Supplemental Table 1. Examples of key studies of targeted therapies in ALK-altered NSCLC (see Table 4 for ALK-altered cancers other than NSCLC)

ALK inhibitors	FDA approval	Control arm	Line of treatment	Examples of targets (IC50) Selleckchem.com	Clinical indications	Median PFS	Clinical trials
Crizotinib	2011 Accelerated approval	No control arm in PROFILE 1005	Second	ALK (24nm), ROS1 (<0.025), and c-MET (11nm)	Unresectable/ metastatic disease ALK-altered NSCLC after failure of ≥1 lines of treatment	8.1 months	PROFILE1005 [111] (Phase II)
Crizotinib		Platinum +pemetrexed (in PROFILE 1014)	First	ALK (24nm), ROS1 (<0.025), and c-MET (11nm)	Unresectable/ metastatic NSCLC (ALK-altered) chemotherapy naïve	10.9 vs 7 months	PROFILE 1014(Phase III) [113]
Crizotinib	2013 Full approval	Docetaxel/pemetrexed	Second	ALK (24nm), ROS1(<0.025), and c-MET (11nm)	unresectable/ metastatic NSCLC (ALK-altered) previously treated with platinum-based chemotherapy	7.7 vs 3 months	PROFILE 1007(Phase III) [114]
Ceritinib	2017	Platinum	First	ALK(0.2nM), IGF-1R (8nM), InsR (7nM), and STK22D (23nM)	Unresectable/ metastatic NSCLC with ALK-altered tumors	16.6 vs 8.1 months	ASCEND 4(Phase III) [118]
Ceritinib	2014	Single-arm studies	Second	ALK(0.2nM), IGF-1R (8nM), InsR (7nM), and STK22D (23nM)	unresectable/ metastatic NSCLC (ALK-altered) prior exposure to crizotinib	6.9 months in patients who had prior exposure to crizotinib in ASCEND 1	ASCEND 1 (Phase I) [119] ASCEND 2 (Phase II) [122]
Ceritinib		Pemetrexed or docetaxel	Second	ALK, IGF-1R, InsR, and ROS1	Unresectable/ metastatic NSCLC (ALK-altered) that have progressed on chemotherapy and crizotinib	5.4 vs 1.6 months	ASCEND 5(Phase III) [116]
Ensartinib	Approved in First line in China	Crizotinib	First	MET, Axl, ABL, EPHA2, LTK, ROS1, and SLK	Unresectable/ metastatic NSCLC (ALK-altered)	25.8 vs 12.7 months	eXalt3 (Phase III) [123]
Brigatinib	2020	Crizotinib	First	ALK (0.6 nM) and ROS1 (0.9 nM), also inhibits IGF-1R, and FLT-3 as well as EGFR deletion and point mutations.	ALK-altered unresectable/ metastatic NSCLC	24 vs 11 months	ALTA-1L(Phase III) [121]
Brigatinib Oral brigatinib 90 mg once daily (arm A) or 180 mg once daily (arm B)	2017	Single arm study	Second	ALK (0.6 nM) and ROS1 (0.9 nM), also inhibits IGF-1R, and FLT-3 as well as EGFR deletion and point mutations.	Crizotinib-pretreated unresectable/ metastatic ALK-altered NSCLC patients	9.2months in arm A and 16.7 months in arm B	ALTA (Phase II) [124]
Alectinib	2017	Crizotinib	First	ALK (1.9nM) and RET (4.8nM) with CNS activity.	ALK-altered unresectable/ metastatic NSCLC	34.8 vs 10.9 months	ALEX (Phase III) [120]
Alectinib	2015	Single arm study	Second	ALK(1.9nM) and RET (4.8nm) with CNS activity.	Crizotinib-pretreated or intolerant unresectable/ metastatic NSCLC	8.1 months	NP28761 (NCT01871805) [115]
Alectinib		Pemetrexed or Docetaxel	Second	ALK(1.9nM) and RET (4.8nm) with CNS activity.	Crizotinib-pretreated or intolerant unresectable/ metastatic NSCLC	7.1months vs 1.6 months	ALUR (Phase III)[127]
Lorlatinib (3rd generation)		Crizotinib	First	ALK wild type (<0.07 nM), ROS1(<0.02 nM), ALK (L1196M) (0.7nM) as well as inhibits TYK1, FER, FPS, TRKA, TRKB, TRKC, FAK, FAK2, and ACK	ALK-altered unresectable/ metastatic NSCLC ALK inhibitor naive	Not evaluable vs 9.3 months	CROWN (Phase III) [117]
Lorlatinib (3rd generation)	2018	Single arm study	Second/Third	ALK wild type (<0.07 nM), ROS1(<0.02 nM), ALK (L1196M) (0.7nM) as well as inhibits TYK1, FER, FPS, TRKA, TRKB, TRKC, FAK, FAK2, and ACK	ALK-altered unresectable/ metastatic NSCLC whose disease progressed on crizotinib and at least one other ALK inhibitor or alectinib or ceritinib used as the first ALK inhibitor	Not reported	B7461001 (Phase II) [112, 125]
Entrectinib FDA approved in 2019 for NTRK fusions and ROS1 fusions only	No	Single arm study	First-line	(Trk) A/B/C, ROS1, NTRK, and ALK	Solid tumors with rearrangements of the TRK family, ROS1, or ALK.	Median PFS of 8.3 months in 7/27 ALK naïve patients in these 2 studies	Alka-372-001 STARTRK-1 [126]

Abbreviations: anaplastic lymphoma kinase tyrosine kinase inhibitors (ALK INHIBITORS); central nervous system (CNS); epidermal growth factor receptor (EGFR); mesenchymal-epithelial transition factor (MET); non-small-cell lung cancer (NSCLC); neurotrophic tyrosine receptor kinase (NTRK); the insulin-like growth factor-1 receptor (IGF1R); rearranged during transfection (RET); c-ros oncogene 1 (ROS1); tropomyosin receptor kinases A/B/C (Trk A/B/C).