Circulating tumor DNA (ctDNA) dynamics and survival outcomes in patients with advanced NSCLC and high (≥50%) PD-L1 expression, randomized to cemiplimab versus chemotherapy

Natalie Vokes,[1] David Gandara,[2] Ahmet Sezer,[3] Saadettin Kilickap,[4] Mahmut Gümüş,[5] Igor Bondarenko,[6] Mustafa Özgüroğlu,[7] Miranda Gogishvili,[8] Haci M Turk,[9] Irfan Cicin,[10] Dmitry Bentsion,[11] Jinrui Liu,[12] Nicholas Giangreco,[12] Olivia Zhu,[12] Matthew F. Wipperman,[12] Debra AG McIntyre,[12] Sara Hamon,[12] Dylan Sun,[12] Fang Wang,[12] Siyu Li,[12] Israel Lowy,[12] Giuseppe Gullo,[12] Petra Rietschel,[12] Jean-Francois Pouliot,[12] Vladimir Jankovic[12]

[1]Thoracic Head & Neck Medical Oncology, MD Anderson Cancer Center, Houston, TX, USA; [2]Division of Hematology/Oncology, Department of Medicine, UC Davis Comprehensive Cancer Center, Sacramento, CA, USA; [3]Department of Medical Oncology, Başkent University, Adana, Turkey; [4]Department of Medical Oncology, Istinye University Faculty of Medicine, Istanbul, Turkey; [5]Department of Medical Oncology, School of Medicine, Istanbul Medeniyet University, Istanbul, Turkey; [6]Department of Oncology and Medical Radiology; Dnipropetrovsk Medical Academy, Dnipro, Ukraine; [7]Cerrahpaşa Medical Faculty, Istanbul University-Cerrahpaşa, Istanbul, Turkey; [8]High Technology Medical Centre, University Clinic, Tbilisi,Georgia; [9]Department of Medical Oncology, Bezmialem Vakif University, Medical Faculty, Istanbul, Turkey; [10]Department of Medical Oncology, Trakya University, Edirne, Turkey; [11]Radiotherapy Department, Sverdlovsk Regional Oncology Centre, Sverdlovsk, Russia ; [12]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA.

Background

- While ctDNA has emerged as a promising tool for monitoring early response to therapy in solid tumors,[1] there are limited data from prospective, randomized, phase 3 studies to establish clear criteria for the application of ctDNA monitoring as a biomarker in clinical practice.
- In the EMPOWER-Lung 1 study (NCT03761108),[2] first line (1L) cemiplimab monotherapy improved overall survival (OS) versus platinum-doublet chemotherapy in patients with advanced non-small cell lung cancer (NSCLC) with PD-L1 ≥50% and no *EGFR*, *ALK*, or *ROS1* aberrations (**Figure S1**).

Objectives

- We performed personalized tumor-specific analysis of ctDNA from patients treated in the EMPOWER-Lung 1 study to evaluate the magnitude of ctDNA variation that is associated with clinical outcomes.

Conclusions and key takeaway

- A deep response (≥90% decrease) in ctDNA was observed in >50% of patients receiving 1L cemiplimab monotherapy or chemotherapy after 3 cycles (9 weeks) of therapy.
  - Thirty-three percent of patients achieved deep ctDNA response by Week 3
  - Almost all patients who reached deep ctDNA response at 3 weeks were still in deep response at Week 9
  - An additional 27% of patients achieved deep ctDNA response by Week 9
- The strongest correlation between ctDNA response and OS was achieved at 9 weeks in patients who received cemiplimab and achieved ctDNA clearance, with a 96% risk reduction compared to ctDNA increase.
- The composite of deep ctDNA and radiographic response at 9 weeks in cemiplimab-treated patients:
  - Allows identification of patients with Response Evaluation Criteria in Solid Tumours (RECIST) stable disease who have a favorable outcome.
  - Allows prediction of which patients with RECIST partial response have poor outcomes.
  - The correlation is not as clear in chemotherapy-treated patients.
- The composite of deep ctDNA reduction and radiographic response may represent a useful tool to guide treatment intensification in patients treated with cemiplimab monotherapy.

References

1. Bratman SV et al. *Nat Cancer*. 2020;1:873–881.
2. Sezer A et al. *Lancet*. 2021;397:592–604.
3. Coombes RC et al. *Clin Cancer Res*. 2019;25:4255–4263.

Acknowledgments

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Disclosures

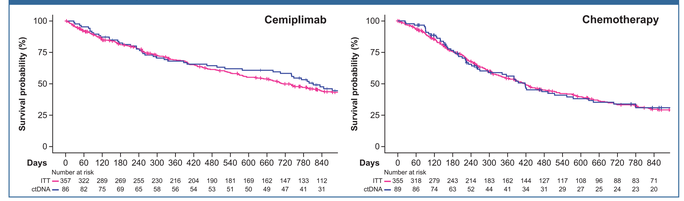
Dr Natalie Vokes declares consulting or advisory roles at Sanofi/Regeneron Pharmaceuticals, Inc., OncoCyte, Lilly, Sanofi, and Regeneron Pharmaceuticals, Inc.; travel/accommodation/expenses from RegeneronPharmaceuticals, Inc.; honoraria from Sanofi; and research funding from OncoCyte and Mirati Therapeutics.

