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ISA event 2024: Bringing immunoscience to the clinic

When to stop or resume immunotherapy: data from NSCLC

Johan Vansteenkiste

Respiratory Oncology Unit
Dept. Pulmonology
Univ. Hospital KU Leuven, Belgium
Leuven Lung Cancer Group
www.LLCG.be **www.LLCG.eu**

Respiratory Oncology Unit
Univ. Hospital Leuven
Leuven Lung Cancer Group
http://www.LLCG.be

Declaration of interests [update 12/2023, alphabetical]

- **Advisory functions**
  - **Abbvie, AstraZeneca, BMS, Daiichi-Sankyo, Janssen, Merck, MSD, Novartis, PDCline, Pfizer, Roche, Sanofi**
- **Lectures**
  - **AstraZeneca, BMS, Daiichi-Sankyo, Janssen, Merck, MSD, Roche, Sanofi**
- **Others**
  - **None**

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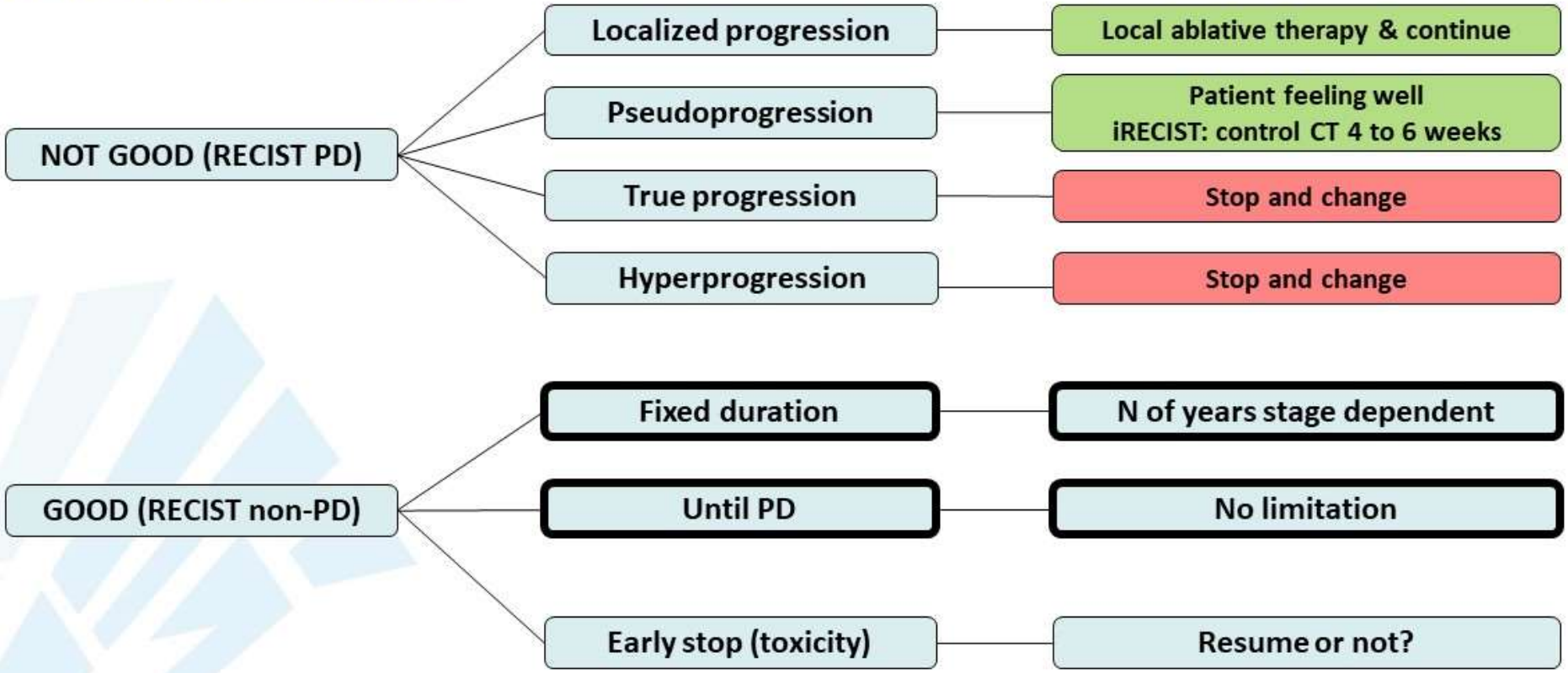
NSCLC immunotherapy

> duration of treatment



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CT, computed tomography; RECIST, Response Evaluation Criteria in Solid Tumours; NSCLC, non-small cell lung cancer; PD, progressive disease.

