**Sample**

We compiled a list of all supplemental and original applications with and without a Breakthrough Therapy designation (BTD) approved between January 2013 and October 2021 for treatment of non-small cell lung cancer (NSCLC) using review documents and labels published in the online database Drugs@FDA. Our sample included 32 supplemental approvals and 20 original approvals.

**Trial Details**

We collected trial details from the label published with the approval letter. Key details included the trial design, clinical trial number (NCT), primary endpoint (pEP) or co-primary endpoint (cpEP), and comparator used. If an NCT was not listed in the label, we used ClinicalTrials.gov to identify the corresponding NCT based on trial details in the label.

**Status of Breakthrough Therapy Designation**

Since BTD drugs typically receive the designation for multiple indications and applications after an initial BTD has been granted, we considered approvals BTDs if they included a drug that received BTD for any indication (I.e., the NSCLC approval in the analysis may not have a BTD but the drug was approved with a BTD for another indication/application). Approvals for drugs that have never received a BTD for any indication/application were assigned to the “Never BTD” category.

Our sample included 41 BTD approvals and 11 Never BTD approvals. There were 24 approvals that received a BTD for the application in this analysis, 11 that received BTD for a different NSCLC application, 5 that converted accelerated approvals (AA) with a BTD to full approval, and 1 that received BTD for a different non-NSCLC application.

**National Comprehensive Cancer Network (NCCN) Recommendations**

NCCN’s clinical guidelines include evidence-based recommendations for appropriate uses of anti-cancer drugs. These guidelines provide a framework to aid physicians in selecting a course of treatment for patients with cancer. The category of evidence indicates the level of evidence supporting a drug’s use and the level of consensus among NCCN’s panel of experts that its use is appropriate. Similarly, the category of preference helps to distinguish treatments that are less toxic, based on superior data, and, in some cases, more affordable. These categories provide additional metrics to compare BTD and Never BTD drugs. We identified the NCCN recommendation that best aligned with each approved NSCLC indication and noted the assigned category of evidence and preference.

Seven AAs that were converted to full approval and one approval that combined prior approvals were excluded from the recommendations analysis to avoid double counting a recommendation for the same indication.

**Outcomes Analysis**

To ensure outcomes were comparable across drugs and trials, we included only approvals supported by randomized controlled trials (RCTs) with overall survival (OS) and/or progression free survival (PFS) as pEP or cpEPs. We excluded approvals that were supported by a non-RCT (n=17) or pooled analysis (n=2), or did not have OS or PFS as a pEP or cpEP (n=1) as these labels did not report a hazard ratio (HR) for OS or PFS, and one approval that combined previously approved indications that did not add any new efficacy data to the label.

Outcomes from 33 trials supporting the labels for 31 approvals were included in the HR analysis. Ten trials reported an HR for OS, 6 reported an HR for OS & PFS, and 17 reported an HR for PFS (including 1 trial that reported an HR for DFS).

