Review

Anti-PD1/PD-L1 Immunotherapy for Non-Small Cell Lung Cancer with Actionable Oncogenic Driver Mutations

Edouard Dantoing 1, Nicolas Piton 2, Mathieu Salaün 1,3,4, Luc Thiberville 1,3,4 and Florian Guisier 1,3,4,*

1 Department of Pneumology, CHU Rouen, 76000 Rouen, France; edouard.dantoing@chu-rouen.fr (E.D.); mathieu.salaun@univ-rouen.fr (M.S.); Luc.thiberville@univ-rouen.fr (L.T.)
2 Department of Pathology, CHU Rouen, 76000 Rouen, France; Nicolas.piton@chu-rouen.fr
3 QuantIF Team, LITIS Lab EA4108, UNIROUEN, Normandie University, 76000 Rouen, France
4 Inserm CIC CRB 1404, CHU Rouen, 76000 Rouen, France
* Correspondence: florian.guisier@chu-rouen.fr

Abstract: Anti-PD1/PD-L1 immunotherapy has emerged as a standard of care for stage III-IV non-small cell lung cancer (NSCLC) over the past decade. Patient selection is usually based on PD-L1 expression by tumor cells and/or tumor mutational burden. However, mutations in oncogenic drivers such as EGFR, ALK, BRAF, or MET modify the immune tumor microenvironment and may promote anti-PD1/PD-L1 resistance. In this review, we discuss the molecular mechanisms associated with these mutations, which shape the immune tumor microenvironment and may impede anti-PD1/PD-L1 efficacy. We provide an overview of the current clinical data on anti-PD1/PD-L1 efficacy in NSCLC with oncogenic driver mutation.

Keywords: non-small cell lung cancer; anti-PD1/PD-L1 immunotherapy; EGFR; ALK; BRAF; MET; HER2; RET; ROS1; oncogenic driver

1. Introduction

Lung cancer is the leading cause of cancer-related death worldwide, with an estimated 1.76 million deaths in 2018 (18.4% of total cancer deaths) [1]. Overall lung cancer has a poor prognosis, with 18.6% of patients surviving 5 years [2]. Approximately 80% of lung cancer cases are attributed to cigarette smoking [3], while 10–25% occur in never smokers [4]. Exposure to environmental carcinogens such as asbestos, radon gas, or other forms of pollution are the other main causes [5].

Lung cancer is classified in two major types: small cell lung cancer (SCLC), which accounts for 15–20% of lung cancer patients, and non-small cell lung cancer (NSCLC), comprising the remaining 80–85% [6] and subclassified in three major histological subtypes: adenocarcinoma (40% of all lung cancer cases), squamous cell carcinoma (20% of all lung cancer cases), and large cell carcinoma (LCC) [7]. Adenocarcinoma is the predominant subtype in never smokers [7]. Over the past two decades, genomic studies of large cohorts have unraveled a complex molecular landscape of lung tumors.

Current guidelines for the diagnosis and management of adenocarcinoma include histological subtyping and molecular analysis. In fact, targeted therapies for several oncogenic alterations have been developed and improve patients’ outcomes (Table 1). In stage IV adenocarcinoma patients, EGFR, ALK, ROS1, BRAF, MET, RET, HER2, KRAS, and NTRK are assessed to offer targeted therapy for eligible patients [8,9]. Alterations in these so-called “actionable” oncogenes are usually mutually exclusive, which indicates that these individual genes are capable of driving lung cancer progression.

Since 2015, anti-programmed death 1 (PD1) or anti-programmed death-ligand 1 (PD-L1) immunotherapy has emerged as a gold-standard treatment for first- or second-line treatment of stage IV NSCLC, either in monotherapy or in combination with chemotherapy, after several clinical trials demonstrated their benefits over chemotherapy in second and
then first-line treatment (Table 2). In most of these studies, patients whose tumor harbored oncogenic alterations (particularly EGFR mutations and ALK and ROS1 rearrangement) were excluded. In fact, efficacy of anti-PD1/PD-L1 immunotherapy was thought to be scarce in EGFR-mutated NSCLC. As a result, few clinical data are available in this subset of patients.

**Table 1.** Actionable oncogene alterations in NSCLC and corresponding targeted therapies.

| Gene Alteration                  | Freq.   | Targeted Therapy | Ref.     |
|----------------------------------|---------|------------------|----------|
| **EGFR activating mutations**    | 15–50%  | Erlotinib         | [10]     |
|                                  |         | Gefitinib         | [11]     |
|                                  |         | Afatinib          | [12]     |
|                                  |         | Dacomitinib       | [13]     |
|                                  |         | Icotinib          | [14]     |
|                                  |         | Osimertinib       | [15]     |
|                                  |         | Mobocertinib      | [16]     |
|                                  |         | Poziotinib        | [17]     |
| **ALK rearrangement**            | 4%      | Crizotinib        | [18]     |
|                                  |         | Ceritinib         | [19]     |
|                                  |         | Alectinib         | [20]     |
|                                  |         | Brigatinib        | [21]     |
|                                  |         | Lorlatinib        | [22]     |
| **MET exon 14 skipping mutations** | 4%      | Crizotinib        | [23,24]  |
|                                  |         | Cabozantinib      | [25]     |
|                                  |         | Capmatinib        | [26]     |
|                                  |         | Tepotinib         | [27]     |
|                                  |         | Savolitinib       | [28]     |
| **BRAF mutations**               | 3%      | Vemurafenib       | [29]     |
|                                  |         | Dabrafenib        | [30]     |
|                                  |         | Dabrafenib + Trametinib | [31] |
| **HER2 mutations**               | 3%      | Trastuzumab       | [32]     |
|                                  |         | Neratinib         | [33,34]  |
|                                  |         | Afatinib          | [35]     |
|                                  |         | Lapatinib         | [36]     |
| **ROS1 rearrangement**           | 1–2%    | Crizotinib        | [37]     |
|                                  |         | Ceritinib         | [38]     |
|                                  |         | Lorlatinib        | [39,40]  |
|                                  |         | Entrectinib       | [41]     |
| **RET rearrangement**            | 1–2%    | Vandetanib        | [42]     |
|                                  |         | Cabozantinib      | [43,44]  |
|                                  |         | Pralsetinib       | [45]     |
|                                  |         | Selpercatinib     | [46]     |
| **NTRK fusion**                  | <1%     | Entrectinib       | [47,48]  |
|                                  |         | Larotrectinib     | [48]     |
|                                  |         | Selitrectinib     | [49]     |
| **Kras G12C mutation**           | 13%     | Sotorasib         | [50]     |
|                                  |         | Adagrasib         | [51]     |

Freq.: percentage among non-squamous NSCLC [8,9,52].

