Neoadjuvant immunotherapy in early stage non-small cell lung cancer

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Abstract: Cancer immunotherapies targeting CTLA-4 and PD-1/PD-L1 relieve tumour induced immune suppression and induce durable tumour regression. When used alone or in combination with other modalities, immune checkpoint inhibitors have had a remarkable clinical impact on the treatment of multiple tumour sites including non-small cell lung cancer (NSCLC). This makes neoadjuvant immunotherapy an attractive option for use in early stage NSCLC. Currently, immunotherapy is used in the UK in both a curative and palliative setting. The use of neoadjuvant immunotherapy has the potential benefit of pathological downstaging prior to surgery, which may facilitate radical approaches to surgery—potentially conferring an improvement in overall survival. This literature review examines current literature and evidence on the use of immunotherapy prior to surgery, both as a single agent and in combination with chemotherapy. We conclude that neoadjuvant immunotherapy is a safe and feasible option for patients with resectable early stage NSCLC. Further investigation is required to determine whether a combined approach with chemotherapy or single agent immunotherapy is superior. Confirmatory Phase III clinical trials are ongoing to assess longer clinical impact on event-free survival (EFS), disease-free survival (DFS) and OS. Predictive and prognostic biomarkers are also needed in this setting, and ongoing work is being conducted to investigate this further.

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Introduction

Cancer immunotherapies targeting CTLA-4 and PD-1/PD-L1 relieve tumour induced immune suppression and induce durable tumour regression. When used alone or in combination (with other immunotherapy or chemotherapy or targeted therapy), immune checkpoint inhibitors have had a remarkable impact on the treatment of multiple tumour sites; including melanoma, Hodgkin's lymphoma, Merkel cell carcinoma, renal cell carcinoma, bladder cancer and notably non-small cell lung cancer (NSCLC) (1).

Current role of immune checkpoint inhibitors in treatment of NSCLC

Currently, immunotherapy with checkpoint inhibitors is approved for use in the treatment of NSCLC both in curative and palliative setting following results showing improvement in overall survival from Phase III clinical trials. In the curative setting, Durvalumab [an anti-PD-L1 monoclonal antibody (Mab)] following standard chemoradiation (CRT) is approved for use by both the Food and Drug Agency (FDA) and European Medicine Agency (EMA) in patients with

stage III unresectable NSCLC following the results of the PACIFIC study, which showed an improvement of median overall survival (OS) of 28.3 months with Durvalumab when compared to 16.2 months with placebo (2). In the metastatic setting, Ipilimumab (an anti-CTLA-4 MAb) and Nivolumab (an anti-PD-1 MAb) combination, Pembrolizumab (an anti-PD-1 MAb) and Atezolizumab (an anti-PD-L1 MAb) are all approved as first line treatment of advanced unresectable NSCLC either on their own or in combination with chemotherapy. Ipilimumab and Nivolumab combination was approved following the results of CHECKMATE 227 trial (as single agent) (3) and CHECKMATE 9LA (in combination with chemotherapy) (4). Single agent use of Pembrolizumab was approved in patients with PD-L1 tumour expression of >50% following the results of KEYNOTE 024 (5) making it the first chemotherapy sparing treatment in NSCLC without a driver mutation. For patients with PD-L1 tumour expression <50%, Pembrolizumab is approved for use in combination with chemotherapy following the results of KEYNOTE 407 (in squamous cell histology) (6) and KEYNOTE 189 (in non-squamous cell histology) (7). Single agent use of Atezolizumab was approved based on the positive results of the IMPOWER 110 trial (8) whilst its use in combination with chemotherapy was approved following the results of IMPOWER 130 (9) and IMPOWER 150 trials (10). Single agent Pembrolizumab, Nivolumab and Atezolizumab are also approved for use as second line treatment in advanced NSCLC based on the KEYNOTE 010 (11), CHECKMATE 017 (12), CHECKMATE 057 (13) and OAK (14) trials respectively.

Five-year overall survival of resected early stage NSCLC decreases from 92% to 24% with increasing stage (15). With its proven efficacy in the metastatic setting, exploring the use of immunotherapy with checkpoint inhibitors in early stage disease to improve clinical outcome in these potentially curative patients is currently a major area of interest in thoracic oncology.

Summary of evidence for neoadjuvant treatment

Neoadjuvant chemotherapy is a treatment option in the management of early stage NSCLC. A 2014 meta-analysis analysed 15 randomised controlled trials involving 2,385 demonstrated a 5-year OS benefit of 5% OS (from 40% to 45%) of chemotherapy when given before surgery. Recurrence-free survival was significantly in favour of neoadjuvant chemotherapy. 92% of all patients in this meta-analysis had stages IB to IIIA disease (16). Toxic effects could not be assessed in this meta-analysis. However, the authors did not find any difference in mortality within 30 days of surgery between treatment and control arms in nine of the trials analysed in the meta-analysis. Based on all 15 trials, the authors also did not identify a deleterious effect of neoadjuvant chemotherapy on mortality within six months of randomisation.