**Supplemental Table 1**. FDA Approvals for Non-Small Cell Lung Cancer, January 2013 – October 2021

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Drug Name (Agent Name(s))** | **Assigned #** | **Application Number** | **AA** | **BTD** | **Approval Date** | **NCT #** | **Reason for Exclusion** |
| **Alecensa (alectinib)** | 1a | NDA 208434 | X | X | 12/11/15 | NCT01588028 | Non-RCT |
| NCT01801111 | Non-RCT |
| 1b | NDA 208434 S-3 | X - Conversion of 1a | X | 11/06/17 | NCT02075840 |  |
| **Alunbrig (brigatinib)** | 2a | NDA 208722 | X | X | 4/28/17 | NCT02094573 | Non-RCT |
| 2b | NDA 208722 S-8 | X - Conversion of 2a | X | 5/22/20 | NCT02737501 |  |
| **Cyramza (ramucirumab + docetaxel)** | 3 | BLA 125477 S-7 |  |  | 12/12/14 | NCT01168973 |  |
| **Cyramza (ramucirumab + erlotinib)** | 4 | BLA 125477 S-34 |  |  | 5/29/20 | NCT02411448 |  |
| **Exkivity (mobocertinib)** | 5 | NDA 215310 | X | X | 9/15/21 | NCT02716116 | Non-RCT |
| **Gavreto (pralsetinib)** | 6 | NDA 213721 | X | X | 9/4/20 | NCT03037385 | Non-RCT |
| **Gilotrif (afatinib)** | 7 | NDA 201292 |  |  | 7/12/13 | NCT00949650 |  |
| **Gilotrif (afatinib)** | 8 | NDA 201292 S-7 |  |  | 4/15/16 | NCT01523587 |  |
| **Gilotrif (afatinib)** | 9 | NDA 201292 S-14 |  |  | 01/12/18 | NCT00525148, NCT00949650, & NCT01121393 | Pooled Analysis |
| **Imfinzi (durvalumab)** | 10 | BLA 761069 S-2 |  | X | 2/16/18 | NCT02125461 |  |
| **Iressa (gefitinib)** | 11 | NDA 206995 |  |  | 7/13/15 | NCT00322452 |  |
| **Keytruda (pembrolizumab + carboplatin + paclitaxel/nab-paclitaxel)** | 12 | BLA 125514 S-41 |  | X | 10/30/18 | NCT02775435 |  |
| **Keytruda (pembrolizumab + pemetrexed + platinum chemotherapy)** | 13a | BLA 125514 S-16 | X | X | 05/10/17 | NCT02039674 | No PFS/OS |
| 13b | BLA 125514 S-35 | X - Conversion of 13a | X | 08/20/18 | NCT02578680 |  |
| **Keytruda (pembrolizumab)** | 14a | BLA 125514 S-5 | X | X | 10/02/15 | NCT01295827 | Non-RCT |
| 14b | BLA 125514 S-12 | X - Conversion of 14a | X | 10/24/16 | NCT02142738 |  |
| 14c | BLA 125514 S-8 | X - Conversion of 14a | X | 10/24/16 | NCT01905657 |  |
| **Keytruda (pembrolizumab)** | 15 | BLA 125514 S-47 |  | X | 4/11/19 | NCT02220894 |  |
| **Libtayo (cemiplimab-rwlc)** | 16 | BLA 761097 S-7 |  | X | 2/22/21 | NCT03088540 |  |
| **Lorbrena (lorlatinib)** | 17a | NDA 210868 | X | X | 11/2/18 | NCT01970865 | Non-RCT |
| 17b | NDA 210868 S-4 | X - Conversion of 17a | X | 3/3/21 | NCT03052608 |  |
| **Lumakras (sotorasib)** | 18 | NDA 214665 | X | X | 5/28/21 | NCT03600883 | Non-RCT |
| **Mekinist (trametinib)** | 19 | NDA 204114 S-5 |  | X | 6/22/17 | NCT01336634 | Non-RCT |