Anti-PD1/PD-L1 immunotherapy acts by blocking an inhibitory lymphocyte receptor, PD1, though releasing the anti-tumor immune cytotoxicity [53].
Table 2. Results of the main trials evaluating anti-PD1/PD-L1 monotherapy in stage IV NSCLC.

| Histology          | PDL1 | n   | ORR (%) * | OS (mo) * | Ref.  |
|--------------------|------|-----|-----------|-----------|-------|
| **First-line**     |      |     |           |           |       |
| Nivolumab          | NSCLC| >5% | 271       | 26 vs. 33 | 13.7 vs. 13.8 | [54] |
| Pembrolizumab      | NSCLC| >50%| 154       | 45 vs. 28 | 30 vs. 14.2  | [55] |
|                    | NSCLC| >1% | 638       | 27 vs. 27 | 16.7 vs. 12.1| [56] |
| Atezolizumab       | NSCLC| >1% | 277       | 38.3 vs. 28.6 | 20.2 vs. 13.1| [57] |
| Durvalumab         | NSCLC| >25%| 369       | 35.6 vs. 37.7 | 16.3 vs. 12.9| [58] |
| Cemiplimab         | NSCLC| >50%| 283       | 37 vs. 21 | 22.1 [17.5-NR] vs. 14.2 | [59] |
| **Second- or third-line** | | |     |           |       |
| Nivolumab          | Squamous | All | 135    | 20 vs. 9 | 9.2 vs. 6 | [60] |
|                    | Adenocarcinoma | All | 292   | 19 vs. 12 | 12.2 vs. 9.4 | [61] |
| Pembrolizumab      | NSCLC| >1% | 344    | 18 vs. 9.3 | 10.4 vs. 8.5 | [62] |
| Atezolizumab       | NSCLC| All | 425    | 14 vs. 13 | 13.8 vs. 9.6 | [63] |

n: number of patients in the experimental arm. ORR: objective response rate. OS: overall survival. * comparison of ORR and OS data is given in the following format: experimental arm (anti-PD1/PD-L1) versus standard of care arm (chemotherapy).

Expression of PD-L1 by tumor and immune cells, high tumor mutational burden (TMB), and tumor infiltration by immune cells are key features associated with a better efficacy of anti-PD1/PD-L1 immunotherapy in stage IV NSCLC [64]. By modeling these 3 characteristics, oncogenic driver mutations may impede anti-PD1/PD-L1 efficacy [65]. In this review, we discuss the immune-related parameters associated with actionable oncogenic driver mutations and provide an overview of the current clinical data on anti-PD1/PD-L1 efficacy in NSCLC with such mutations.

2. NSCLC Actionable Oncogenic Drivers and the Immune Micro-Environment

2.1. PDL1 Expression in NSCLC with Actionable Oncogenic Driver Mutation

Contradictory results have been reported regarding PD-L1 expression in EGFR-mutated NSCLC (Table 3). Early reports showed upregulation of PD-L1 in EGFR-mutated NSCLC cell lines and animal models [66,67] as well as some patient data [68–70]. Noteworthy, PD-L1 assessment in these studies used various non-standardized assays. The most recent studies used clinically validated assays and tested samples from treatment-naïve patients. A pooled analysis of 15 public studies gathering 1050 EGFR-mutated NSCLC patients showed that patients with EGFR mutations had decreased PD-L1 expression (odds ratio: 1.79, 95% CI: 1.10–2.93; p = 0.02) [71]. This was consistent with data from 237 lung adenocarcinomas from The Cancer Genome Atlas [72] and with a recent report on 336 treatment-naïve patients with EGFR-mutated NSCLC [73].

In 319 patients with EGFR-mutant NSCLC, Cho et al. showed that PD-L1 expression is more prevalent in stage II-IV than in stage I tumors, and in exon 19 deletion than in L858R mutation [74].

When a tumor progresses after EGFR targeted therapy, EGFR T790M mutation is found in 50% of cases. Tumors that are T790M negative are more likely to express PD-L1 and patients may have greater benefit from anti-PD1/PD-L1 therapy in this setting [75,76]. In a recent paper, PD-L1 expression was found to be higher in EGFR T790M positive after progression on Osimertinib: 5/10 had PD-L1 expression > 1% after progression vs. 0/10 at baseline [77]. Among other EGFR mutations, exon 20 insertions were associated with a higher frequency of PD-L1 expression [78,79].

In 111 NSCLC patients with MET exon 14 skipping mutations, Sabari et al. found a higher PD-L1 expression than expected from the above-mentioned studies, with 22%, and 41% having PD-L1 expression of 1–49%, and ≥ 50%, respectively [80]. This result was confirmed in a recent analysis [81]. Nevertheless, the median TMB of MET exon 14-altered lung cancers was lower than that of unselected NSCLCs. Similar results were recently reported in two series of 14 and 20 NSCLC patients with MET exon 14 skipping mutations [82,83].
Among 122 patients with HER2-mutated NSCLC, PD-L1 expression was found to be low, with 13% of patients having PD-L1 expression over 50% [84]. In another study, 1/9 patient had PDL-1 over 50% [85]. Similarly, no tumors had PD-L1 expression over 50% in two other series of 15 and 13 HER2-mutated NSCLC patients [82,83]. In the latter series, TMB was ≤5 Mut/Mb in all 13 cases. Recently, two more studies reported data on 13 and 21 HER2-mutated NSCLC patients, respectively, showing that 3/13 had a PD-L1 expression > 50% [79] and 4/21 tumors a PD-L1 expression > 1% [78].

A retrospective cohort of 39 patients with BRAF-mutant NSCLC (21 V600E- and 18 non-V600E) was recently reported, showing that 45% of patients had high PDL-1 expression (>50%) [86]. In this study, TMB was ≥20 Mut/Mb in 25% of BRAF V600E tumors but 0% of non-V600E mutant tumors. Similar findings were reported in 18 BRAF-mutant NSCLC (9 V600E and 9 non-V600E) [82].

Data for other oncogenic drivers are scarce. In ALK-rearranged NSCLC, PD-L1 expression over 50% was reported in 5/19, 4/10, 0/11, and 2/9 tumors [83,87–89]. NTRK gene fusions in NSCLC may be associated with higher TMB and PD-L1 expression than other molecularly defined subgroups [90]. In KRAS G12C mutation NSCLC, PD-L1 expression was reported to be ≥1% in 16/40 tumors [91]. Controversial data have been reported for ROS1 and RET rearranged NSCLC [82,83,85,89–94].

### 2.2. Immunogenicity and Lymphocyte Infiltration of NSCLC with Actionable Oncogenic Driver Mutation

The infiltration of CD8+ T lymphocytes has been found to reduce in EGFR-mutated NSCLCs compared to those with EGFR WT [71,73,95]. In a study of 336 treatment-naïve EGFR-mutated NSCLC, authors also provided evidence for a low immunogenicity of EGFR-mutated NSCLC by analyzing the TCGA data and an independent validation cohort of patients [73]. They found that patients with EGFR mutation had lower TMB than those with EGFR wild-type. More importantly, there was a significant difference in TMB between EGFR-sensitive (exon 19Del, L858R, L861Q, G719X, S768I) and EGFR-resistant/unknown mutations: from the TCGA cohort, the EGFR-sensitive mutant group showed a significantly lower TMB than the resistant/unknown group (median: 60 vs. 283; p < 0.001). This was confirmed in a recent study analyzing 153 patients with EGFR-mutant lung cancer [96].