Potential benefits of neoadjuvant immunotherapy in early stage NSCLC

With this in mind, it is unsurprising that the idea of neoadjuvant immunotherapy in early stage NSCLC is appealing. Immunotherapy may confer superior clinical outcome if used in the neoadjuvant setting as opposed to using it as adjuvant therapy. A concern with adjuvant treatment is that agents which target PD-1/PD-L1 axis require a dynamic interaction between CD8+ T-cells and antigen presenting cells. Thus, it makes biological sense that neoadjuvant treatment, when the tumour and locoregional lymph nodes are still present will allow dynamic immune related interactions, and this may be a more rational approach to therapy. There also exists uncertainty as to whether these cellular interactions will occur sufficiently in surgically treated patients with micro-metastatic disease (15). Currently, there is no clinical data to confirm clinical benefit of giving adjuvant immunotherapy following resection of early stage NSCLC, although these clinical trials are ongoing.

Pre-clinical data has suggested that treatment with PD-L1 inhibitors prior to the removal of tumour could improve overall survival in mice, as there is a production of stronger tumour specific CD8 and T-cell responses. Small clinical trials in other tumour sites such as glioma (17) and melanoma (18) have demonstrated an overall survival benefit of neoadjuvant immunotherapy in comparison to adjuvant treatment (19). It is hypothesised that use of immune checkpoint inhibition stimulates neoantigens from dying tumour cells and promotes the priming and expansion of neoantigen specific T-cells in the tumour prior to surgical resection, which translated into a greater therapeutic efficacy of neoadjuvant compared to adjuvant immunotherapy following tumour resection (20).

From a surgical point of view, neoadjuvant immunotherapy is appealing in the potential to facilitate pathological downstaging, which may enable a more radical approach to surgery, thereby improving overall survival. The use of major pathological response (MPR)

as a surrogate end point for survival is an area receiving much attention. First described in the chemotherapy era, patients with regression grade IIB or III (described as <10% vital tumour tissue in their post neoadjuvant chemotherapy resection specimen) had a significantly longer overall survival that those with lower regression grades (21).

Single agent neoadjuvant immunotherapy trials

Several studies describing the use of single agent immunotherapy have been reported. A small retrospective analysis (22) of 19 patients who underwent lung resection within six months of treatment with checkpoint inhibitors (Nivolumab, Pembrolizumab or Ipilimumab) in unresectable or metastatic cancer demonstrated that this was a safe approach with the all but one complications were of grades 1 or 2 and high rate of R0 resection (95%) (23).

The safety and feasibility of neoadjuvant Nivolumab in patients with untreated stages I to IIIA NSCLC was examined in a phase I trial (24) of 22 patients, 20 of whom underwent resection post immunotherapy. In this study, patients underwent neoadjuvant therapy with two cycles of Nivolumab, four and two weeks before resection. In its initial report, there were no delays to surgical resection and there was no operative mortality. Morbidity occurred in 50% of patients with the most common postoperative complication was atrial arrhythmia in 30% of patients. Overall, rates of perioperative morbidity were similar to those previously reported in other trials, but rates of atrial arrhythmia in this trial were higher than in other trials compared. It is unknown whether this difference was treatment related or due to the small sample size. Technically, more than half (54%) of the video-assisted thoracoscopic surgery/robotic cases were converted to thoracotomy, often because of hilar inflammation and fibrosis (23).

A subsequent report of the study (24) revealed adverse effects of any grade occurred in 23% of patients with only one event at grade 3 or higher. MPR occurred in up to 45% of resected tumours. At median follow up of 30 months, 15 of 20 patients are disease-free and alive. Two patients have died with one patient died from relapsed disease. Median recurrence free survival (RFS) has not been reached with the 24-months RFS rate is 69%.

The benefit of neoadjuvant Atezolizumab in patients with untreated stages IB to IIIB NSCLC was examined in LCMC3, a phase II trial with a planned recruitment of 180 patients (25). In this study, patients underwent neoadjuvant therapy with two cycles of Atezolizumab before undergoing resection. The primary endpoint for this study is MPR with secondary endpoints include safety and correlation of response with PD-L1 expression, tumour mutation burden (TMB) and gene expression signatures. Following an interim efficacy analysis, results of the first 101 patients were reported. Ninety patients had surgery. Excluding patients who had driver mutations, MPR rate was 18% with four patients (5%) had pathological complete response (pCR). There were two treatment-unrelated grade 5 adverse events including cardiac death post-surgical resection and death due to disease progression) with 6% treatment-related grade 3 or 4 adverse effects. The authors concluded that Atezolizumab in the neoadjuvant setting was well tolerated with encouraging pCR and MPR rates.

The PRINCEPS study (26) examined one cycle neoadjuvant Atezolizumab in 30 patients with untreated stages I to IIIB NSCLC with a primary endpoint of 2-month tolerance rate. The secondary endpoints for this study include toxicities and postoperative morbidities as well as pCR, disease-free survival (DFS) and OS rates. 23% of patients had complication within one month after surgery. MPR rate was 14% with 41% of patients had pathological response 50%. The authors concluded that Atezolizumab in the neoadjuvant setting was safe and did not impair surgery.