Duration in metastatic NSCLC

editorials

To Continue or Not to Continue? That Is the Question

Marina Chiara Garassino, MD[1]; Benjamin Besse, MD, PhD[2]; and Valter Torri, MD[3]

"Current data do not allow us to definitively answer the question on the optimal duration of treatment yet. For the time being, in the absence of clear data, the integration of patients' preferences could help, especially in decisions in which uncertainty is highly likely in this case"

Editorial by M. Garassino et al, J Clin Oncol 38:3830-3834, 2020

NSCLC, non-small cell lung cancer.
Garassino M. et al. *J Clin Oncol* 2020; 38:3830-2

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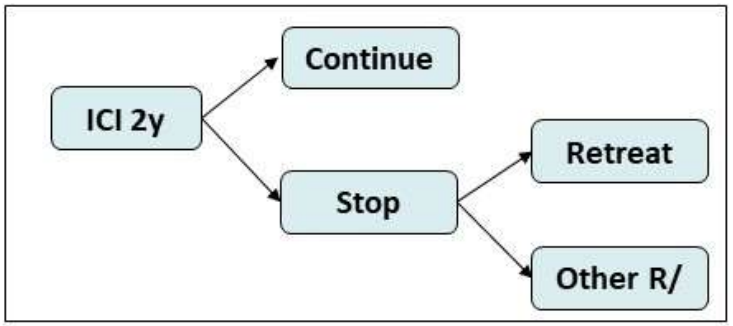
Metastatic NSCLC immunotherapy

> duration of immunotherapy

- No solid answer, no dedicated RCTs
- ESMO guidelines: “silence”
- Regulatory decision (e.g. 2y max. UK)



- Learn from follow-up of prospective trials
- Real-world experiences / retrospective analyses
- …

NSCLC, non-small cell lung cancer; RCT, randomized controlled trial; y, years.

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Metastatic NSCLC immunotherapy

> RCT continuous vs. fixed 1-year 2L/3L nivolumab [CM-153]

Checkmate 153

Pre-treated advanced NSCLC

- ≥1 prior systemic therapy
- PS 0–2
- Treated CNS mets allowed
- Started Nivolumab (N=1245)

- Nivolumab at 1 year (N=252)*

* All patients on treatment at 1 year were randomised **regardless of response status**

R

N=125 — **Stop nivolumab after 1 year***

* Retreatment allowed: N=39

N=127 — **Continue nivolumab***

* Nivolumab until PD, unacceptable toxicity, or withdrawal. Treatment beyond PD admitted

Primary endpoint

- **Incidence of high-grade TRAEs**

Exploratory endpoints

- Efficacy
- Biomarkers

NSCLC, non-small cell lung cancer; PS, performance status; TRAEs, treatment related adverse events.
Waterhouse D, et al. *J Clin Oncol* 2020;38:3863-73.

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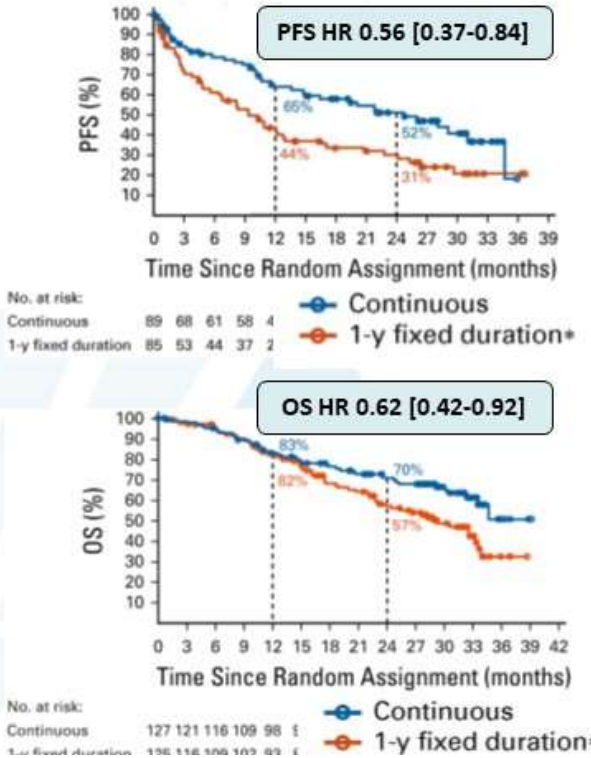
Metastatic NSCLC immunotherapy

