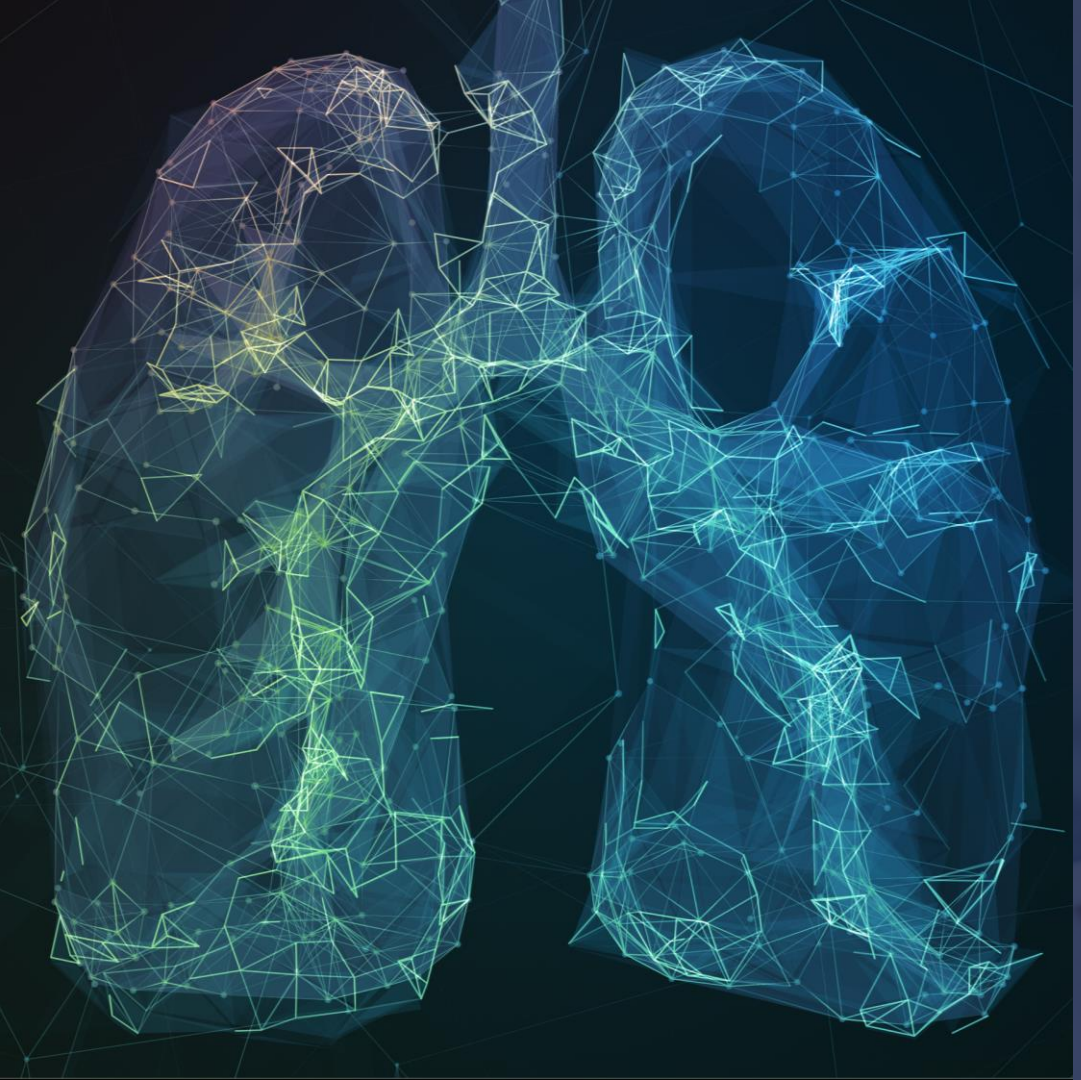

touchPANEL DISCUSSION

How is our understanding of treating *MET* exon 14 skipping mutations in NSCLC evolving?