The safety and scheduling of neoadjuvant Pembrolizumab in patients with untreated stages I to II NSCLC was examined in a phase I trial, MK3475-223 (27). All patients received 200 mg Pembrolizumab. The trials objectives include to determine safety, recommended phase 2 dose/schedule as well as pathological and radiological responses. In updated results, no dose limiting toxicity occurred. Ten patients received two cycles of neo-adjuvant Pembrolizumab with 40% MPR. Interestingly, the authors found that all of the MPR cases had a relatively long interval from first dose of Pembrolizumab till surgery. The authors concluded that neoadjuvant Pembrolizumab is safe and feasible with a promising sign of efficacy is seen and achieving MPR might require a longer first treatment to surgery interval.

A phase II trial, NEOSTAR randomised patients with stages I to IIIA NSCLC to receive either three doses of neoadjuvant Nivolumab or neoadjuvant Ipilimumab and Nivolumab combination given two weeks apart (28). Forty-four patients were randomised with 23 patients received Nivolumab and 21 patients received combination treatment. Only 7% received < three scheduled doses due to treatment-related adverse events. Thirty-four patients had surgery post immunotherapy with 7 patients not resected and three

patients pending surgery. MPR was achieved in 24% of patients, of which 15% were pCR. Among 34 resected patients, MPR rate was 29%. Median percentage of viable tumour was lower post combination treatment compared to Nivolumab (P=0.097). Treatment-related grade 3 to 5 adverse events included one death due to broncho-pulmonary fistula post steroid-treated pneumonitis (in the Nivolumab arm), pneumonia, hypoxia, hypermagnesemia and diarrhoea.

A single-arm Phase II trial (29), IoNESCO IFCT-1601 investigated the use of three doses of neoadjuvant Durvalumab in patients with resectable stages II to IIIA non-N2 NSCLC. Fifty patients were enrolled with 46 patients received neoadjuvant treatment. 89.1% of patients achieved the study's primary endpoint of percentage of complete surgical resection (R0) that is considered as a pre-specified trial efficacy boundary. MPR rate was 14% and was associated with the best DFS. The 12-month DFS and OS were 78.2% and 89.1% respectively. The study was prematurely stopped because of an excess in 90-day post-operative mortality with 4 deaths (9%). Mortality were due to post-operative complications most likely due to comorbidities and were not direct to Durvalumab toxicity.

A single-arm Phase II trial, TOP1201 investigated the use of three cycles neoadjuvant platinum doublet chemotherapy with Ipilimumab added in the last two cycles in patients with resectable stages IB to IIIA NSCLC (30). Twenty-four treatment-naive patients were enrolled and received neoadjuvant treatment. Two patients had a delay in surgery of 4 and 5 weeks due to Ipilimumab-related diarrhoea. Thirteen patients were treated with chemotherapy and Ipilimumab, followed by surgical resection less than 12 weeks after neoadjuvant therapy. Forty-six percent of patients experienced treatment related grade 3 or 4 or adverse events. Immune-related adverse events felt to be related to Ipilimumab were grade 2 pneumonitis (4%), grade 3 adrenal insufficiency (17%), and grade 3 diarrhoea/colitis (13%). Following neoadjuvant treatment, 58% of patients had partial response, 33% had stable disease and 8% had progressive disease. Median OS was 29.2 months whereas 12-months OS was 82.2% and 24-month OS was 73.0% respectively. There have been no deaths at 24 months for the patients who underwent surgical resection of their lung cancer.

Combination neoadjuvant immunotherapy trials

The argument for combining immunotherapy with other treatment modalities including chemotherapy in the neoadjuvant setting has also been raised in light of its efficacy in the treatment of advanced NSCLC. Immunotherapy and chemotherapy combination have been assessed with several clinical trials.

A phase II open label trial investigated the use of neoadjuvant Atezolizumab in combination chemotherapy in stages IB to IIIA NSCLC. The study enrolled 30 patients where they were treated to up to 4 cycles of Atezolizumab in combination carboplatin and nab-paclitaxel chemotherapy given every three weeks before undergoing surgical resection (31). Seventy-seven percent of these patients had stage IIIA disease. Neoadjuvant combination chemotherapy with immunotherapy did not seem to have an adverse effect on treatment delays. 97% proceeded to surgery with 87% underwent successful R0 resection and 57% of patients had an MPR. Pathological responses were observed regardless of tumour PD-L1 expression. Ten patients (33%) had pCR with six of whom had stage IIIA disease at presentation. At median follow up of 12.9 months, 63% of all 30 patients, and 73% of those who had a successful R0 resection were alive. 30% had disease recurrence and 7% had suspected disease progression on treatment. Longer follow up results revealed median DFS in patients who had an MPR of more than 90% was 34·5 months compared with 14·3 months in patients who had an MPR of less than 90%.

