

Supplementary information

Non-small-cell lung cancer

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Supplementary table 1. Advantages and disadvantages of sample types for NSCLC biomarker testing.

Sample	Sample types	Advantages	Disadvantages
Tumour tissue	Surgically resected tumour, tumour biopsy, tumour cytology samples	Generally available for initial diagnosis Seamless integration into diagnostic workflow Direct representation of patient's disease Only suitable material for IHC and FISH	Clinical samples often very small with low tumour content May be consumed by initial diagnostic workflow Requires re-biopsy when testing is required on disease relapse
Plasma	Plasma is by far the most common source of cell-free DNA (the so-called Liquid Biopsy) but other body fluids such as urine or cerebrospinal fluid have been used. A very small proportion of circulating cell-free DNA (cfDNA) from plasma incorporates DNA shed from the patient's tumour. Any detected sequence variants are presumed to be derived from the tumour. Dilution by DNA shed by normal physiological mechanisms creates issues with sensitivity of detection in clinical situations	Readily available through relatively non-invasive venipuncture Repeat samples easily obtained Ideal for monitoring dynamic changes in detected alterations May overcome biomarker heterogeneity in patient's tumour burden Avoids tissue processing steps, therefore sequencing underway more quickly Specificity of positive findings generally high	Relative lack of sensitivity due to dilution by circulating germ-line DNA; significant false-negative rates Usually only effective with high tumour burden (advanced disease) False-positive mutations (clonal haematopoiesis) Clinically important variants may exist in benign or pre-invasive disease^a Unsuitable for IHC or FISH-based biomarkers

^aIn most circumstances the disease burden would be low, so this problem is unlikely. However, synchronous or metachronous malignancy of another organ could harbour the same alteration and confound interpretation.

Supplementary Table 2. Ongoing multimodal immunotherapy trials and clinical questions in patients with locally advanced NSCLC

Questions	Ongoing and recently completed studies	Trial identifier or reference
<i>Patient characteristics</i>		
Do elderly patients benefit from the addition of immunotherapy ?	PACIFIC-5. Phase III study of durvalumab after either concurrent or sequential chemoradiotherapy (CRT) in patients with stage III NSCLC.	¹ NCT03706690
Do patients with performance status 2 benefit from the addition of immunotherapy ?	PACIFIC 6. Durvalumab After Sequential Chemoradiotherapy in Stage III, Unresectable NSCLC: The Phase 2 PACIFIC-6 Trial ¹ .	² NCT03693300
Do patients treated with sequential CRT or RT alone benefit from the addition of immunotherapy?	SWOG 1933. A Pilot Study of Hypofractionated Radiotherapy Followed by Atezolizumab Consolidation in Stage II or III NSCLC Patients With Borderline Performance Status.	NCT04310020
	DUART. Phase II open-label, single-arm, multicenter, international study to evaluate the clinical activity of durvalumab in patients with Stage III unresectable NSCLC who are deemed to be ineligible for chemotherapy.	³ NCT04249362
	TRADE-hypo. Thoracic Radiotherapy Plus Durvalumab in Elderly and/or Frail NSCLC Stage III Patients Unfit for Chemotherapy - Employing Optimized (Hypofractionated) Radiotherapy to Foster Durvalumab Efficacy.	⁴ NCT04351256
	AIRING. A Phase II Trial Evaluating Conformational Intensity Modulated Radiotherapy With Concomitant Nivolumab Followed by Nivolumab for Patients With Locally Advanced NSCLC.	NCT04577638
	NRG LU0004. Phase I Trial of Accelerated or Conventionally Fractionated Radiotherapy Combined With MEDI4736 (Durvalumab) in PD-L1 High Locally Advanced NSCLC.	⁵ NCT03801902

<i>Tumour characteristics</i>		
Do patients with PDL1<1% benefit from the addition of immunotherapy ?	COAST. An Open-Label, Phase II, Multidrug Platform Study of Durvalumab Alone or in Combination With Oleclumab or Monalizumab in Patients With Unresectable, Stage III NSCLC ² .	⁶ NCT03822351
Do patients with driver mutations (such as EGFR mutations) benefit from the addition of immunotherapy ?		
Should we add immune modulators to immune check point inhibitors, particularly in patients with a suppressive TME?	PACIFIC 8. A Phase III, Randomised, Double-blind, Placebo-controlled, Multicentre, International Study of Durvalumab Plus Domvanalimab(AB154) in Participants With Locally Advanced (Stage III), Unresectable NSCLC Whose Disease Has Not Progressed Following Definitive Platinum-based Concurrent Chemoradiation Therapy.	⁷ NCT05211895
	PACIFIC 9. A phase III study to Assess the Effects of Durvalumab With Oleclumab or Durvalumab With Monalizumab Following Concurrent Chemoradiation in Patients With Stage III Unresectable NSCLC.	⁸ NCT05221840
	KEYVIBE-006. Open-label Phase 3 Study of MK-7684A (Coformulation of Vibostolimab With Pembrolizumab) in Combination With Concurrent Chemoradiotherapy Followed by MK-7684A Versus Concurrent Chemoradiotherapy Followed by Durvalumab in Participants With Unresectable, Locally Advanced, Stage III NSCLC.	⁹ NCT05298423
	SKYSCRAPER 03. A Phase III, Open-Label, Randomized Study of Atezolizumab and Tiragolumab Compared With Durvalumab in Patients With Locally Advanced, Unresectable Stage III NSCLC Who Have Not Progressed After Concurrent Platinum-Based Chemoradiation.	¹⁰ NCT04513925
<i>Sequencing of (CT) RT and immunotherapy</i>		
	NICOLAS. Phase 2 study of concurrent Nivolumab With Standard Concurrent	¹¹ NCT02434081