Funded by an independent medical education request from Merck KGaA

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Expert panel

Prof. David Planchard (Chair)
Associate Professor and Head of the Thoracic Cancer Group, Institut Gustave Roussy, Villejuif, France

Prof. Enriqueta Felip
Head of the Thoracic Cancer Unit, Vall d'Hebron University Hospital, Barcelona, Spain

Prof. Frank Griesinger
Director of the Clinic for Haematology and Oncology, Pius Hospital Oldenburg, Oldenburg, Germany

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Update on therapeutic options for patients with *MET*ex14+ NSCLC post-ESMO 2019

Prof. David Planchard
(Chair)
Associate Professor and Head
of the Thoracic Cancer Group,
Institut Gustave Roussy,
Villejuif, France

*MET*ex14+, MET exon 14-skipping positive; NSCLC, non-small cell lung cancer.

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Key efficacy data for MET TKIs in *MET*ex14+ NSCLC

TKI	Crizotinib[1]	Capmatinib[2]		Tepotinib[3]		Savolitinib[4]
Dose	250 mg BD	400 mg BD		500 mg QD		600 mg QD
n	65	28 (1L)	69 (≥2L)	Tissue Bx Liquid Bx	18 (1L) 17 (1L)	33 (≥2L) 31 (≥2L)	31
ORR (%) [95% CI]	**32.0* [21–45]**	**67.9 (1L) [47.6–84.1]**	**40.6 (≥2L) [28.9–53.1]**	**Tissue Bx** **Liquid Bx**	**44.4 (1L) [21.5–69.2]** **58.8 (1L) [32.9–81.6]**	**45.5 (≥2L) [28.1–63.6]** **45.2 (≥2L) [27.3–64.0]**	**38.7* (12/31 confirmed PRs)**
Median DoR (months) [95% CI]	**9.1* [6.1–12.7]**	**11.1 (1L) [5.6–NE]**	**9.7 (≥2L) [5.6–13.0]**		**14.3* [6.6–NE]**		–
Median PFS (months)	7.3* [5.4–9.1]	9.7 (1L) [5.5–13.9]	5.4 (≥2L) [4.2–7.0]	Tissue Bx Liquid Bx	10.8 [6.9–NE] 9.5 [6.7–NE]		–

*investigator-reported/not specified; other data are independently reviewed

The FDA has granted breakthrough designations for METex14+ NSCLC to capmatinib (first-line) and crizotinib and tepotinib (after platinum-based chemotherapy)[5–7]

1L, first-line; 2L, second-line; BD, twice daily; Bx, biopsy; CI, confidence interval; DoR, duration of response; ORR, overall response rate; CI, confidence interval; NE, not evaluable; NSCLC, non-small cell lung cancer; PFS, progression-free survival; PR, partial response; QD, once daily; TKI, tyrosine kinase inhibitor.

1. Drilon A, et al. World Conference on Lung Cancer (WCLC) 2018; abstract OA12.02; 2. Wolf J, et al. Oral presentation at ASCO 2019:abstract 9004; 3. Paik PK, et al. Oral presentation at ASCO 2019: abstract 9005; 4. Lu S, et al. Proceedings: AACR Annual Meeting 2019:abstract CT031; 5. https://www.onclive.com/web-exclusives/fda-grants-capmatinib-breakthrough-designation-in-frontline-metex14-mutated-nsclc (accessed Sep 2019); 6. https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=310610 (accessed Sep 2019); 7. https://www.merckgroup.com/en/news/tepotinib-breakthrough-therapy-designation-11-09-2019.html (accessed Sep 2019).

Key safety data for MET TKIs in *MET*ex14+ NSCLC

Most common TRAEs (%)	Crizotinib[1] (N=18)	Capmatinib[2] (N=334)		Tepotinib[3] (N=87)		Savolitinib[4] (N=34)
	All grades	All grades	Grade 3/4	All grades	Grade 3	All grades
Peripheral oedema/Oedema	35	41.6	7.5	48.3	8.0	38
Nausea	35	33.2	1.8	23.0	0	41
Vision disorder	29					
Vomiting	24	18.9	1.8			21
Bradycardia	24					
Increased blood creatinine		19.5	0	12.6	0	
Diarrhoea		11.4	0.3	20.7	1.1	
Increased ALT				6.9	1.1	32
Increased AST						29