Similar results were found in another study in 100 patients from Japan: 10 NSCLC had a high-TMB (>20 mutations/Mb), among whom 2 harbored a driver mutation (1 ALK rearrangement and 1 HER2 mutation), whereas 57 of the 90 specimens with low-TMB harbored an actionable oncogenic driver mutation (ALK, ROS1, or RET rearrangement or EGFR, HER2, or MET mutation) (p < 0.05) [97].

### Table 3. PD-L1 expression in NSCLC with actionable oncogenic driver mutation.

| Gene   | Study        | Population         | PD-L1 Status | Ref. |
|--------|--------------|-------------------|--------------|-----|
| EGFR   | Liu, 2018    | EGFR+, all, n = 341 | <1% 78%  1% 22% | [73] |
|        |              | T790M+, n = 32     | ≥50% 49% 1% 22% |     |
|        |              | T790M-, n = 309    | ≥50% 49% 1% 22% |     |
| Hata, 2017 | EGFR+, all, n = 67 | <1% 51%  1% 49% | [76] |
|        |              | T790M+, n = 26     | ≥50% 49% 1% 49% |     |
|        |              | T790M-, n = 41     | ≥50% 49% 1% 49% |     |
| Cho, 2018 | EGFR+, all, n = 319 | <1% 48% 1% 52% | [74] |
|        |              | Del19+, n = 145    | ≥50% 48% 1% 52% |     |
|        |              | L858R, n = 121     | ≥50% 48% 1% 52% |     |
|        | Yoneshima, 2018 | EGFR+, all, n = 70 | <1% 57% 1% 43% | [89] |
|        |              | Del19+, n = 40     | ≥50% 57% 1% 43% |     |
|        |              | L858R, n = 30      | ≥50% 57% 1% 43% |     |
Table 3. Cont.

| Gene       | Study                   | Population          | PD-L1 Status | Ref. |
|------------|-------------------------|---------------------|--------------|------|
|            |                         |                     | <1%          | ≥1%  | ≥50% |
| EGFR+      | Lau, 2020               | Del19/L858R, n = 13 | 29%          | 71%  | 41%  |
|            |                         | Ex20ins, n = 4      | 23%          | 77%  | 38%  |
|            | Mazieres, 2019          | EGFR+, all, n = 49  | 37%          | 63%  | 29%  |
|            | Gainor, 2016            | EGFR+, pre-TKI, n = 62 | 76%         | 24%  | 11%  |
|            |                         | EGFR+, post-TKI, n = 63 | 69%         | 31%  | 14%  |
|            | Karatasoglou, 2020      | EGFR+, n = 18       | 44%          | 56%  | 6%   |
|            | Rangachari, 2017        | EGFR+, n = 13       |              |      |      |
|            | Chen, 2020              | EGFR Ex20ins, n = 35 | 51%          | 49%  |      |
| KRAS G12C  | Tao, 2020               | KRAS G12C, n = 40   | 60%          | 40%  |      |
| MET exon 14| Sabari, 2018            | MET exon 14, n = 111 | 37%         | 63%  | 41%  |
|            | Mazieres, 2019          | MET exon 14, n = 20 | 25%          | 75%  | 46%  |
|            | Guisier, 2020           | MET exon 14, n = 14 | 8%           | 92%  | 79%  |
|            | Dudnik, 2018            | MET exon 14, n = 9  | 22%          | 78%  | 67%  |
| BRAF       | Dudnik, 2018            | BRAF+, all, n = 29  | 31%          | 69%  | 45%  |
|            |                         | V600E, n = 19        | 36%          | 74%  | 42%  |
|            |                         | nonV600E, n = 10     | 40%          | 60%  | 50%  |
|            | Guisier, 2020           | BRAF+, all, n = 21  | 24%          | 76%  | 57%  |
|            |                         | V600E, n = 14        | 21%          | 79%  | 71%  |
|            |                         | nonV600E, n = 7      | 39%          | 71%  | 29%  |
|            | Dudnik, 2018            | BRAF+, all, n = 13  | 31%          | 69%  | 38%  |
|            |                         | V600E, n = 8         | 25%          | 75%  | 25%  |
|            |                         | nonV600E, n = 5      | 40%          | 60%  | 60%  |
|            | Mazieres, 2019          | BRAF+, n = 10       | 30%          | 70%  | 56%  |
| HER2       | Lai, 2018               | HER2+, n = 87       | 77%          | 23%  |      |
|            | Chen, 2020              | HER2+, n = 21       | 81%          | 19%  |      |
|            | Mazieres, 2019          | HER2+, n = 15       | 47%          | 53%  | 0%   |
|            | Lau, 2020               | HER2+, n = 13       | 38%          | 62%  | 23%  |
|            | Guisier, 2020           | HER2+, n = 8        | 50%          | 50%  | 13%  |
| ALK        | Gainor, 2016            | ALK+, pre-TKI, n = 19 | 37%         | 63%  | 26%  |
|            |                         | ALK+, post-TKI, n = 12 | 58%         | 42%  | 17%  |
|            | Mazieres, 2019          | ALK+, n = 11        | 36%          | 64%  | 40%  |
|            | Karatasoglou, 2020      | ALK+, n = 11        | 55%          | 45%  | 0%   |
| ROS1       | Dudnik, 2018            | ROS1+, n = 5        | 20%          | 80%  | 40%  |
| RET        | Mazieres, 2019          | RET1+, n = 5        | 0%           | 100% | 60%  |
|            | Dudnik, 2018            | RET+, n = 8         | 25%          | 75%  | 50%  |
|            | Guisier, 2020           | RET+, n = 8         | 50%          | 50%  | 13%  |

TKI: tyrosine kinase inhibitor.
3. Clinical Data on Anti-PD1/PD-L1 Efficacy in NSCLC with Actionable Oncogenic Driver Alterations

Few NSCLC patients with actionable oncogenic driver mutations were included in the pivotal clinical trials evaluating anti-PD1 therapy and the only available data concern EGFR (Table 4). A phase 2 trial was initiated to evaluate Pembrolizumab in the EGFR+ population, specifically. Enrollment was ceased for lack of efficacy after the first 11 patients were treated [98]. Only one patient had an objective response, but repeat analysis of this patient’s tumor definitively showed the original report of an EGFR mutation to be erroneous.

In a meta-analysis of three trials that compared an anti-PD1/PD-L1 immunotherapy to a second- or third-line chemotherapy with docetaxel, 185 patients had EGFR-mutated NSCLC. In this subgroup, there was no benefit of immunotherapy over chemotherapy: HR for OS 1.05 (0.70–1.55) [99].