Scan the QR code for Supplementary Figures (S1–S5).

Methods and results

- Tumor tissue next-generation sequencing was performed to identify tumor-specific DNA variants.
- ctDNA levels in the plasma were monitored using personalized[3] patient-specific probe sets (Natera; Foundation Medicine) at:
  - Baseline
  - End of Week 3
  - End of Week 9.
- Clinical endpoints included OS (from the time of ctDNA sample collection) and overall response rate (complete or partial response, stable disease, and progressive disease per RECIST 1.1). Data cut-off for clinical outcomes was March 4, 2022.
- The association between changes in ctDNA levels and clinical endpoints was tested in patient groups by ctDNA change categories (increase; <90% decrease; ≥90–<100% decrease; and clearance 100%).

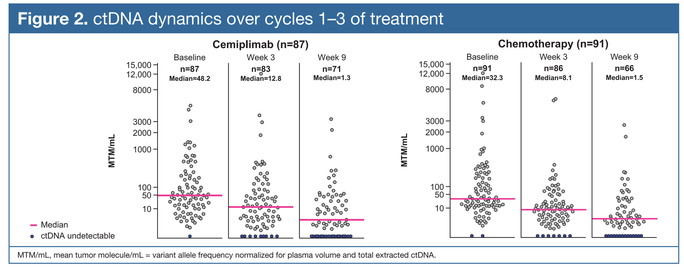
Figure 1. Clinical efficacy outcomes in the ctDNA population are representative of the overall study population



Demographics and baseline characteristics	ctDNA population (n=175)	ITT population (n=712)
Age		
Median (Q1 : Q3)	63.0 (58.0 : 69.0)	63.0 (57.0 : 69.0)
≥65, n (%)	67 (38.3)	321 (45.1)
Sex, n (%)		
Male	158 (90.3)	607 (85.3)
Female	17 (9.7)	105 (14.7)
Histology, n (%)		
Squamous	76 (43.4)	313 (44.0)
Non-squamous	99 (56.6)	399 (56.0)
PD-L1, % of tumor cells, median (Q1 : Q3)	72.5 (55.0 : 90.0)	70.0 (50.0 : 90.0)

Best overall response, n (%)	ctDNA population (n=175)	ITT population (n=712)
Complete response	8 (4.6)	36 (5.1)
Partial response	57 (32.6)	191 (26.8)
Stable disease	67 (38.3)	265 (37.2)
Progressive disease	35 (20)	132 (18.5)
Not evaluable	7 (4)	82 (11.5)
Non-complete response or non-progressive disease	1 (0.6)	6 (0.8)

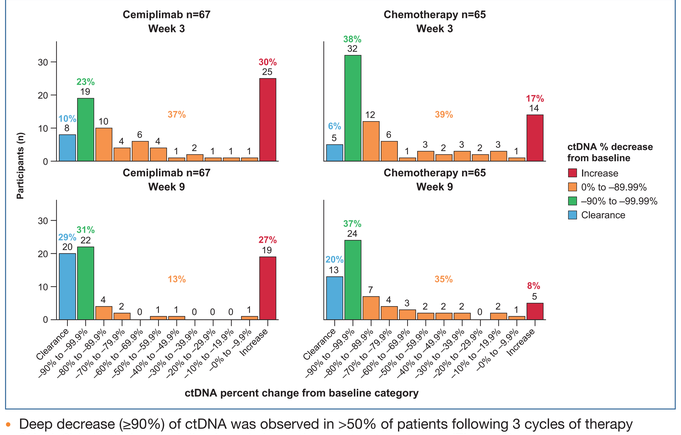
Figure 2. ctDNA dynamics over cycles 1–3 of treatment



MTM/mL, mean tumor molecule/mL = variant allele frequency normalized for plasma volume and total extracted ctDNA.

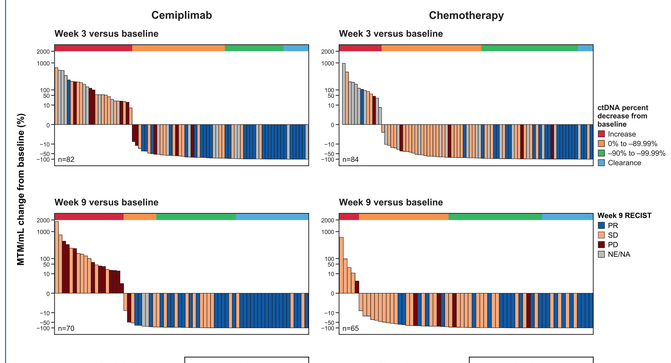
- At baseline, ctDNA level was detectable in majority of tested samples (**Figures S2–S4**).
- A trend of decrease in ctDNA levels was observed through the first 3 treatment cycles (through Week 9) in both treatment arms (**Figure 2**).
- ctDNA became undetectable in increasing number of patients between Week 3 and Week 9 in both treatment arms (**Figure 2**).