Should immunotherapy be delivered concurrently with radiotherapy?	Chemoradiotherapy in Locally Advanced Stage IIIA-B NSCLC ³ .	
How soon we start should immunotherapy after CRT?	DETERED. Phase II Trial of Concurrent Atezolizumab With Chemoradiation for Unresectable NSCLC ⁴ .	¹² NCT02525757
Should induction treatment be delivered prior to CTRT and consolidation immunotherapy?	PACIFIC 2. Phase 3 study of concurrent durvalumab and platinum-based chemoradiotherapy in patients with unresectable, stage III NSCLC.	¹³ NCT02125461
	KeyLynk 012. A Phase 3 Study of Pembrolizumab (MK-3475) in Combination With Concurrent Chemoradiation Therapy Followed by Pembrolizumab With or Without Olaparib vs Concurrent Chemoradiation Therapy Followed by Durvalumab in Participants With Unresectable, Locally Advanced, Stage III NSCLC.	¹⁴ NCT04380636
	CheckMate 73L. A Phase 3 Study Comparing Nivolumab Plus Concurrent Chemoradiotherapy Followed by Nivolumab With or Without Ipilimumab Versus Concurrent Chemoradiotherapy Followed by Durvalumab for Previously Untreated, Locally Advanced Stage III NSCLC.	¹⁵ NCT04026412
	EA5181. Randomized Phase III Trial of Durvalumab as Concurrent and Consolidative Therapy or Consolidative Therapy Alone for Unresectable Stage 3 NSCLC.	¹⁶ NCT04092283
	APOLO. A Phase II Trial of Atezolizumab Plus Induction Chemotherapy (CT) Plus Chemo-radiotherapy and Atezolizumab Maintenance Therapy in Non-resectable Stage IIIA-IIIB NSCLC Patients.	NCT04776447
	DEDALUS. An Open-label, Multi-center, Phase 2 Study of Chemo-immunotherapy Followed by Reduced-dose Hypofractionated RT and Maintenance Immunotherapy for Stage III Unresectable NSCLC.	¹⁷ NCT05128630

	BRIDGE Trial: Phase II Trial of durvalumab and chemotherapy induction followed by durvalumab and radiotherapy in large volume stage 3 NSCLC.	NCT04765709
<i>Immunotherapy drug of choice</i>		
What drugs, other than durvalumab, have an impact on survival in the stage 3 unresectable setting?	RTOG 3505. Randomized, Double Blinded Phase III Trial of Cisplatin and Etoposide Plus Thoracic Radiation Therapy Followed By Nivolumab/Placebo For Locally Advanced NSCLC.	¹⁸ NCT02768558
	Hoosier Cancer Research Network LUN 14-179. A phase 2 trial of consolidation pembrolizumab following concurrent chemoradiation for patients with unresectable stage III NSCLC.	¹⁹ NCT02343952
	KEYNOTE-799. A Phase 2 Trial of Pembrolizumab in Combination With Platinum Doublet Chemotherapy and Radiotherapy for Participants With Unresectable, Locally Advanced Stage III NSCLC.	²⁰ NCT03631784
	GEMSTONE-301. Sugemalimab versus placebo after concurrent or sequential chemoradiotherapy in patients with locally advanced, unresectable, stage III NSCLC in China.	²¹ NCT03728556
	BTCRC-LUN16-081. Phase II Study of Consolidation Immunotherapy With Nivolumab and Ipilimumab or Nivolumab Alone Following Concurrent Chemoradiotherapy for Unresectable Stage IIIA/IIIB NSCLC.	²² NCT03285321
<i>Biomarkers</i>		
Can we use ctDNA to tailor immunotherapy consolidation treatments ?	Personalized Escalation of Consolidation Treatment Following Chemoradiotherapy and Immunotherapy in Stage III NSCLC.	NCT04585490

CTRT, chemo-radiotherapy; NSCLC, non-small cell lung cancer; RT, radiotherapy.

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