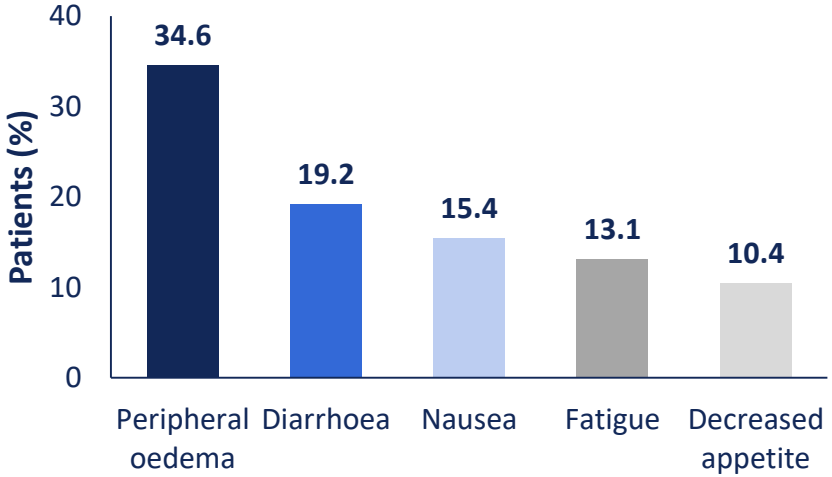
ALT, alanine aminotransferase; AST, aspartate aminotransferase; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor; TRAE, treatment-emergent adverse event.

1. Drilon A, et al. *J Clin Oncol.* 2016;**34**(suppl):abstract 108; 2. Wolf J, et al. Oral presentation at ASCO 2019:abstract 9004;
3. Paik PK, et al. Oral presentation at ASCO 2019:abstract 9005; 4. Lu S, et al. Proceedings: AACR Annual Meeting 2019:abstract CT031.

Pooled Phase I/II safety data for tepotinib in advanced solid tumours

- 260 patients overall received tepotinib 500 mg OD across 5 studies
- 48% primary liver tumours, 37% primary lung tumours
- Median treatment duration was 12 weeks (range 0–118 weeks)
  - 20.1 weeks in NSCLC patients with *MET* alterations (VISION study)
- Grade ≥3 events occurred in >1 patient only for ALT increase and AST increase (both n=3; 13%)

Most common treatment-related adverse events (all grades)



ALT, alanine aminotransferase; AST, aspartate aminotransferase; NSCLC, non-small cell lung cancer; OD, once daily.
Decaens T, *et al.* ESMO Congress 2019, Barcelona, Spain; Poster 479P.

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How important is liquid biopsy in the identification of *MET*-aberrant NSCLC?

Prof. David Planchard
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Associate Professor and Head
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Villejuif, France

NSCLC, non-small cell lung cancer.

MET and liquid biopsy recommendations in advanced NSCLC

NCCN[1]

- *EGFR*, *ALK*, *ROS1* and *BRAF* part of standard tissue profiling
- High-level *MET* amplification and *MET* exon 14 skipping mutations considered 'emerging biomarkers'
- cf/ct DNA not to be used in lieu of tissue diagnosis

IASLC[2]

- ctDNA with NGS where surgical/tissue biopsy specimen not sufficient for molecular testing
- *EGFR*, *ALK*, *ROS1* and *BRAF* as standard; panel suggested if available

ESMO[3]

- Liquid biopsy only recommended in relation to *EGFR T790M* testing
- *MET* exon 14 skipping mutations and *MET* amplification have therapeutic potential
- Crizotinib has demonstrated potential clinical efficacy, but needs confirmation

All guidelines recommend entry into clinical trials for *MET* aberrations

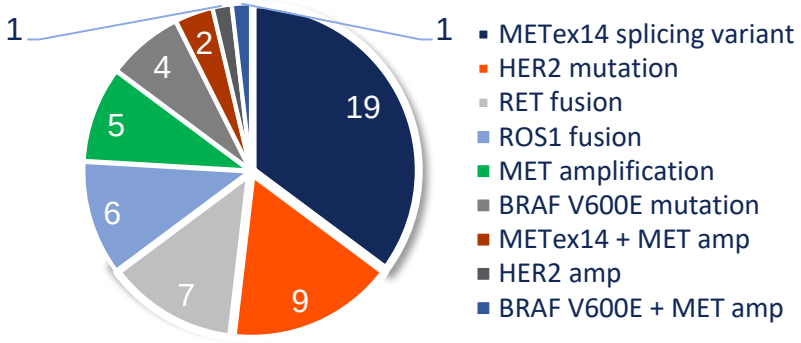
cf, cell free; ct, circulating tumour; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer.