Of note, combination of anti-PD-L1 therapy with chemotherapy demonstrated some efficacy [100,101]. The IMPower 150 trial compared a four-drug regimen with Atezolizumab, Bevacizumab, Carboplatin, and Paclitaxel (ABCP) with ACP and BCP as first-line treatment in stage IV NSCLC. Among patients with EGFR-mutated NSCLC (n = 79), overall survival was longer in the ABCP arm (not reached), although the difference was not significant (HR 0.61 (0.29–1.28)). Similar results were found in PFS, with a significant advantage to the ABCP regimen over the BCP regimen in the subgroup of patients that were previously treated with EGFR inhibitors (HR 0.42, IC95 (0.22–0.80)). These results suggest that the combination of immunotherapy plus chemotherapy plus anti-VEGF is a promising regimen for patients failing TKIs [100].

Since 2015 and the advent of anti-PD1 in routine practice, some real-world data have been published (Table 3). The largest study of this kind was the ImmunoTarget multicentric worldwide retrospective study [83], which gathered 125 EGFR, 43 BRAF, 36 MET, 29 HER2, 23 ALK, 16 RET, and 7 ROS1 NSCLC patients treated with anti-PD1 (92%) or anti-PD-L1, mostly in second- (42%), third- (26%) or later treatment lines (27%). Overall real-world studies show a lack of efficacy of anti-PD1/PD-L1 monotherapy for EGFR, ALK, and HER2 subgroups, and mixed results for RET and ROS1 patients, with a lower number of patients reported so far. On the other hand, BRAF and MET patients had similar benefits of anti-PD1/PD-L1 therapy as compared to patients with no known driver mutation.

Recently, Yamada et al. reported a series of 27 EGFR-mutated NSCLC patients treated with anti-PD1/PD-L1 immunotherapy. They showed that uncommon EGFR mutations were associated with a higher response rate and longer PFS than common activating EGFR mutations and/or T790M mutation [102]. Two other retrospective studies also reported ORR in exon 20 EGFR-mutated NSCLC patients treated with anti-PD1/PD-L1 immunotherapy. In these studies 3/6 and 2/9 EGFR-Ex20ins patients exhibited a tumor response [78,79].

In line with the above-mentioned results of anti-PD1/PD-L1 immunotherapy in EGFR- or HER2-mutated stage IV NSCLC, a recent retrospective analysis of patients with unresectable stage III NSCLC treated with consolidation durvalumab after definitive chemoradiation reported a shorter PFS in the EGFR- or HER2-mutated NSCLC patients subgroup (7.5 mo vs. not reached, p = 0.04) [103].

Table 4. Clinical data on anti-PD1 efficacy in NSCLC with actionable oncogenic driver alterations.

| Study          | Main Results                                      | Ref.   |
|----------------|---------------------------------------------------|--------|
| **Randomized Clinical Trials** |                       |        |
| CheckMate 057  | Nivolumab vs. Docetaxel EGFR (n = 82): HR 1.38 (0.69–2) ALK (n = 21): no subgroup analysis | [61]   |
| Keynote 010    | Pembrolizumab vs. Docetaxel EGFR (n = 86): HR 0.89 (0.45–1.70) ALK (n = 8): no subgroup analysis | [62]   |
### Table 4. Cont.

| Study                | Main Results                                                                 | Ref. |
|----------------------|-----------------------------------------------------------------------------|------|
| **OAK**              | Atezolizumab vs. Docetaxel                                                   |      |
|                      | EGFR ($n = 85$): HR 1.24 (0.71–2.18)                                        | [63] |
|                      | ALK ($n = 2$): no subgroup analysis                                         |      |
| **Atlantic (phase II)** | Durvalumab                                                             |      |
|                      | EGFR/ALK ($n = 107$): ORR: 16%, OS: 12.3, PFS 1.9                           | [104]|
| **IMPOWER 150**      | AtezolizumabBCP vs. BCP                                                    |      |
|                      | EGFR ($n = 79$): HR for OS 0.61 (0.36–1.03)                                 |      |
|                      | Subgroup previously treated by TKI ($n = 50$): HR for OS 0.39 (0.14–1.07); |      |
|                      | HR for PFS 0.42 (0.22–0.80)                                                 |      |
|                      | ALK ($n = 31$): no subgroup analysis                                        |      |

#### Real-world Studies

| Study                | Main Results                                                                 | Ref. |
|----------------------|-----------------------------------------------------------------------------|------|
| Gainor, 2016         | 28 EGFR/ALK+ vs. 30 WT                                                      | [87] |
|                      | RR 3.6% vs. 23.3%                                                          |      |
| Dudnik, 2018         | 12 BRAF V600E                                                              | [86] |
|                      | 10 other BRAF                                                              |      |
|                      | RR 25%, PFS 3.7 (1.6–6.6)                                                  |      |
|                      | RR 33% PFS 4.1 (0.1–19.6)                                                  |      |
| Sabari, 2018          | 24 MET ex14                                                                | [80] |
|                      | RR 17% (6–36), PFS 1.9                                                     |      |
|                      | (1.7–2.7)                                                                  |      |
| Rizvi, 2018           | 17 EGFR, 7 ROS1, 9 BRAF, 2 ALK, 2 RET                                      | [64] |
|                      | Durable clinical benefit in 2 EGFR, 4 BRAF, 2 HER2 and 1 ROS1 patients     |      |
| Liu, 2018             | 6 EGFR1 1 ALK                                                             | [73] |
|                      | 1 EGFR with partial response                                               |      |
| Garassino, 2018       | 102 EGFR+ vs. 1293 WT                                                      | [105]|
|                      | RR 8.8% vs. 19.6% *                                                        |      |
|                      | OS 8.3 vs. 11.0 *                                                          |      |
| Wei-Chu, 2018         | 26 HER2                                                                    | [84] |
|                      | RR 12%, PFS 1.9, OS 10.4                                                   |      |
| Mazieres, 2019        | 125 EGFR                                                                  | [83] |
|                      | 43 BRAF                                                                    |      |
|                      | RR 12%, PFS 2.1                                                            |      |
|                      | 36 MET                                                                     |      |
|                      | RR 16%, PFS 3.4                                                            |      |
|                      | 29 HER2                                                                    |      |
|                      | RR 7%, PFS 2.5                                                             |      |
|                      | 23 ALK                                                                     |      |
|                      | RR 0%, PFS 2.5                                                             |      |
|                      | 16 RET                                                                     |      |
|                      | RR 6%, PFS 2.1                                                             |      |
|                      | 7 ROS1                                                                     |      |
|                      | RR 17%                                                                     |      |
| Morita, 2019          | 116 EGFR                                                                   | [106]|
|                      | OS 12.1 vs. 14.6 *                                                         |      |
|                      | PFS 1.5 vs. 2.3 *                                                          |      |
|                      | RR 8.6% vs. 22.6 *                                                         |      |
| Bylicki, 2020         | 42 EGFR                                                                    | [85] |
|                      | 8 ALK                                                                      |      |
|                      | OS 13.9 (8.8–20), PFS 2.2 (1.4–3.2)                                       |      |
|                      | 1 ROS1                                                                     |      |
|                      | OS 19.2 (13.1-NR), PFS 2.4 (2.1-NR)                                       |      |
|                      | OS 2.8, PFS 1.4                                                            |      |
| Barlesi, 2020         | 44 EGFR                                                                    | [107]|
|                      | OS 8.1 vs. 12.2                                                            |      |
| Guisier, 2020         | 26 BRAF V600                                                               | [85] |
|                      | 18 BRAF NV600                                                              |      |
|                      | 30 MET                                                                     |      |
|                      | 23 HER 2                                                                  |      |
|                      | 9 RET                                                                      |      |
|                      | RR 26%, PFS 5.3, OS 22.5                                                   |      |
|                      | RR 35%, PFS 5.3, OS 12                                                     |      |
|                      | RR 36%, PFS 4.9, OS 13.4                                                   |      |
|                      | RR 27%, PFS 2.2, OS 20.4                                                   |      |
|                      | RR 37%, PFS 7.6, OS NR                                                     |      |
| Lau, 2021             | 28 EGFR SM                                                                 | [79] |
|                      | RR 11%, PFS 1.7                                                            |      |
|                      | 6 EGFR-Ex20ins                                                             |      |
|                      | RR 50%, PFS 4.8,                                                          |      |
|                      | 14 HER 2                                                                   |      |
|                      | RR 29%, PFS 3.6                                                            |      |
| Chen, 2021            | 9 EGFR-Ex20ins                                                             | [78] |
|                      | RR 22%                                                                     |      |
|                      | 6 HER2-Ex20ins                                                             |      |
|                      | RR 0%                                                                      |      |
| Yamada, 2021          | 20 common EGFR                                                             | [102]|
|                      | RR 10%, PFS 1.6                                                            |      |
|                      | 7 uncommon EGFR                                                            |      |
|                      | RR 57%, PFS 8.5                                                            |      |