| **Opdivo (nivolumab + ipilimumab)** | 20 | BLA 125554 S-80 |  | X | 05/15/20 | NCT02477826 |  |
| **Opdivo (nivolumab + ipilimumab)** | 21 | BLA 125554 S-82 |  | X | 05/26/20 | NCT03215706 |  |
| **Opdivo (nivolumab)** | 22 | BLA 125527 |  | X | 03/04/15 | NCT01642004 |  |
| **Opdivo (nivolumab)** | 23 | BLA 125554 S-5 |  | X | 10/09/15 | NCT01673867 |  |
| **Portrazza (necitumumab + gemcitabine + cisplatin)** | 24 | BLA 125547 |  |  | 11/24/15 | NCT00981058 |  |
| **Retevmo (selpercatinib)** | 25 | NDA 213246 | X | X | 5/8/20 | NCT03157128 | Non-RCT |
| **Rozlytrek (entrectinib)** | 26 | NDA 212725 |  | X | 8/15/19 | NCT02097810 & NCT02568267 | Pooled Analysis |
| **Rybrevant (amivantamab-vmjw)** | 27 | BLA 761210 | X | X | 5/21/21 | NCT02609776 | Non-RCT |
| **Tabrecta (capmatinib)** | 28 | NDA 213591 | X | X | 5/6/20 | NCT02414139 | Non-RCT |
| **Tafinlar (dabrafenib)** | 29 | NDA 202806 S-6 |  | X | 6/22/17 | NCT01336634 | Non-RCT |
| **Tagrisso (osimertinib)** | 30a | NDA 208065 | X | X | 11/13/15 | NCT01802632 | Non-RCT |
| NCT02094261 | Non-RCT |
| 30b | NDA 208065 S-6 | X - Conversion of 30a | X | 3/30/17 | NCT02151981 |  |
| **Tagrisso (osimertinib)** | 31 | NDA 208065 S-8 |  | X | 4/18/18 | NCT02296125 |  |
| **Tagrisso (osimertinib)** | 32 | NDA 208065 S-21 |  | X | 12/18/20 | NCT02511106 |  |
| **Tarceva (erlotinib)** | 33 | NDA 021743 S-18 |  |  | 05/14/13 | NCT00446225 |  |
| **Tarceva (erlotinib)** | 34 | NDA 021743 S-25 |  |  | 10/18/16 | N/a | No New Trial Information - Combined Previously Approved Indications |
| **Tecentriq (atezolizumab + bevacizumab + paclitaxel + carboplatin)** | 35 | BLA 761034 S-9 |  | X | 12/6/18 | NCT02366143 |  |
| **Tecentriq (atezolizumab + paclitaxel protein-bound + carboplatin)** | 36 | BLA 761034 S-21 |  | X | 12/3/19 | NCT02367781 |  |
| **Tecentriq (atezolizumab)** | 37 | BLA 761041 |  | X | 10/18/16 | NCT02008227 |  |
| NCT01903993 |  |
| **Tecentriq (atezolizumab)** | 38 | BLA 761034 S-27 |  | X | 5/18/20 | NCT02409342 |  |
| **Tepmetko (tepotinib)** | 39 | NDA 214096 | X |  | 2/3/21 | NCT02864992 | Non-RCT |
| **Vitrakvi (larotrectinib)** | 40 | NDA 210861 | X | X | 11/26/18 | NCT02122913 | Non-RCT |
| NCT02637687 | Non-RCT |
| NCT02576431 | Non-RCT |
| **Vizimpro (dacomitinib)** | 41 | NDA 211288 |  |  | 9/27/18 | NCT01774721 |  |
| **Xalkori (crizotinib)** | 42 | NDA 202570 S-6 | X - Conversion of pre-2013 AA | X | 11/20/13 | NCT00932893 |  |
| NCT01154140 |  |
| **Xalkori (crizotinib)** | 43 | NDA 202570 S-16 |  | X | 3/11/16 | NCT00585195 | Non-RCT |
| **Zykadia (ceritinib)** | 44a | NDA 205755 | X | X | 4/29/14 | NCT01283516 | Non-RCT |
| 44b | NDA 205755 S-9 | X - Conversion of 44a | X | 05/26/17 | NCT01828099 |  |