With regards to toxicity, 97% of patients completed at least three cycles of treatment with all three drugs, 67% required a dose reduction of carboplatin or nab-paclitaxel or both. Seventeen percent proceeded to surgery early due to treatment toxicity, four patients due to myelosuppression and one patient due to neuropathy. Treatment related adverse effects included neutropenia (87%) anaemia (77%) thrombocytopenia (63%) fatigue (57%) alopecia (47%) and nausea (43%). However, these findings are consistent with side effects previously published data on carboplatin and nab-paclitaxel in metastatic NSCLC. Similarly, immune related adverse effects were as expected, with perioperative morbidity reported to be similar to previously published data in neoadjuvant chemotherapy alone. One patient died of respiratory failure secondary to pneumonia after surgery, but this was deemed unrelated to study treatments. Most common treatment-related grade 3 or 4 adverse events were neutropenia (50%), increased alanine aminotransferase (ALT) concentration, increased aspartate aminotransferase (AST) concentration and thrombocytopenia (7% each). Serious treatment-related adverse events included one (3%) patient with grade 3 febrile neutropenia, one (3%) patient

with grade 4 hyperglycaemia and one (3%) patient with grade 2 bronchopulmonary haemorrhage. There were no treatment-related deaths.

A phase II single arm trial, NADIM investigated the use of three cycles of neoadjuvant Nivolumab in combination paclitaxel and carboplatin given at three-weekly intervals in patients with stage IIIA N2 NSCLC followed by adjuvant Nivolumab for one year (32). The study aims to recruit 46 patients. The primary endpoint is progression-free survival (PFS) at 24 months. An initial report included 30 patients with 13 patients underwent surgery. Nivolumab and chemotherapy combination was well tolerated and surgery was not delayed in any patient. None of the patients withdrew from the study preoperatively due to progression or toxicity. Of the 13 surgeries performed, all tumours were deemed resectable with 69.2% achieved pCR and 25.4% achieved MPR making the overall response rate (ORR) of 84.6%.

Another small study investigated the use of the use of three cycles of neoadjuvant Nivolumab in combination paclitaxel and carboplatin (or gemcitabine) given at three-weekly intervals in patients with stage IB to IIIA NSCLC with no driver mutations (33). The primary objective is MPR and deemed to be reached if 29% of the planned patients have at least an MPR. Thirteen patients were enrolled all of whom had surgery. Grade 3 toxicities were neutropenia, anaemia and renal complication. One patient developed hypothyroidism four months after surgery. One patient died 6 weeks after surgery from complications unrelated to study drugs. Eighty-five percent of patients had at least an MPR with 46% and 38% having an MPR and pCR respectively. MPR was seen independent of PD-L1 score. Radiologic response rate was seen in 46% of patients with one case of complete response. After a median follow-up of 10 months, there are no recurrences reported. The authors concluded that the combination of Nivolumab added to platinum doublets was well tolerated. MPR was seen independent of PD-L1 score.

A phase II single arm trial, SAKK 16/14 investigated the use of three cycles of neoadjuvant chemotherapy with cisplatin and docetaxel followed by two cycles of Durvalumab in patients with stage IIIA N2 NSCLC followed by adjuvant Durvalumab for 1 year (34). The primary endpoint is event-free survival (EFS) at 12 months. An initial report included 68 patients with 81.1% of patients underwent resection. The main reason for not undergoing surgery was disease progression (33.3% of patients). Thirty-day postoperative mortality was observed in one patient Radiographic response was seen in 44.8% of patients after neoadjuvant chemotherapy and 59.7% after additional neoadjuvant immunotherapy. One-year EFS was 73.3% The authors concluded that the addition of perioperative Durvalumab to standard of care chemotherapy is safe and leads to a high response rate and a very encouraging 1-year EFS rate that appears substantially higher than with chemotherapy alone.

The use of sequential immunotherapy with Durvalumab following CRT has improved OS in patients with unresectable stage III NSCLC (35). The safety and feasibility of concurrent neoadjuvant Pembrolizumab and CRT in resectable stage IIIA NSCLC was investigated in a small phase I trial with a total of nine patients were enrolled (36). Patients received neoadjuvant concurrent chemotherapy and immunotherapy combination consisting of cisplatin, etoposide, and Pembrolizumab at three-weekly intervals with thoracic radiotherapy at a dose of 45 Gy in 25 fractions followed by surgery and six months of consolidation Pembrolizumab. The radiographic response with an ORR was 75% in 8 assessable patients. One patient came off study for progression prior to surgery and one had pleural metastases found during surgery so resection was aborted. Six patients underwent complete resection with a pCR rate of 67%. Consolidation Pembrolizumab was started on four patients with three patients completing treatment and one patient declined further treatment after three cycles. At a median follow-up of 19.6 months, the median PFS has not been reached with none of the patients who underwent resection have recurred. Serious adverse events were reported in all nine patients with most significant being two grade 5 events including one case of pneumocystis pneumonia post resection and one case of cardiac arrest during the neoadjuvant phase. Grade 3 events included one episode each of pneumonitis, bronchopleural fistula, acute kidney injury, colon perforation, and febrile neutropenia. The authors concluded that the addition of Pembrolizumab to neoadjuvant CRT in resectable stage IIIA patients resulted in a high pCR rate at resection. However, the trial was halted as the stopping rule for infeasibility was met with occurrence of two grade 5 events.