BCP: Bevacizumab + carboplatin + paclitaxel, SM: sensitizing mutations, WT: wild-type, RR: response rate, PFS: progression-free survival, OS: overall survival. PFS and OS are given in months. * comparisons are shown between EGFR-mutated and EGFR wild type NSCLC patients.
4. Future Directions

Use of anti-PD1/PD-L1 monotherapy in NSCLC harboring common EGFR mutation or ALK rearrangement can be ruled out as a standard strategy given the bad outcomes of patients treated in this setting. After EGFR/ALK TKI failure, the combination of chemo-immunotherapy with an antiangiogenic agent is under investigation (NCT04042558) and may improve outcomes over chemotherapy alone or combined with an antiangiogenic agent.

In KRAS or BRAF mutated NSCLC, anti-PD1/PD-L1 immunotherapy exhibits high efficacy. As more targeted therapies are developed in this setting, the question is now to evaluate the best sequence and/or combination of treatments. KRAS G12C inhibitors sotorasilb and adagrasib have a favorable safety profile that may allow combination with anti-PD1/PD-L1 treatment, a strategy that is under investigation for first-line treatment (NCTXXX). BRAF V600E inhibition with anti-BRAF and anti-MEK inhibitors is associated with more toxicities, which may preclude their use in combination with anti-PD1/PD-L1 agents. Comparison of first-line treatment with TKIs or chemo-immunotherapy is needed in this setting. The same question is arising for MET and HER2 mutated as new targeted therapies are being developed and reach first- or second-line treatment.

For other rare targetable drivers, data is too scarce to draw definitive conclusions about the place of anti-PD1/PD-L1. Gathering large cohorts of patients in this setting is challenging but collaborative efforts are ongoing such as the RET-MAP study.

5. Conclusions

NSCLC with driver mutations represent a challenging population for the clinician as large clinical trials often do not take into account the particular biology of these subgroups. Preclinical data are useful for evidence-based decisions, but real-world studies are particularly important to assess their relevance. Network efforts to gather large cohort should be encouraged in this perspective.

Anti-PD1/PD-L1 therapy has been a revolution in the field of advanced NSCLC, notably by improving the prognosis of stage IV disease. It gave rise to a whole new population of patients, the long-term survivors, who did not exist in that setting before the immunotherapy era. Nevertheless, here we showed that some subgroups of patients do not derive a benefit from these drugs, particularly patients with EGFR- or HER2-mutated or ALK-rearranged NSCLC. On the other hand, BRAF- and MET-mutated NSCLC seem to be as sensitive to anti-PD1/PD-L1 immunotherapy as unselected NSCLC. Patient selection using validated biomarkers and inclusion in clinical trials are key to improve their outcome. Biomarker studies beyond PDL-1 expression are needed and achievable in EGFR, ALK, BRAF, HER2, RET, NTRK, KRAS G12C, and MET-mutated NSCLC patients.

Author Contributions: Conceptualization, validation and writing—review and editing, all authors; writing—original draft preparation, E.D. and F.G.; supervision, F.G. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: F.G. reports personal fees from BMS, MSD/MERCK US, ASTRA ZENECA, BOEHRINGER INGELHEIM, Amgen, and ROCHE, and non-financial support from BMS, BOEHRINGER INGELHEIM, CHUGAI, and PFIZER, outside the submitted work.

References
1. Hanahan, D.; Weinberg, R.A. Hallmarks of Cancer: The Next Generation. Cell 2011, 144, 646–674. [CrossRef] [PubMed]
2. Noone, A.-M.; Cronin, K.A.; Altekruse, S.F.; Howlader, N.; Lewis, D.R.; Petkov, V.I.; Penberthy, L. Cancer Incidence and Survival Trends by Subtype Using Data from the Surveillance Epidemiology and End Results Program, 1992–2013. Cancer Epidemiol. Prev. Biomark. 2017, 26, 632–641. [CrossRef] [PubMed]
3. Ridge, C.A.; McErlean, A.M.; Ginsberg, M.S. Epidemiology of lung cancer. In Seminars in Interventional Radiology; Thieme Medical Publishers: New York, NY, USA, 2013; Volume 30, pp. 93–98.
4. Thun, M.J.; Hannan, L.M.; Adams-Campbell, L.L.; Boffetta, P.; Buring, J.E.; Feskanich, D.; Flanders, W.D.; Lee, S.H.; Katanoda, K.; Kolonel, L.N.; et al. Lung Cancer Occurrence in Never-Smokers: An Analysis of 13 Cohorts and 22 Cancer Registry Studies. PloS Med. 2008, 5, e185. [CrossRef] [PubMed]

5. Cruz, C.S.D.; Tanoue, L.T.; Mathay, R.A. Lung cancer: Epidemiology, etiology, and prevention. Clin. Chest Med. 2011, 32, 605–644. [CrossRef]

6. Pikor, L.A.; Ramaraine, V.R.; Lam, S.; Lam, W.L. Genetic alterations defining NSCLC subtypes and their therapeutic implications. Lung Cancer 2013, 82, 179–189. [CrossRef]

7. Chen, Z.; Fillmore, C.M.; Hammerman, P.S.; Kim, C.F.; Wong, K-K. Non-small-cell lung cancers: A heterogeneous set of diseases. Nat. Rev. Cancer 2014, 14, 535–546. [CrossRef]