> RCT continuous vs. fixed 1-year 2L/3L nivolumab [CM-153]



CAREFUL INTERPRETATION

- Phase IV community study – no preplanned study hypothesis
- Primary endpoint = safety
- Outcome added as exploratory aanlysis
- Moderate numbers
- Less relevant nowadays (2nd line ICI)

HR, hazard ratio; ICI, immune checkpoint inhibitor; L, line; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; RCT, randomized clinical trial.

Waterhouse D, et al. *J Clin Oncol* 2020;38:3863-73.

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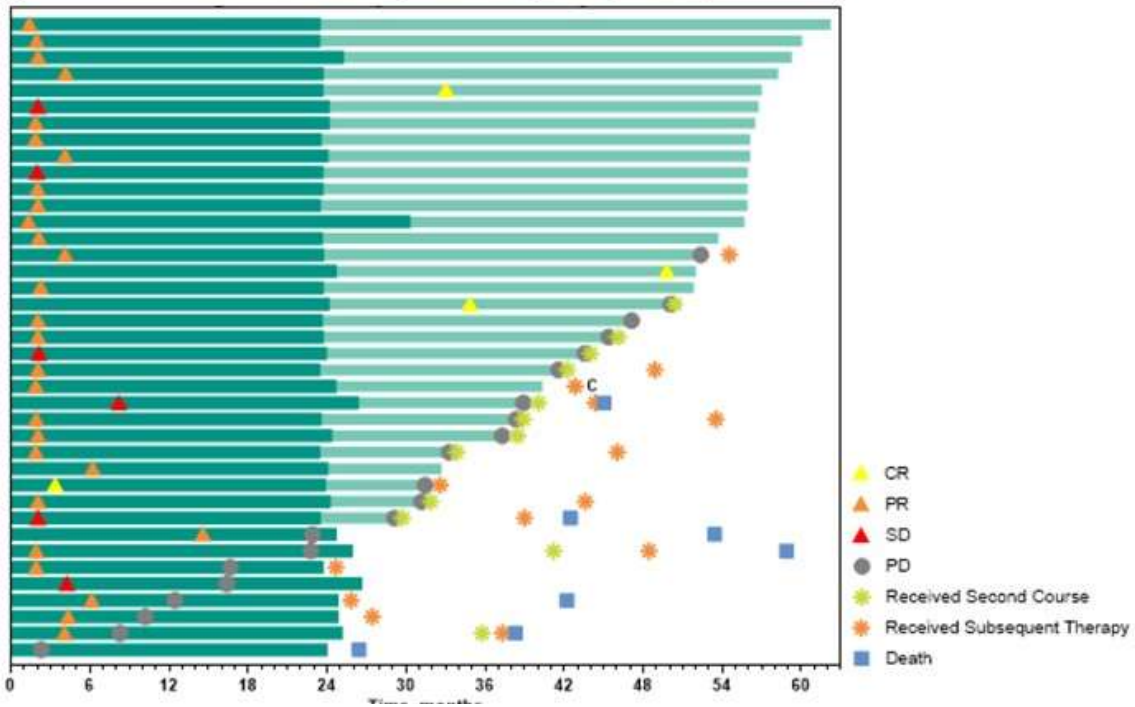
Metastatic NSCLC immunotherapy

> learn from prospective studies: ph3 Pembro 1L study [KN-024] 5Y update

Patients who completed 2 years (N=39)



KN-024: 1L in PD-L1 ≥50%

39/154 (25.3%) patients had 2Y of pembro

- **32 of these were responders**
- **3Y survival rate from pembro discontinuation was 81%**

At data cut-off

- **15 patients alive without Tx**
- **12 had 2nd course of immunotherapy**
- **10 had other first relapse Tx**
- **2 died without further Tx**

CR, complete response; NSCLC, non-small cell lung cancer; PD-L1; programmed cell death ligan-1; PD, progressive disease; PR, partial response; SD, stable disease.

Brahmer J, et al. *Ann Oncol* 2020;31(suppl_4):S1142-S1215. 10.1016/annonc/annonc325.