**Supplemental Table 2.** CorrespondingTrial Details for Randomized Controlled Trials Supporting NSCLC Approvals Included in Figure 1

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Assigned # (Label Linked)** | **NCT # Identified as Match** | **Treatment Comparison** | **Analysis Population** | **OS HR (95% CI)** | **PFS HR (95% CI)** |
| [1b](https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208434s003lbl.pdf) | NCT02075840 | alectinib vs. crizotinib | All Patients |  | 0.53 (0.38, 0.73) |
| [2b](https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208772s008lbl.pdf) | NCT02737501 | brigatinib vs. crizotinib | All Patients |  | 0.49 (0.35, 0.68) |
| [3](https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125477s007lbl.pdf) | NCT01168973 | ramucirumab + chemotherapy vs. chemotherapy | All Patients | 0.86 (0.75, 0.98) |  |
| [4](https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125477s034lbl.pdf) | NCT02411448 | ramucirumab + erlotinib vs. erlotinib | All Patients |  | 0.59 (0.46, 0.76) |
| [7](https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/201292s000lbl.pdf) | NCT00949650 | afatinib vs. chemotherapy | All Patients |  | 0.58 (0.43, 0.78) |
| [8](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/201292s007lbl.pdf) | NCT01523587 | afatinib vs. erlotinib | All Patients |  | 0.82 (0.68, 0.998) |
| [10](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761069s002lbl.pdf) | NCT02125461 | durvalumab vs. placebo | Pre-specified interim analysis at 371 events |  | 0.52 (0.42, 0.65) |
| [11](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/206995s003lbl.pdf) | NCT00322452 | gefitinib vs. carboplatin/paclitaxel | Exploratory subgroup analysis |  | 0.54 (0.38, 0.79) |
| [12](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125514s041lbl.pdf) | NCT02775435 | pembrolizumab + chemotherapy vs. chemotherapy | All Patients | 0.64 (0.49, 0.85) | 0.56 (0.45, 0.7) |
| [13b](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125514s041lbl.pdf) | NCT02578680 | pembrolizumab + chemotherapy vs. chemotherapy | All Patients | 0.49 (0.38, 0.64) | 0.52 (0.43, 0.64) |
| [14b](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125514s012lbl.pdf) | NCT02142738 | pembrolizumab vs. chemotherapy | All Patients |  | 0.5 (0.37, 0.68) |
| [14c](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125514s008s012lbl.pdf) | NCT01905657 | pembrolizumab 10 mg/kg vs. chemotherapy | PD-L1 >= 1% | 0.61 (0.49, 0.75) | 0.79 (0.66, 0.94) |
| pembrolizumab 2 mg/kg vs. chemotherapy | PD-L1 >= 1% | 0.71 (0.58, 0.88) | 0.88 (0.73, 1.04) |
| [15](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125514s047lbl.pdf) | NCT02220894 | pembrolizumab vs. chemotherapy | PD-L1 >= 1% | 0.81 (0.71, 0.93) |  |
| [16](https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761097s007lbl.pdf) | NCT03088540 | cemiplimab vs. chemotherapy | All Patients | 0.68 (0.53, 0.87) | 0.59 (0.49, 0.72) |
| [17b](https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/210868s004lbl.pdf) | NCT03052608 | lorlatinib vs. crizotinib | All Patients |  | 0.28 (0.19, 0.41) |
| [20](https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125554s080lbl.pdf) | NCT02477826 | nivolumab + ipilimumab vs. chemotherapy | PD-L1 >= 1% | 0.79 (0.67, 0.94) |  |
| [21](https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125554s082lbl.pdf) | NCT03215706 | nivolumab + ipilimumab + chemotherapy vs. chemotherapy | Pre-specified interim analysis at 351 events | 0.69 (0.55, 0.87) |  |
| [22](https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125527s000lbl.pdf) | NCT01642004 | nivolumab vs. chemotherapy | Pre-specified interim analysis at 199 events | 0.59 (0.44, 0.79) |  |
| [23](https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125554s005lbl.pdf) | NCT01673867 | nivolumab vs. chemotherapy | Pre-specified interim analysis at 413 events | 0.73 (0.6, 0.89) |  |
| [24](https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125547s000lbl.pdf) | NCT00981058 | necitumumab + chemotherapy vs. chemotherapy | All Patients | 0.84 (0.74, 0.96) |  |
| [30b](https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208065s006lbl.pdf) | NCT02151981 | osimertinib vs. chemotherapy | All Patients |  | 0.3 (0.23, 0.41) |
| [31](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208065s008lbl.pdf) | NCT02296125 | osimertinib vs. gefitinib | All Patients |  | 0.46 (0.37, 0.57) |
| [32](https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208065s021lbl.pdf) | NCT02511106 | osimertinib vs. placebo | Stage II-IIIA |  | 0.17 (0.12, 0.23) |
| Stage IB-IIIA |  | 0.2 (0.15, 0.27) |
| [33](https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021743s018lbl.pdf) | NCT00446225 | erlotinib vs. chemotherapy | All Patients |  | 0.34 (0.23, 0.49) |
| [35](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761034s009lbl.pdf) | NCT02366143 | atezolizumab + bevacizumab + chemotherapy vs. bevacizumab + chemotherapy | Patients without EGFR+ or ALK+ (ITT-WT) | 0.78 (0.64, 0.96) | 0.71 (0.59, 0.85) |
| [36](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761034s021lbl.pdf) | NCT02367781 | atezolizumab + chemotherapy vs. chemotherapy | Patients without EGFR+ or ALK+ (ITT-WT) | 0.8 (0.64, 0.99) | 0.75 (0.63, 0.91) |
| [37](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/761041s000lbl.pdf) | NCT02008227 | atezolizumab vs. chemotherapy | Primary Analysis Population (ITT-850) | 0.74 (0.63, 0.87) |  |
| NCT01903993 | atezolizumab vs. docetaxel | All Patients | 0.69 (0.52, 0.92) |  |
| [38](https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761034s027lbl.pdf) | NCT02409342 | atezolizumab vs. chemotherapy | PD-L1-High (IC >= 10% or PD-L1 TC >= 50%) | 0.59 (0.4, 0.89) |  |
| [41](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/211288s000lbl.pdf) | NCT01774721 | dacomitinib vs. gefitinib | All Patients |  | 0.59 (0.47, 0.74) |
| [42](https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/202570s006lbl.pdf) | NCT00932893 | crizotinib vs. chemotherapy | All Patients |  | 0.49 (0.37, 0.64) |
| NCT01154140 | crizotinib vs. chemotherapy | All Patients |  | 0.45 (0.35, 0.6) |
| [44b](https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/205755s009lbl.pdf) | NCT01828099 | ceritinib vs. chemotherapy | All Patients |  | 0.55 (0.42, 0.73) |