8. Barlesi, F.; Mazieres, J.; Merlio, J.-P.; Debelleuvre, D.; Mosser, J.; Lena, H.; Ouaif, L.H.; Besse, B.; Rouquette, I.; Westeel, V.; et al. Routine molecular profiling of patients with advanced non-small-cell lung cancer: Results of a 1-year nationwide programme of the French Cooperative Thoracic Intergroup (IFCT). Lancet 2016, 387, 1415–1426. [CrossRef]

9. Imyanitov, E.N.; Iyevleva, A.G.; Levchenko, E.V. Molecular testing and targeted therapy for non-small cell lung cancer: Current status and perspectives. Crit. Rev. Oncol. 2021, 157, 103194. [CrossRef]

10. Zhou, C.; Wu, Y.-L.; Chen, G.; Feng, J.; Liu, X.-Q.; Wang, C.; Zhang, S.; Wang, J.; Zhou, S.; Ren, S.; et al. Erlotinib versus chemotherapy as first-line treatment for patients with EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): A multicentre, open-label, randomised, phase 3 study. Lancet Oncol. 2011, 12, 735–742. [CrossRef]

11. Mok, T.S.; Wu, Y.L.; Thongprasert, S.; Yang, C.H.; Chu, D.T.; Saijo, N. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N. Engl. J. Med. 2009, 361, 947–957. [CrossRef]

12. Park, K.; Tan, E.H.; O’Byrne, K.; Zhang, L.; Boyer, M.; Mok, T.; Hirsh, V.; Yang, J.C.-H.; Lee, K.H.; Lu, S.; et al. Afatinib versus gefitinib as second-line treatment of EGFR mutation-positive non-small cell lung cancer (ARCHER 1050): A randomised, open-label, phase 3 trial. Lancet Oncol. 2016, 17, 577–589. [CrossRef]

13. Wu, Y.-L.; Cheng, Y.; Zhou, X.; Lee, K.H.; Nakagawa, K.; Niho, S.; Tsujii, F.; Linke, R.; Rosell, R.; Corral, J.; et al. Dacomitinib versus gefitinib as second-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): A randomised, open-label, phase 3 trial. Lancet Oncol. 2017, 18, 1454–1466. [CrossRef]

14. Shi, Y.; Zhang, L.; Liu, X.; Zhou, C.; Zhang, S.; Wang, D.; Li, Q.; Qin, S.; Hu, C.; Zhang, Y.; et al. Icotinib versus gefitinib in previously treated advanced non-small-cell lung cancer (ICOGEN): A randomised, double-blind phase 3 non-inferiority trial. Lancet Oncol. 2013, 14, 953–961. [CrossRef]

15. Soria, J.-C.; Ohe, Y.; Vansteenkiste, J.; Reungwetwattana, T.; Chewaskulyong, B.; Lee, K.H.; Dechaphunkul, A.; Imamura, F.; Nogami, N.; Kurata, T.; et al. Osimertinib in UntreatedEGFR-Mutated Advanced Non–Small-Cell Lung Cancer. N. Engl. J. Med. 2018, 378, 137–145. [CrossRef]

16. Riely, G.J.; Neal, J.W.; Camidge, D.R.; Spira, A.I.; Piotrowska, Z.; Costa, D.B.; Ahn, J.S.; Kim, D.-W.; Coudert, B.; Patel, J.D.; et al. lorlatinib in patients with ALK-positive non-small-cell lung cancer: Results from a global phase 2 study. Lancet Oncol. 2018, 19, 1654–1667. [CrossRef]

17. Le, X.; Goldman, J.W.; Clarke, J.M.; Tchekmedyian, N.; Piotrowska, Z.; Chu, D.; Bhat, G.; Lebel, F.M.; Socinski, M.A. Poziotinib skipping mutation-positive non-small-cell lung cancers with response to crizotinib and cabozantinib. Anti Cancer Drugs 2019, 30, 537–541. [CrossRef]
26. Wolf, J.; Seto, T.; Han, J.Y.; Reguart, N.; Garon, E.B.; Groen, H.J.; Tan, D.S.W.; Hida, T.; de Jonge, M.; Orlov, S.V.; et al. Capmatinib in MET Exon 14-Mutated or MET-Amplified Non-Small-Cell Lung Cancer. *N. Engl. J. Med.* 2020, 383, 944–957. [CrossRef]

27. Paik, P.K.; Felip, E.; Veillon, R.; Sakai, H.; Cortot, A.B.; Garassino, M.C.; Mazieres, J.; Viteri, S.; Senellart, H.; Van Meerbeeck, J.; et al. Tepotinib in Non–Small-Cell Lung Cancer with MET Exon 14 Skipping Mutations. *N. Engl. J. Med.* 2020, 383, 931–943. [CrossRef]

28. Lu, S.; Fang, J.; Li, X.; Cao, L.; Zhou, J.; Guo, Q.; Liang, Z.; Cheng, Y.; Jiang, L.; Yang, N.; et al. Phase II study of savolitinib in patients (pts) with pulmonary sarcomatoid carcinoma (PSC) and other types of non-small cell lung cancer (NSCLC) harboring MET exon 14 skipping mutations (METex14+). *J. Clin. Oncol.* 2020, 38 (Suppl. 15), 9519. [CrossRef]

29. Hyman, D.M.; Puzanov, I.; Subbiah, V.; Faris, J.E.; Chau, I.; Blay, J.-Y.; Wolf, J.L.; Raje, N.S.; Diamond, E.L.; Hollebecque, A.; et al. Vemurafenib in Multiple Nonmelanoma Cancers with BRAF V600 Mutations. *N. Engl. J. Med.* 2015, 373, 726–736. [CrossRef]

30. Planchard, D.; Kim, T.M.; Mazieres, J.; Quoix, E.; Riely, G.; Barlesi, F. Dabrafenib in patients with BRAF(V600E)-positive advanced non-small-cell lung cancer: A single-arm, multicentre, open-label, phase 2 trial. *Lancet Oncol.* 2016, 17, 642–650. [CrossRef]

31. Planchard, D.; Smit, E.F.; Groen, H.J.M.; Mazieres, J.; Bessè, B.; Helland, A. Dabrafenib plus trametinib in patients with previously untreated BRAF(V600E)-mutant non-small-cell lung cancer: An open-label, phase 2 trial. *Lancet Oncol.* 2017, 18, 1307–1316. [CrossRef]

32. Mazieres, J.; Peters, S.; Lepage, B.; Cortot, A.B.; Barlesi, F.; Beau-Faller, M. Lung cancer that harbors an HER2 mutation: Epidemiologic characteristics and therapeutic perspectives. *J. Clin. Oncol.* 2013, 31, 1997–2003. [CrossRef] [PubMed]