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Metastatic NSCLC immunotherapy
> learn from real-world/retrospective studies

- **Kim et al.** (Cancer 2022)**: multi-center retrospective study of Korean patients**
  - **N=96 completed 2 years of ICI ---> 1-year PFS/OS after cessation were 81.1% and 96.4%**
  - **N=43 had 6 mo of ICI and stopped early (toxicity) ---> 1-year PFS/OS after cessation were 81.0% and 90.0%**

- **Kobayashi et al.** (Clin Lung Cancer 2023)**: single-center retrospective study of 425 Japanese patients**
  - **N=41 had therapy ≥2 years**
  - **N=12 had fixed 2-year therapy ---> time-to-treatment failure Not Reached**
  - **N=29 had ICI until PD ---> time-to-treatment failure 48.3 mo; rate of AEs higher**

AE, adverse event; ICI, immune checkpoint inhibitor; mo, month; NSCLC, non-small cell lung cancer; OS, overall survival; PD, progressive disease; PFS, progression-free survival.

Kim H, et al. *Cancer* 2022;128:778-87; Kobayashi H, et al. *Clin Lung Cancer* 2023;24:498-506.e3. doi: 10.1016/j.cllc.2023.06.005.

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Metastatic NSCLC immunotherapy
> learn from real-world/retrosp. studies

JAMA Oncology | Original Investigation

Association Between Duration of Immunotherapy and Overall Survival in Advanced Non-Small Cell Lung Cancer

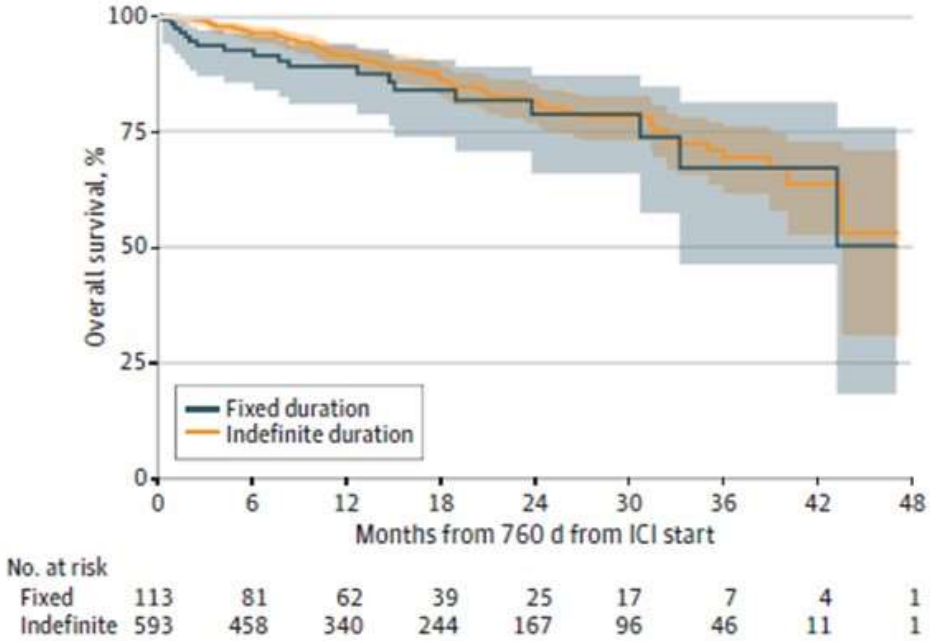
- Retrospective, population-based, cohort study in clinical database 2016-2020 on 1L ICI based treatment
  - Compare ICI 1L therapy for 2 years vs. continuation beyond 2 years
  - Primary endpoint: OS from day 760 onwards
- Approximately 1/5 patients discontinued immunotherapy at 2 years in the absence of progression
  - 113 patients (median age 69, 54.9% female) in fixed-duration group
  - 593 patients (median age 69, 47.6% female) in indefinite-duration group
  - Fixed-duration group were more likely smokers (99% vs 93%; P=0.01) and treated at academic center (22% vs 11%; P=0.001)

ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; OS, overall survival.
Sun L, et al. *JAMA Oncol* 2023;9:1075-82.