Ongoing neoadjuvant immunotherapy studies

Following the proof of feasibility from these early phase studies, there are currently multiple ongoing phase III neoadjuvant immunotherapy studies for early stage NSCLC.

CHECKMATE 816 (NCT02998528) is a three-armed

Phase III randomised clinical trial currently recruiting patients with stages IB to IIIA resectable NSCLC. Enrolled patients are randomised to receive either standard platinum-doublet chemotherapy or platinum doublet chemotherapy in combination with Nivolumab or combination immunotherapy with Nivolumab and Ipilimumab for three cycles. The primary endpoints are EFS and pCR. Key secondary endpoints are OS and MPR. An estimated 642 will be enrolled with the estimated primary completion date of May 2023. Recruitment to the combination immunotherapy arm was closed in December 2019 (37).

CHECKMATE 77T (NCT04025879) is a phase III double blind randomised clinical trial currently recruiting patients with stages IIA to IIIB resectable NSCLC. Patients with non-squamous NSCLC with activating EGFR mutations or ALK translocation are excluded. Enrolled patients are randomised to receive platinum doublet chemotherapy in combination with Nivolumab, followed by surgery and followed by adjuvant Nivolumab or platinum doublet chemotherapy in combination with placebo, followed by surgery and followed by adjuvant placebo. The primary endpoint is EFS. Key secondary endpoints are OS, pCR, MPR assessed by blind independent pathological review, safety and tolerability. An estimated 452 will be enrolled with the estimated primary completion date is May 2023 (38).

KEYNOTE 671 (NCT03425643) is a phase III double blind randomised clinical trial currently recruiting patients with stages IIB to IIIA resectable NSCLC. Enrolled patients are randomised to receive either neoadjuvant chemotherapy of cisplatin with gemcitabine (for squamous histology) or pemetrexed (for non-squamous histology) combined with either Pembrolizumab or placebo given at three-weekly intervals for four cycles, followed by surgery and followed by adjuvant Pembrolizumab or placebo for 13 cycles. Primary endpoints are EFS (defined as time from randomisation to first of disease/local progression, unresectable tumour, local/distant recurrence, or death) and OS. Secondary endpoints are MPR, pCR, safety, and patient-reported outcomes (PRO). An estimated 786 patients will be enrolled with estimated primary completion date in January 2024 (39).

IMPOWER 030 (NCT03456063) is a phase III double blind randomised clinical trial currently recruiting patients with stages IIB to IIIB resectable NSCLC. Patients with non-squamous NSCLC with activating EGFR mutations or ALK translocation are excluded. Enrolled patients are randomised to receive four cycles of neoadjuvant Atezolizumab or placebo in combination with an investigator-selected platinum-doublet chemotherapy regimen. Following unblinding, patients in Arm A will receive adjuvant Atezolizumab treatment for ≤16 cycles and patients in Arm B will receive best supportive care and scheduled observational follow-up. Primary endpoints are independent-review facility assessed EFS and MPR. Secondary endpoints are investigator-assessed EFS and DFS, OS, ORR, pCR and PRO. An estimated 374 patients will be enrolled with estimated primary completion date in November 2024 (40).

AEGEAN (NCT03800134) is a phase III double blind randomised clinical trial currently recruiting patients with stages IIA to IIIB resectable NSCLC. Enrolled patients are randomised to receive either neoadjuvant platinum doublet chemotherapy combined with either Durvalumab or placebo given at three-weekly intervals for four cycles, followed by surgery and followed by adjuvant Durvalumab or placebo. Primary endpoints are MPR and EFS. Secondary endpoints include DFS, OS and PRO. An estimated 800 patients will be enrolled with estimated primary completion date in January 2024 (41).

INCREASE (EudraCT-Number: 2019–003454-83) is a phase II single arm clinical trial currently recruiting patients with resectable or borderline resectable T3-4N0-1 NSCLC. This trial is planning to enrol 29 patients who will receive concurrent CRT, ipilimumab and nivolumab on day 1 followed by nivolumab after 3 weeks. Radiotherapy consists of once-daily doses of 2 Gy to a total of 50 Gy and chemotherapy will consist of a platinum-doublet. Pulmonary resection is planned 6 weeks after the last day of radiotherapy. The primary study objective is to establish the safety of adding immunotherapy to pre-operative CRT, and its impact on pathological tumour response. Secondary objectives are to assess the impact of adding immunotherapy to CRT on DFS and OS (42).