33. Mazieres, J.; Barlesi, F.; Fillieron, T.; Besse, B.; Monnet, I.; Beau-Faller, M.; Peters, S.; Dansin, E.; Früh, M.; Pless, M.; et al. Lung cancer patients with HER2 mutations treated with chemotherapy and HER2-targeted drugs: Results from the European EUHER2 cohort. *Ann. Oncol.* 2016, 27, 281–286. [CrossRef] [PubMed]

34. Hyman, D.M.; Piha-Paul, S.A.; Won, H.; Rodon, J.; Saurat, C.; Shapiro, G.I.; Juric, D.; Quinn, D.I.; Moreno, V.; Doger, B.; et al. HER kinase inhibition in patients with HER2- and HER3-mutant cancers. *Nat. Cell Biol.* 2018, 554, 189–194. [CrossRef] [PubMed]

35. Lai, W.V.; Lebas, L.; Barnes, T.A.; Milia, J.; Ni, A.; Gautschi, O.; Peters, S.; Ferrara, R.; Plodkowski, A.J.; Kavanagh, J.; et al. Aftinatinib in patients with metastatic or recurrent HER2-mutant lung cancers: A retrospective international multicentre study. *Eur. J. Cancer* 2019, 109, 28–35. [CrossRef]

36. Lung Cancer Patients with HER2 Mutations Treated with Chemotherapy and HER2-Targeted Drugs: Results from the European EUHER2 Cohort—Annals of Oncology [Internet]. Available online: https://www.annalsofoncology.org/article/S0923-7534(19)35565-6/fulltext (accessed on 10 June 2021).

37. Shaw, A.T.; Ou, S.-H.I.; Bang, Y.-J.; Camidge, D.R.; Solomon, B.J.; Salgia, R.; Riely, G.J.; Varella-Garcia, M.; Shapiro, G.I.; Costa, D.B.; et al. Crizotinib in ROS1-Rearranged Non–Small-Cell Lung Cancer. *N. Engl. J. Med.* 2014, 371, 1963–1971. [CrossRef]

38. Lim, S.M.; Kim, H.R.; Lee, J.S.; Lee, K.H.; Lee, Y.G.; Min, Y.J. Phase II Study of Ceritinib in Patients With Non-Small-Cell Lung Cancer Harboring ROS1 Rearrangement. *J. Clin. Oncol.* 2017, 35, 2613–2618. [CrossRef]

39. Shaw, A.T.; Felip, E.; Bauer, T.M.; Besse, B.; Navarro, A.; Postel-Vinay, S.; Gainor, J.F.; Johnson, M.; Dietrich, J.; James, L.P.; et al. Lorlatinib in non-small-cell lung cancer with ALK or ROS1 rearrangement: An international, multicentre, open-label, single-arm first-in-man phase 1 trial. *Lancet Oncol.* 2017, 18, 1590–1599. [CrossRef]

40. Guisier, F.; Piton, N.; Salaun, M.; Thiberville, L. ROS1-rearranged NSCLC With Secondary Resistance Mutation: Case Report and Current Perspectives. *Clin. Lung Cancer* 2020, 21, e593–e596. [CrossRef]

41. Drilon, A.; Siena, S.; Dzidziuszko, R.; Barlesi, F.; Krebs, M.G.; Shaw, A.T.; de Braud, F.; Rolfo, C.; Ahn, M.-J.; Wolf, J.; et al. Entrectinib in patients with advanced non-small cell lung cancer harboring RET rearrangement: A phase II clinical trial. *Ann. Oncol.* 2017, 28, 292–297. [CrossRef]

42. Drilon, A.; Rekhtman, N.; Arcila, M.; Wang, L.; Ni, A.; Albano, M.; Van Voorthuysen, M.; Somwar, R.; Smith, R.S.; Montecalvo, J.; et al. Cabozantinib in patients with advanced RET -rearranged non-small-cell lung cancer: An open-label, single-centre, phase 2, single-arm trial. *Lancet Oncol.* 2016, 17, 1653–1660. [CrossRef]

43. Oxnard, G.; Subbiah, V.; Park, K.; Bauer, T.; Wirth, L.; Velcheti, V.; Shah, M.; Besse, B.; Boni, V.; Reckamp, K.; et al. OA12.07 Clinical Activity of LOXO-292, a Highly Selective RET Inhibitor, in Patients with RET Fusion+ Non-Small Cell Lung Cancer. *J. Thorac. Oncol.* 2018, 13, S349–S350. [CrossRef]

44. Gainer, J.F.; Lee, D.H.; Curigiano, G.; Doebbe, R.C.; Kim, D.-W.; Baik, C.S.; Tan, D.S.-W.; Lopes, G.; Gadgeel, S.M.; Cassier, P.A.; et al. Clinical activity and tolerability of BLU-667, a highly potent and selective RET inhibitor, in patients (pts) with advanced RET-fusion+ non-small cell lung cancer (NSCLC). *J. Clin. Oncol.* 2019, 37 (Suppl. 15), 9008. [CrossRef]

45. Drilon, A.; Oxnard, G.R.; Tan, D.S.; Loong, H.H.; Johnson, M.; Gainer, J.; McCoach, C.E.; Gautschi, O.; Besse, B.; Cho, B.C.; et al. Efficacy of Selpercatinib in RET-Fusion–Positive Non–Small-Cell Lung Cancer. *N. Engl. J. Med.* 2020, 383, 813–824. [CrossRef]

46. Doebbe, R.C.; Drilon, A.; Paz-Ares, L.; Siena, S.; Shaw, A.T.; Farago, A.F.; Blakely, C.M.; Seto, T.; Cho, B.C.; Tosi, D.; et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: Integrated analysis of three phase 1–2 trials. *Lancet Oncol.* 2020, 21, 271–282. [CrossRef]
48. Roth, J.A.; Carlson, J.J.; Xia, F.; Williamson, T.; Sullivan, S.D. The Potential Long-Term Comparative Effectiveness of Larotrectinib and Entrectinib for Second-Line Treatment of TRK Fusion-Positive Metastatic Lung Cancer. J. Manag. Care Spec. Pharm. 2020, 26, 981–986. [CrossRef]

49. Hyman, D.; Kummer, S.; Farago, A.; Geographer, B.; Mau-Sorensen, M.; Taylor, M.; Garralda, E.; Nagasubramanian, R.; Natheson, M.; Song, L.; et al. Abstract CT1271: Phase I and expanded access experience of LOXO-195 (BAY 2731954), a selective next-generation TRK inhibitor (TRKi). Cancer Res. 2019, 79 (Suppl. 13), CT127.