1. NCCN NSCLC Guidelines Version 7.2019. Available at https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf; 2. Rolfo C, et al. *J Thorac Oncol.* 2018;13:1248–1268; 3. Planchard D, et al. *Ann Oncol.* 2018;29 (Suppl 4):iv192–iv237.

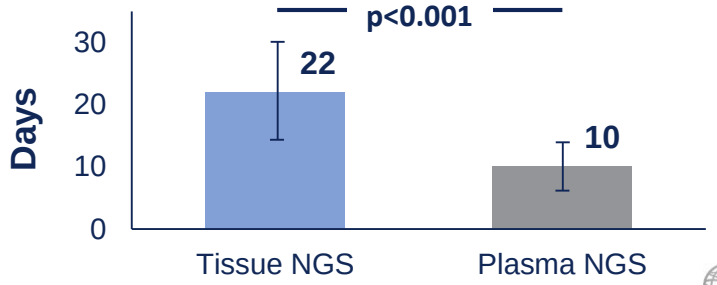
Plasma vs. tissue NGS in NSCLC with uncommon driver oncogenes

- 631 patients enrolled with IIIB/IIIC/IV or recurrent metastatic NSCLC
- 35/49 patients (71.4%) had plasma NGS uncommon drivers concordant with tissue NGS
- 35/57 (61.4%) of tissue NGS uncommon drivers concordant with plasma NGS
- 41/54 patients (76%) matched to targeted therapy
  - **16 PR, ORR 39%** (95% CI: 26–54)

- Uncommon drivers detected by plasma NGS in 54 patients (9%), including:



- Shorter mean turnaround time with plasma NGS:



CI, confidence interval; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; ORR, objective response rate.

Tu H-Y, et al. World Conference on Lung Cancer (WCLC) 2019; poster P1.01-122.

Further implications of *MET* alterations in NSCLC

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NSCLC, non-small cell lung cancer.

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Improved response to tepotinib + gefitinib vs. chemotherapy in *MET*-amplified *EGFR*-mutant NSCLC

- Patients with EGFR TKI-resistant locally advanced/metastatic, *EGFR*+, *T790M*–, *MET*+ (IHC or *MET* amplification) NSCLC randomized to tepotinib 500 mg + gefitinib 250 mg daily (n=31) or 6 x 21-day cycles pemetrexed-cisplatin-carboplatin (n=24)
- Improved PFS and OS with tepotinib/gefitinib in *MET*-amplified tumours

Median PFS (n=19)

16.6 months (tepotinib + gefitinib)

4.2 months (chemotherapy)

HR = 0.13 (90%CI 0.04–0.43)

Median OS (n=19)

37.3 months (tepotinib + gefitinib)

13.1 months (chemotherapy)

HR = 0.09 (90%CI 0.01–0.54)

CI, confidence interval; EGFR, epidermal growth factor receptor; HR, hazard ratio; IHC, immunohistochemistry; NSCLC, non-small cell lung cancer, OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

Wu Y-L, et al. World Conference on Lung Cancer (WCLC) 2019; presentation MA09.09.