On top of ongoing Phase III clinical trials investigating the use of established Immune checkpoint inhibitors in the neoadjuvant setting for early stage NSCLC, novel immunotherapy agents beyond PD-1/PD-L1 axis blockade are also being tested. Canakinumab is a selective interleukin-1b inhibitor associated with reduced incidence and mortality from NSCLC in patients with stable post-myocardial infarction with elevated high-sensitivity C-reactive protein (hs-CRP) levels (43). In the ongoing CANOPY-A trial (NCT03447769), it is currently being investigated as adjuvant therapy for post resection in early stage NSCLC (44). In pre-clinical NSCLC humanised

models, treatment with Canakinumab in combination with anti-PD-1 inhibitor could lead to anti-tumour activity (45). Combination of Canakinumab and Pembrolizumab is expected to enhance the efficacy of PD-1 inhibition by inhibiting dysregulated inflammation in tumour microenvironment. The CANOPY-N trial (NCT03968419) is a phase II, randomised, open-label trial investigating the effect of Canakinumab or Pembrolizumab monotherapy or in combination as neoadjuvant treatment in resectable stages IIB to IIIA NSCLC patients (46). Enrolled patients are randomised to one of the treatment arms to receive a total of two doses of Canakinumab alone or in combination with Pembrolizumab or Pembrolizumab alone in 2:2:1 ratio. Primary endpoint for the trial is the MPR rate with secondary endpoints include determination of ORR, MPR rate based on local review, surgical feasibility rates, anti-drug antibodies incidence and PK parameters. An estimated 110 patients will be enrolled with estimated primary completion date in September 2021.

Biomarkers for neoadjuvant immunotherapy in NSCLC

Predictive biomarkers are needed to correctly select early stage NSCLC patients who will benefit from neoadjuvant immunotherapy whilst prognostic biomarkers will help predict survivorship of patients. Following neoadjuvant chemotherapy in early stage NSCLC, pCR and the tumour draining lymph nodes, MPR and downstaging of lymph node status could be the most favourable predictors of survival (47). The availability of pre-treatment tissue sample on diagnostic biopsy and post-treatment tissue sample from surgical resection allows the opportunity for translational research to be done in neoadjuvant studies. MPR is significantly predictive of long-term OS in neoadjuvant chemotherapy—treated patients with NSCLC. MPR may serve as a surrogate endpoint for evaluating novel chemotherapies and immunotherapy response in biomarker-driven translational clinical trials. Correlation of MPR with other established biomarkers associated with immunotherapy would be key to further understand the efficacy of these agents and patient selection in the neoadjuvant setting.

PD-L1 expression based on tumour proportion score (TPS) derived immunohistochemistry is an example of a predictive biomarkers utilised by clinicians to guide treatment options for patients with advanced NSCLC. Single agent Pembrolizumab was approved for use in advanced NSCLC with PD-L1 status of >50%. In the phase I trial evaluating the use of neoadjuvant Nivolumab, the expression of PD-L1 could be evaluated in pre-treatment biopsy samples obtained from 15 patients. An MPR occurred in both PD-L1–positive and PD-L1–negative tumours. Tumour mutational burden was predictive of pathological response to PD-1 blockade (48). Interestingly, this was also observed in the NADIM, NEOSTAR, PRINCEPS and MK3475-223 trials respectively. In the LCMC3 trial, two methods of determining PD-L1 expression was used (25). Eight percent of patients with negative PD-L1 expression (based on TC0 and IC0 score with Mab clone SP142) compared to 29% of patients with positive PD-L1 expression (P=0.055). Using a different diagnostic antibody (clone 22C3), 11% of patients with PD-L1 TPS <50 had an MPR compared to 35% of patients with PD-L1 TPS >50 (P=0.040). In a post-hoc analysis of imaging, objective responses were achieved regardless of PD-L1 expression. In patients with less than 1% PD-L1 expression, the median best percentage change in tumour size was –34% compared with –40% in patients with PD-L1 expression of 1% or higher (P=0.18). In the NEOSTAR study (28), median pre-treatment tumour PD-L1 was higher in responders compared to non-responders (P=0.024) and the percentage of viable tumour was lower in tumours with PD-L1 >1% compared PD-L1 ≤1% (P=0.046). The two trials suggest that anti-tumour activity was associated with higher pre-treatment PD-L1 levels.

There is currently no clear role for TMB as a predictive or prognostic biomarker in NSCLC but its significance in as a biomarker in other tumour types are established. In June 2020, the FDA granted accelerated approval to Pembrolizumab for the treatment of adult and paediatric patients with unresectable or metastatic TMB-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumours that have progressed following prior treatment and who have no satisfactory alternative treatment options with FoundationOneCDx assay approved as a companion diagnostic for Pembrolizumab (48).

In the Phase I study investigating the use of neoadjuvant Nivolumab, there was a significant correlation between the pathological response and the pre-treatment TMB. The number of T-cell clones that were found in both the tumour and peripheral blood increased systemically after PD-1 blockade in eight of nine patients who were evaluated. Mutation-associated, neoantigen-specific T-cell clones from a primary tumour with a complete response on pathological assessment rapidly expanded in peripheral blood at two

to four weeks after treatment; some of these clones were not detected before the administration of Nivolumab. The authors suggested that systemic priming of anti-tumour T-cells may potentially eliminate micro-metastatic cancer, which drives post-surgical collapse (48). These findings support the notion that neoadjuvant immunotherapy with checkpoint inhibitors can amplify systemic anti-tumour immunity, and that such effects could persist after curative surgery, as noted in other melanoma studies (49). However, such correlation was not seen in the LCMC3 trial (25), where TMB was not correlated with MPR or pathological regression. In this study, exome sequencing data was available for 47 out of 101 patients. Median TMB was 10.4 mutations per Mb and was not different in those with MPR compared with those without MPR.