50. Hong, D.S.; Fakih, M.G.; Strickler, J.H.; Desai, J.; Durm, G.A.; Shapiro, G.I.; Falchook, G.S.; Price, T.J.; Sacher, A.; Denlinger, C.S.; et al. KRASG12C Inhibition with Sotorasib in Advanced Solid Tumors. N. Engl. J. Med. 2020, 383, 1207–1217. [CrossRef]

51. Riely, G.J.; Ou, S.I.; Rybkin, I.; Spira, A.; Papadopoulos, K.; Sabari, J.K.; Johnson, M.; Heist, R.S.; Bazhenova, L.; Barve, M.; et al. 99O PR KRYSIT-1: Activity and preliminary pharmacodynamic (PD) analysis of adagrasib (MRTX849) in patients (Pts) with advanced non–small cell lung cancer (NSCLC) harboring KRASG12C mutation. J. Thorac. Oncol. 2021, 16, S751–S752. [CrossRef]

52. Shi, Y.; Au, J.S.; Thongprasert, S.; Sririnivasan, S.; Tsai, C.M.; Khoa, M.T. A prospective, molecular epidemiology study of EGFR mutations in Asian patients with advanced non-small-cell lung cancer of adenocarcinoma histology (PIONEER). J. Thorac. Oncol. 2014, 9, 154–162. [CrossRef]

53. Ribas, A. Tumor Immunotherapy Directed at PD-1. N. Engl. J. Med. 2012, 366, 2517–2519. [CrossRef]

54. Carbone, D.P.; Reck, M.; Paz-Ares, L.; Creeylan, B.; Horn, L.; Steins, M. First-Line Nivolumab in Stage IV or Recurrent Non-Small-Cell Lung Cancer. N. Engl. J. Med. 2017, 376, 2415–2426. [CrossRef]

55. Reck, M.; Rodriguez-Abreu, D.; Robinson, A.G.; Hui, R.; Csoszi, T.; Fülöp, A.; Gottfried, M.; Peled, N.; Tafreshi, A.; Cuffe, S.; et al. Updated Analysis of KEYNOTE-024: Pembrolizumab Versus Platinum-Based Chemotherapy for Advanced Non–Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score of 50% or Greater. J. Clin. Oncol. 2019, 37, 537–546. [CrossRef]

56. Mok, T.S.K.; Wu, Y.-L.; Kudaba, I.; Kowalski, D.M.; Cho, B.C.; Turna, H.Z.; Castro, G.; Sriniminnimit, V.; Laktionov, K.K.; Bondarenko, I.; et al. Pembrolizumab versus chemotherapy for previously untreated, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): A randomised, open-label, controlled trial. Lancet 2019, 393, 1819–1830. [CrossRef]

57. Herbst, R.S.; Giaccone, G.; De Marinis, F.; Reinmuth, N.; Vignnegre, A.; Barrios, C.H.; Morise, M.; Felip, E.; Andric, Z.; Geater, S.; et al. Atezolizumab for First-Line Treatment of PD-L1–Selected Patients with NSCLC. N. Engl. J. Med. 2020, 383, 1328–1339. [CrossRef]

58. Rizvi, N.A.; Cho, B.C.; Reinmuth, N.; Lee, K.H.; Luft, A.; Ahn, M.-J.; van den Heuvel, M.M.; Cobo, M.; Vicente, D.; Smolin, A.; et al. Durvalumab With or Without Tremelimumab as Standard Chemotherapy in First-line Treatment of Metastatic Non-Small Cell Lung Cancer: The MYSTIC Phase 3 Randomized Clinical Trial. JAMA Oncol. 2020, 6, 661–674. [CrossRef]

59. Sezer, A.; Kiliçkap, S.; Gümüş, M.; Bondarenko, I.; Özgüroğlu, M.; Gogishvili, M.; Turk, H.M.; Cicin, I.; Bentsion, D.; Gladkov, O.; et al. Cemiplimab monotherapy for first-line treatment of advanced non-small-cell lung cancer with PD-L1 of at least 50%: A multicentre, open-label, global, phase 3, randomised, controlled trial. Lancet 2021, 397, 592–604. [CrossRef]

60. Brahmer, J.; Reckamp, K.L.; Baas, P.; Crino, L.; Eberhardt, W.E.; Poddubskaya, E. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N. Engl. J. Med. 2015, 373, 123–135. [CrossRef]

61. Borghaei, H.; Paz-Ares, L.; Horn, L.; Spigel, D.R.; Steins, M.; Ready, N.E.; Chow, L.Q.; Vokes, E.E.; Felip, E.; Holgado, E.; et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N. Engl. J. Med. 2015, 373, 1627–1639. [CrossRef]

62. Herbst, R.S.; Baas, P.; Kim, D.-W.; Felip, E.; Perez-Gracia, J.L.; Han, J.-Y.; Molina, J.; Kim, J.-H.; Arvis, C.D.; Ahn, M.-J.; et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): A randomised controlled trial. Lancet 2016, 387, 1540–1550. [CrossRef]

63. Rittmeyer, A.; Barlesi, F.; Waterkamp, D.; Park, K.; Ciardiello, F.; von Pawel, J.; Gadgeel, S.M.; Hida, T.; Kowalski, D.; Dols, M.C.; et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): A phase 3, open-label, multicentre randomised controlled trial. Lancet 2017, 389, 255–265. [CrossRef]

64. Rizvi, H.; Sanchez-Vega, F.; La, K.; Chatila, W.; Jonsson, P.; Halpenny, D.; Plodkowski, A.; Long, N.; Sauter, J.L.; Rekhtman, N.; et al. Molecular Determinants of Response to Anti–Programmed Cell Death (PD-1) and Anti–Programmed Death-Ligand 1 (PD-L1) Blockade in Patients With Non–Small Cell Lung Cancer Profiled With Targeted Next-Generation Sequencing. J. Clin. Oncol. 2018, 36, 633–641. [CrossRef] [PubMed]

65. Bylicki, O.;Paleiron, N.; Margery, J.; Giusier, F.; Vergnenerge, A.; Robinet, G.; Auliac, J.-B.; Gervais, R.; Chouaid, C. Targeting the PD-1/PD-L1 Immune Checkpoint in EGFR-Mutated or ALK-Translocated Non-Small-Cell Lung Cancer. Target. Oncol. 2017, 12, 563–569. [CrossRef] [PubMed]

66. Rech, A.J.; Vanderheide, R.H. Dynamic Interplay of Oncogenes and T Cells Induces PD-L1 in the Tumor Microenvironment. Cancer Discov. 2013, 3, 1330–1332. [CrossRef]

67. Chen, N.; Fang, W.; Zhan, J.; Hong, S.; Tang, Y.; Kang, S.; Zhang, Y.; He, X.; Zhou, T.; Qin, T.; et al. Upregulation of PD-L1 by EGFR Activation Mediates the Immune Escape in EGFR-Driven NSCLC: Implication for Optional Immune Targeted Therapy for NSCLC Patients with EGFR Mutation. J. Thorac. Oncol. 2015, 10, 910–923. [CrossRef]

68. Azuma, K.; Ota, K.; Kawahara, A.; Hattori, S.; Iwama, E.; Harada, T.; Matsumoto, K.; Takayama, K.; Takamori, S.; Kage, M.; et al. Association of PD-L1 overexpression with activating EGFR mutations in surgically resected nonsmall-cell lung cancer. Ann. Oncol. 2014, 25, 1935–1940. [CrossRef]

Int. J. Mol. Sci. 2021, 22, 6288
11 of 13
