (only for patients in

	(NCT02367781)								Canada, Belgium, France, Germany, Italy, Spain, and Israel	The protocol mentioned Keynote-024 having OS benefit for high PDL1 group, and pembrolizumab was approved on this basis.	the chemotherapy group enrolled before June 15 2016)
	Checkmate-227 (NCT02477826)	Nivolumab +Ipilimumab vs. Nivolumab vs. Chemo	583 (192)	Aug 2015	Nov 2016	Aug 28, 2024 (estimated)	Nov 21, 2019	Recruiting (Sep 21, 2021)	United States, Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, China, Colombia, Czechia, Finland, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Japan, Republic of Korea, Lebanon, Mexico, Netherlands, Peru, Poland, Romania, Russian Federation, Saudi Arabia, South Africa, Spain, Switzerland, Taiwan, Turkey,	No Mentioned Keynote-024 having ORR and PFS benefit but did not mention OS benefit.	No

									United Arab Emirates, United Kingdom		
	Impower131 (NCT02367794)	Atezolizumab +Chemo (Carboplatin/Paclitaxel) vs. Atezolizumab + Chemo (Carboplatin/Nab-Paclitaxel) vs. Chemo (Carboplatin/Nab-Paclitaxel)	340 (44)	Jun 2015	Mar 2017	Oct 3, 2018	Aug 1, 2020	Completed (Apr 13, 2021)	United States, Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Canada, Chile, France, Germany, Israel, Italy, Japan, Latvia, Lithuania, Mexico, Netherlands, Peru, Portugal, Russian Federation, Singapore, Slovakia, Spain, Taiwan, Ukraine	No The protocol mentioned Keynote-024 having OS benefit for high PDL1 group, and pembrolizumab was approved on this basis.	No
	Impower110 (NCT02409342)	Atezolizumab vs. Chemo	287 (98)	Jul 21, 2015	Feb 20, 2018	Feb 4, 2020	Oct 1, 2020	Active, not recruiting (Nov 3, 2021)	United States, Brazil, China, France, Germany, Greece, Hungary, Italy, Japan, Republic of Korea, Poland, Romania, Russian Federation,	No The protocol mentioned Keynote-024 having OS benefit for high PDL1 group, and pembrolizumab was approved on this basis.	

									Serbia, Spain, Thailand, Turkey, Ukraine, United Kingdom		
Before Pembrolizum ab approval	MYSTIC (NCT0245328 2)	Durvalumab vs. Durvalumab +Tremelimumab vs. Chemo	372 (107)	Jul 21, 2015	Jun 8, 2016	Oct 4, 2018	Apr 9, 2020	Active, not recruiting (Oct 27, 2021)	United States, Australia, Belgium, Canada, France, Germany, Hungary, Italy, Japan, Republic of Korea, Netherland s, Russian Federation, Spain, Switzerland , Taiwan, Thailand, Vietnam	N/A	No

^This study had 2 parts, and part 2 enrolled patients irrespective of PD-L1 expression