In a subgroup of patients in the neoadjuvant Nivolumab study (50), longitudinal molecular data was assessed in peripheral blood for circulating tumour DNA (ctDNA) and dynamics of tumour-infiltrating T-cell clonotypes. At a longer follow up, presence of ctDNA at diagnosis and MPR do not associate with RFS. All patients who had ≥30% reduction in viable tumour in response to Nivolumab demonstrated clearance of detectable ctDNA from blood prior to surgery. Patients with MPR experienced expansion of neoantigen-specific T-cells in peripheral blood. In one patient with ongoing disease-free status, expansion of tumour-associated T-cells has persisted in peripheral blood beyond 15 months from surgery. By contrast, in a patient who had detectable peri-operative ctDNA and 75% residual disease at surgery, minimal T-cell expansion was observed in peripheral blood, with a decreasing frequency of expanded T-cell clones over time that correlated with eventual cancer relapse. The authors concluded that analysis of ctDNA and peripheral T-cell expansion in responders compared with non-responders suggests potential biomarkers for response and surveillance.

In the same study (50), a subset of patients (n=12) underwent whole-exome sequencing of pre-treatment tumours. A median of 92 somatic mutations per tumour were noted and specific driver mutations identified, including in TP53, KRAS, CDKN2A, ARID1A, NOTCH1, and RB1, consistent with previous observations in patients with NSCLC. Eleven patients had undergone complete tumour resection and could be evaluated for tumour response. A significantly higher mean TMB was observed in tumours with an MPR than in tumours without an MPR. No significant correlation was noted between TMB and tumour PD-L1 expression. Deep sequencing of T-cell receptor-β chain CDR3 regions (TCRseq) to examine the effects of the drug on the repertoire of T-cell clones found both in tumours and in peripheral blood was performed in nine patients. Tumours with an MPR had a higher frequency of T-cell clones that were shared between intra-tumoral and peripheral compartments and a higher clonality of the T-cell population than did tumours without an MPR. This finding is in concordance with analyses in patients with advanced melanoma, who had increased clonality of tumour-infiltrating lymphocytes (TILs) in response to PD-1 blockade (51). Post-treatment, eight out of nine patients for whom blood samples obtained before and after treatment were available had peripheral expansion of multiple T-cell clones that were also found in the tumour at the time of resection with many of these clones were not detected in the peripheral blood before treatment.

The NADIM trial also characterised the peripheral blood T-cell receptor (TCR) repertoire of 30 if its participants (52). PFS and OS median follow-up times were longer than 20 months at data analysis. No statistically significant differences in TCR repertoire in terms of evenness (P=0.373), diversity (P=0.691) or convergence (P=0.054) between pre- and post-neoadjuvant treatment were observed. A detailed analysis of the clones showed that the percentage of frequent clones (greater than 0.1%) that increase after neoadjuvant therapy does show differences between the different pathological response groups, being elevated in patients who presented responses greater than 90% (P=0.0385). Having this parameter higher than the median (43.9% in this cohort) is associated with a higher PFS (P=0.0490) and OS (P=0.078). The same study evaluated the neutrophil-to-lymphocyte ratio (NLR) and platelets-to-lymphocyte ratio (PLR), described as indicators of systemic inflammation, for use as biomarkers of response to immunotherapy (48). PLR variation was significantly different between pCR and incomplete responders whereas NLR and the rest of the immune populations were no different between subgroups. The authors concluded that NLR is not associated to neoadjuvant treatment response with a higher decrease on PLR post neoadjuvant treatment is associated to an incomplete pathological response.

The NEOSTAR trial (28) is another trial that characterised TCR repertoire of both tumour and peripheral blood in a longitudinal fashion by sequencing of the variable CDR3β chain of TCR involved in antigen binding in a small number of patients (28). Diversity in the blood at baseline and in the tumuor post-therapy were positively correlated (P=0.023), which may reflect an influx of cells from the periphery

following treatment. Higher baseline T-cell clonality in the blood was associated with a lower percentage of viable tumour at time of surgery in both treatment arms (P=0.04). CD3+ and CD103+ tissue resident memory CD8+ TILs were higher with combination treatment compared to Nivolumab alone (P=0.069). Neoadjuvant combination treatment with checkpoint inhibitors is associated with higher clonality in tumours and lower clonality in blood post-therapy, suggesting increased T-cell trafficking into the tumour. A lower pre-treatment clonality in the periphery was correlated with higher percentage of viable tumour post-neoadjuvant immunotherapy.

Profound CD28-dependent activation of both CD4 and CD8 cells in the peripheral blood mononuclear cells (PBMCs) was observed following neoadjuvant Ipilimumab in combination with chemotherapy in the TOP1021 study (53). Significant increases in the frequencies of CD4+ cells expressing activation markers ICOS, HLA-DR, CTLA-4, and PD-1 were apparent. Increased frequencies of CD8+ cells expressing the same activation markers, with the exception of PD-1, were also observed. Examination of seven resected tumours found higher frequencies of activated TILs than those observed in PBMCs.