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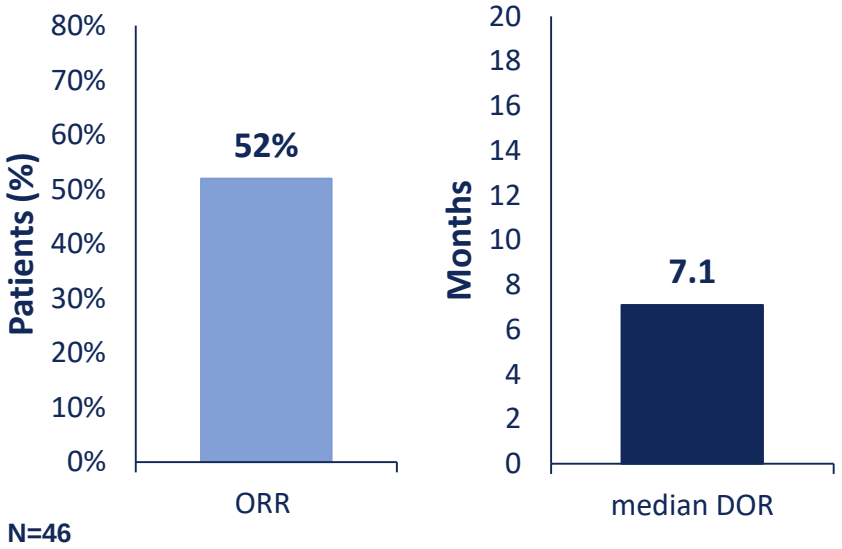
Savolitinib + osimertinib in patients with *MET*+ EGFR TKI-resistant NSCLC



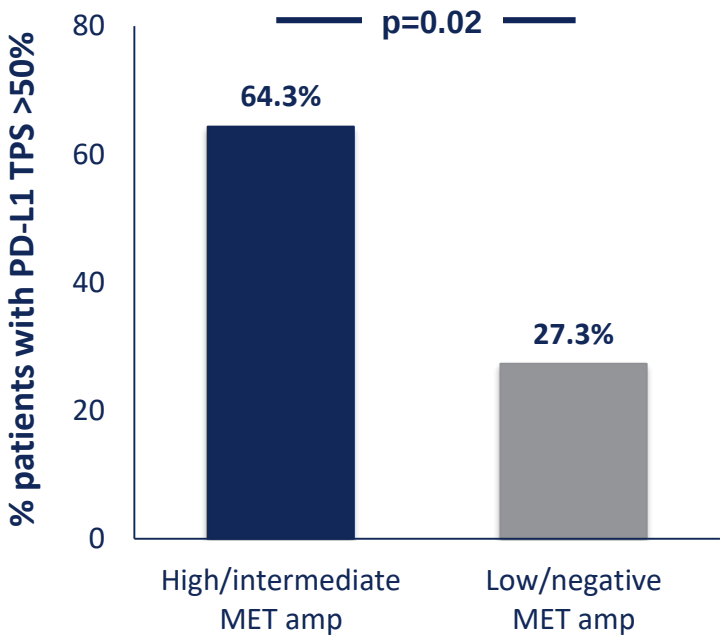
N=46

- Patients had progressed on ≥1 prior first/second-generation EGFR-TKI
- *MET*-positive status by NGS, FISH (MET gene copy ≥5 or *MET/CEP7* ratio ≥2), or IHC3+ in ≥50% of tumour cells
- Most common all-causality AEs:
  - nausea (n=17, 37%)
  - diarrhoea (n=14, 30%)
  - fatigue (n=13, 28%)
  - decreased appetite (n=13, 28%)
  - pyrexia (n=12, 26%)
  - vomiting (n=10, 22%)

Savolitinib 600 mg and osimertinib 80 mg both given once daily.
AE, adverse event; DOR, duration of response; EGFR, epidermal growth factor receptor IHC, immunohistochemistry; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; ORR, objective response rate; TKI, tyrosine kinase inhibitor.
Yu H, et al. Proceedings: AACR Annual Meeting 2019, Atlanta, GA, USA, 29 March–3 April, 2019; abstract CT032.

Checkpoint inhibitors in *MET*-positive NSCLC?

- PD-L1 expression evaluated in 50 patients with *MET*-amplified NSCLC[1]
- High/intermediate *MET* amplification associated with PD-L1 positivity (TPS>1%) vs low/negative *MET* amplification (p=0.001), and with high PD-L1 expression (figure)
- Prolonged responses to immune checkpoint inhibitors in 6 patients with NSCLC[2]
  - PD-L1 expression 20–90%
  - 5 PR and 1 CR
  - ICI treatment lasting 15–42+ months
- Could ICI be an alternative treatment in *MET* exon 14-mutated NSCLC?