Figure 3. Changes in ctDNA levels at Week 3 and Week 9



- Deep decrease (≥90%) of ctDNA was observed in >50% of patients following 3 cycles of therapy (Week 9) in both the cemiplimab and chemotherapy treatment arms (**Figure 3**).
- Following cemiplimab treatment, changes in ctDNA level were notably bi-modal, with a majority of patients showing clearance, deep decrease, or increase (**Figure 3**).

Figure 4. Association of early ctDNA dynamics with first radiographic response (RECIST) at Week 9



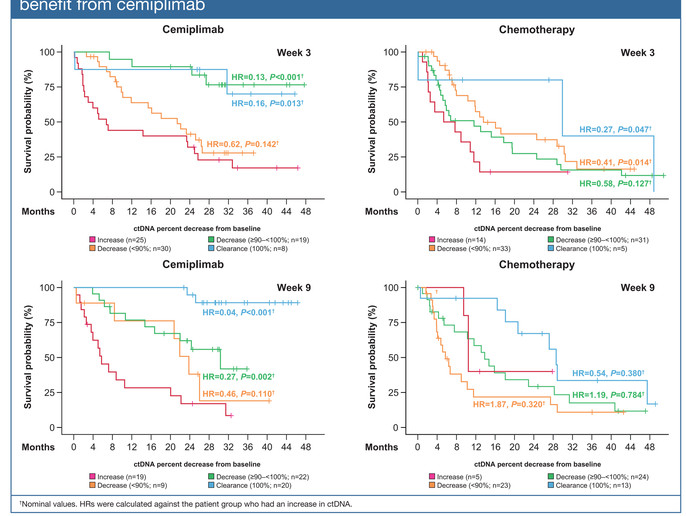
Cemiplimab	Week 9 RECIST, n (%)		
Timepoint (ctDNA reduction)	CR/PR	SD	PD
Week 3 ≥90% decrease (n=22)	19 (86)	3 (14)	0
Week 9 ≥90% decrease (n=39)	27 (69)	12 (31)	0

Chemotherapy	Week 9 RECIST, n (%)		
Timepoint (ctDNA reduction)	CR/PR	SD	PD
Week 3 ≥90% decrease (n=30)	19 (63)	9 (30)	2 (7)
Week 9 ≥90% decrease (n=34)	16 (47)	16 (47)	2 (6)

MTM/mL, mean tumor molecule/mL = variant allele frequency normalized for plasma volume and total extracted ctDNA.

- Waterfall plots of ctDNA percent change from baseline indicate association between early (Week 9) radiographic response among patients with ≥90% decrease and clearance in ctDNA levels; this was more pronounced in the cemiplimab treatment arm (**Figure 4**).

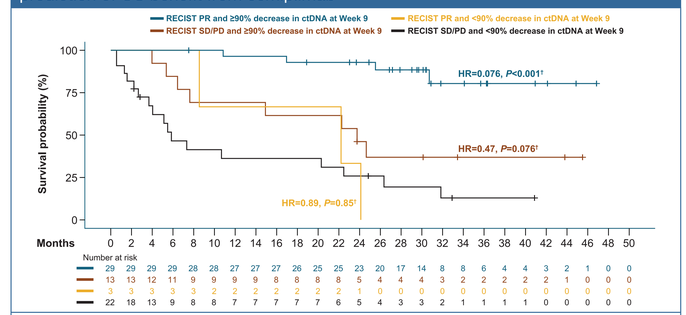
Figure 5. Early changes in ctDNA correlate with the risk of death or overall survival benefit from cemiplimab



†Nominal values. HRs were calculated against the patient group who had an increase in ctDNA.

- In the cemiplimab arm, ctDNA increase was associated with the highest risk of death. Compared to ctDNA increase, ctDNA deep decrease (≥90%) and clearance were associated with significantly improved OS (**Figure 5**).
- In the cemiplimab arm, 67 patients had available Week 3 and Week 9 ctDNA results.
  - Of 23 patients with ≥90% ctDNA decrease at Week 3, 20 maintained ≥90% decrease at Week 9 (87%).
  - Of 43 patients with <90% ctDNA decrease at Week 3, 21 achieved >90% decrease at Week 9 (43%).
- This association of ctDNA change patterns and OS outcomes was less obvious in the chemotherapy arm, especially for ctDNA changes at Week 9 (**Figure 5**).

Figure 6. Composite ctDNA and RECIST assessment at Week 9 may improve early prediction of OS benefit from cemiplimab



In addition, statistically improved association with OS benefit from cemiplimab was observed when ctDNA is included in a multivariable model with continuous measures of early radiographic response (Sum of Lesion Diameters) and baseline biomarker PD-L1 (Figure S5). †Nominal values.

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