In a trial investigating the use of neoadjuvant Atezolizumab, a subset of patients (n=13) with adenocarcinomas underwent molecular tumour testing. Two (15%) of these patients had KRAS mutations, two (15%) had STK11 mutations, one (8%) had KRAS and STK11 co-mutations, four (31%) had EGFR mutations (one patient with exon 19 deletion, one with the L858R mutation, one with the L858R/S768I mutation, and one with exon 20 insertion), and one with a HER2 mutation. None of the three patients with a STK11 mutations met the RECIST criteria for a partial response; one patient had 100% of viable residual tumour at the time of surgery, one patient had 72% viable residual tumour, and the third patient was found to not have resectable disease at time of surgery. Although the number of patients is small, this may support the growing evidence suggests that STK11/LKB1 mutations confer resistance to immunotherapy in KRAS mutant NSCLC. Of the four patients with EGFR mutations, two patients (with L858R and L858R/S768I mutations) had a pCR, and the remaining two patients (with an exon 20 insertion and an exon 19 deletion) did not have a major pathological response. Genotyping of the tumour or plasma by targeted next generation sequencing could be of interest to further decipher the effect of neoadjuvant immunotherapy. This may have an influence on the design of future clinical trials as most immunotherapy in advanced NSCLC did not include tumours with activating mutations (31).

All the trials described above used the standard Response Evaluation Criteria in Solid Tumours version 1.1. (RECIST v1.1.) to monitor treatment response radiologically. A phase I study investigating the use of neoadjuvant single agent Nivolumab highlighted a discrepancy between radiological response and pathological findings at resection (49). Imaging with CT scan following two cycles of neoadjuvant Nivolumab suggested only 10% had a radiological partial response and 86% had stable disease despite the high rate of MPR. This was also observed in the PRINCEPS (26) trial where the authors concluded no correlation was seen between pathological response and RECIST response rate when patients were treated with neoadjuvant Atezolizumab. The LCMC3 (31) trial demonstrated that pathological regression moderately correlated with target lesion measurements by RECIST, whereas the NEOSTAR (28) trial showed that the proportion of complete response and partial response on imaging for patient who had MPR (60%), was higher than for those who did not have an MPR (7%) (P<0.001). The IoNESCO IFCT-1601 trial (29), observed a significant association between radiographical and pathological response (P=0.028) in patients who were treated with neoadjuvant Durvalumab. As using RECIST may not be the best way to predict tumour response, a small study investigated the association between MPR and radiomic features (RF) in [^{18}F]-fluorodeoxyglucose ([^{18}F]-FDG) PET and standard CT images obtained at baseline and after neoadjuvant Nivolumab (54). Scans of 24 patients were analysed with 29% of the patients had MPR. The authors identified a significant increase in heterogeneity in post-treatment CT images of NSCLC tumours that had MPR. This association may reflect increased T-cell infiltration or tumour necrosis. In contrast, most [^{18}F]-FDG-based RFs did not distinguish between MPR and non-MPR tumours, although the authors acknowledge that the sample size was limited and will investigate this in a larger patient cohort.

Discussion

Current evidence for neoadjuvant immunotherapy in early NSCLC suggests that this approach is feasible, safe and does not delay patients receiving surgery. The majority of adverse events from drug treatment are not entirely unexpected or out of proportion with current data for these

agents in the metastatic setting.

The small early phase trials done so far do not answer the question of whether neoadjuvant immunotherapy in early stage resectable NSCLC should be given as single agent checkpoint inhibitor or in combination with other modalities. The optimum duration of neoadjuvant treatment has yet to be answered although conventional neoadjuvant practice advocates the use of two to four cycles of treatment. Four of the major ongoing phase III clinical trials (CHECKMATE 77T, CHECKMATE 861, AEGEAN and IMPOWER 030) are exploring continuity of immunotherapy post-surgical resection as adjuvant therapy. Novel immunotherapy agents are also being tested as neoadjuvant treatment in early stage resectable NSCLC in smaller earlier phase clinical trials.

Small clinical trials have shown that neoadjuvant immunotherapy is associated with a higher rate of MPR on tumour resection, compared to those seen historically with neoadjuvant chemotherapy. MPR is being used as primary or secondary endpoints on several clinical trials and over time, the data will guide to whether it can be used as a valid surrogate biomarker predictive for EFS, DFS or OS. Correlation between MPR and other immunological correlates such as PD-L1 expression and TMB will give better understanding on which patients who will benefit from neoadjuvant immunotherapy. Several trials have performed longitudinal biomarker studies of immunological correlates from peripheral blood and tumour samples that have led to interesting results although they need to be prospectively validated in bigger cohort numbers. This should be feasible in the context of ongoing large clinical trials.

Conclusions

Neoadjuvant immunotherapy prior to surgery for NSCLC shows promising potential in several phase II studies. Confirmatory Phase III clinical trials are ongoing to assess longer clinical impact on EFS, DFS and OS. Predictive and prognostic biomarkers are also needed in this setting.

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Footnote

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