CR, complete response; ICI, immune checkpoint inhibitors; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1; PR, partial response; TPS, tumour proportion score.

1. Carcereny E, et al. World Conference on Lung Cancer (WCLC) 2019; poster EP1.04-25; 2. Mayenga M, et al. World Conference on Lung Cancer (WCLC) 2019; presentation MA03.09

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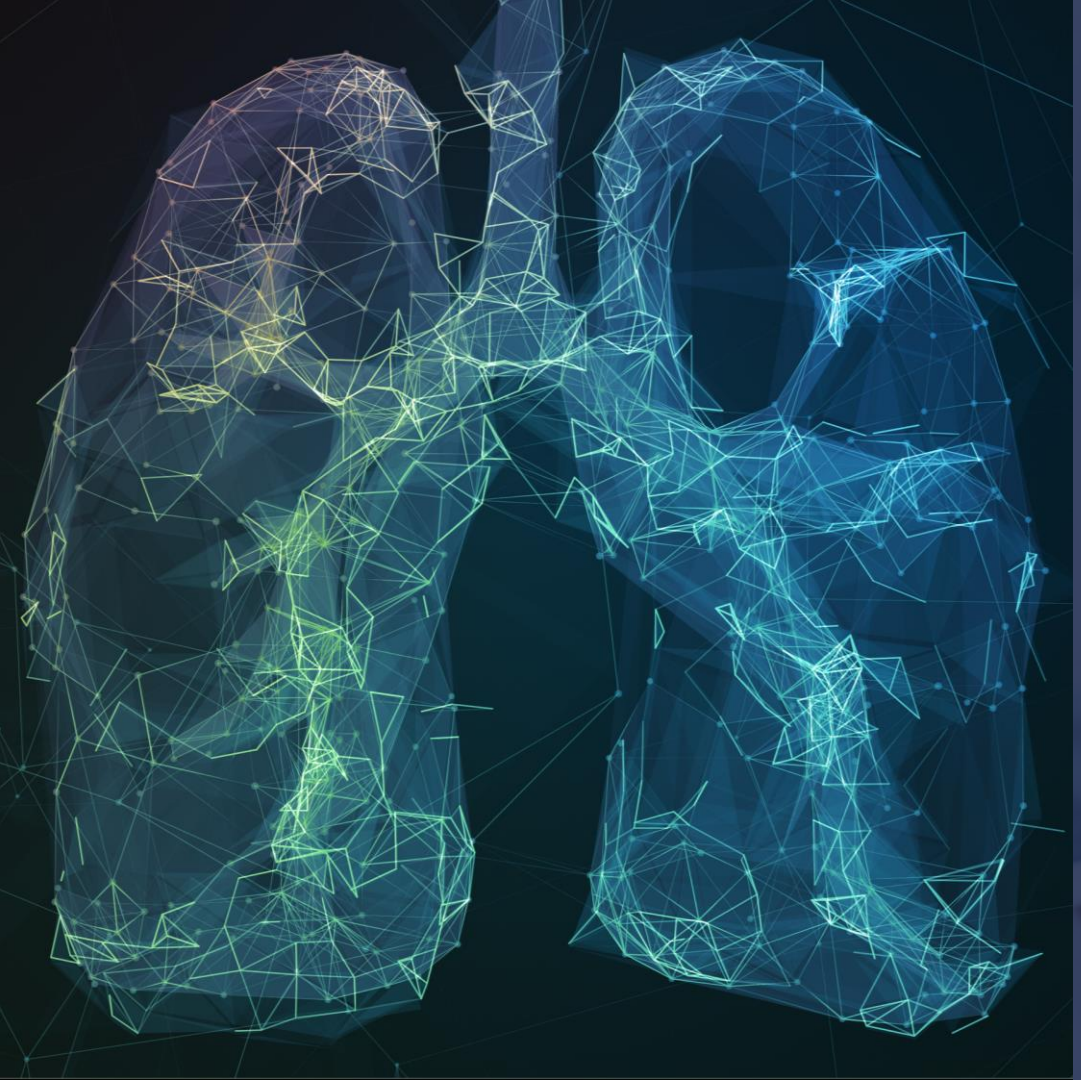

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Thank you for watching this on-demand event

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