Metastatic NSCLC immunotherapy
> learn from real-world/retrosp. studies

JAMA Oncology | Original Investigation

Association Between Duration of Immunotherapy and Overall Survival in Advanced Non-Small Cell Lung Cancer



Survival Characteristic	Fixed duration (n = 113)	Indefinite duration (n = 593)
Overall survival probability		
3 y (12 mos from 760 d)	0.89 (0.81-0.94)	0.91 (0.88-0.94)
4 y (24 mos from 760 d)	0.79 (0.66-0.87)	0.81 (0.77-0.85)
Hazard ratio for death		
Unadjusted	1.26 (0.77-2.08)	1 [Reference]
P value	.36	
Adjusted[a]	1.33 (0.78-2.25)	1 [Reference]
P value	.29	

- **Lack of significant OS advantage for the indefinite-duration cohort provides reassurance to patients and clinicians who wish to discontinue immunotherapy at 2 years**

ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; OS, overall survival.
Sun L, et al. *JAMA Oncol* 2023;9:1075-82.

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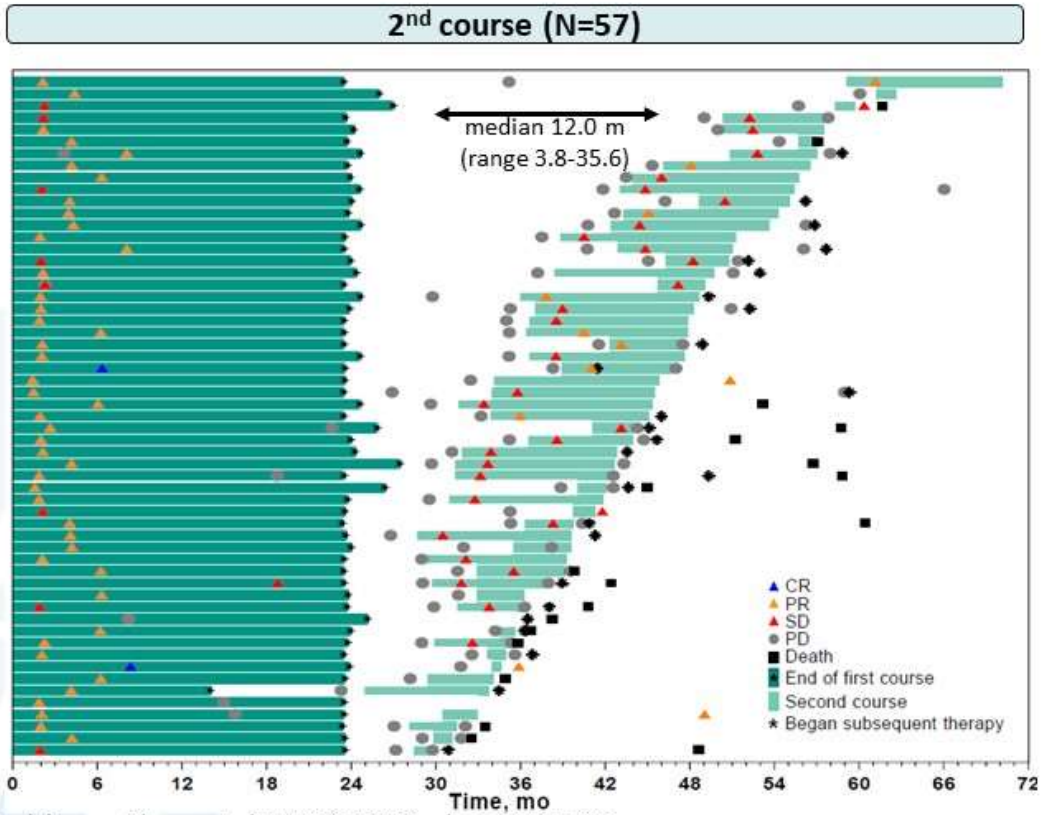
Metastatic NSCLC immunotherapy

> resuming pembro after ICI monotherapy [pooled KN-024; KN-042; KN598]



	Cohort 1 (pembro monotherapy) N = 57
ORR[a] (95% CI), %	19.3 (10.0–31.9)
DCR[a] (95% CI), %	73.7 (60.3–84.5)
Best overall response,[a] n (%)	
CR	0
PR	11 (19.3)
SD	31 (54.4)
PD	8 (14.0)
NA[b]	7 (12.3)
DOR,[a] median (range), mo	NR (0.0+ to 20.0+)
DOR ≥6 mo, %	78.8
OS,[c] median (95% CI), mo	27.5 (21.7–NR)
6-mo rate (95% CI), %	85.1 (72.4–92.3)
PFS,[a,c] median (95% CI), mo	10.3 (5.6–14.0)
6-mo rate (95% CI), %	60.8 (46.0–72.7)

CR, complete response; DCR, disease control rate; DOR, duration of response; ICI, immune checkpoint inhibitor; mo, month; NSCLC, non-small cell lung cancer; NA, not assessed; NR, not reached; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease. Rodriguez-Abreu D, et al. *J Thorac Oncol* 2022;17:S42–3.OA15.06.

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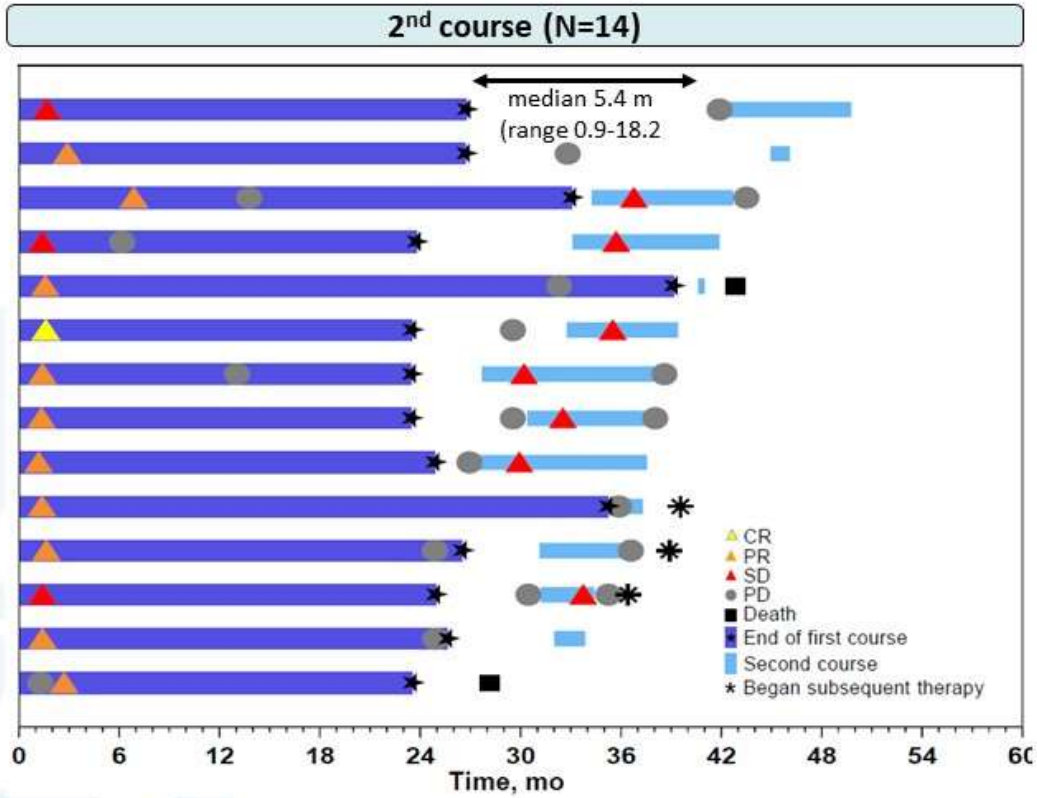
Metastatic NSCLC immunotherapy

> resuming pembro after ICI+ChT [pooled KN-189; KN-407]



	Cohort 2 (pembro + chemo) N = 14
ORR[a] (95% CI), %	0 (0.0–23.2)
DCR[a] (95% CI), %	50.0 (23.0–77.0)
Best overall response,[a] n (%)	
CR	0
PR	0
SD	7 (50.0)
PD	2 (14.3)
NA[b]	5 (35.7)
DOR,[a] median (range), mo	–
DOR ≥6 mo, %	–
OS,[c] median (95% CI), mo	NR (NR–NR)
6-mo rate (95% CI), %	85.1 (52.3–96.1)
PFS,[a,c] median (95% CI), mo	7.7 (1.8–NR)
6-mo rate (95% CI), %	54.5 (22.9–78.0)

CR, complete response; DCR, disease control rate; DOR, duration of response; ICI, immune checkpoint inhibitor; mo, month; NSCLC, non-small cell lung cancer; NA, not assessed; NR, not reached; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease. Rodriguez-Abreu D, et al. *J Thorac Oncol* 2022;17:S42–3.OA15.06.

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Duration in non-metastatic NSCLC

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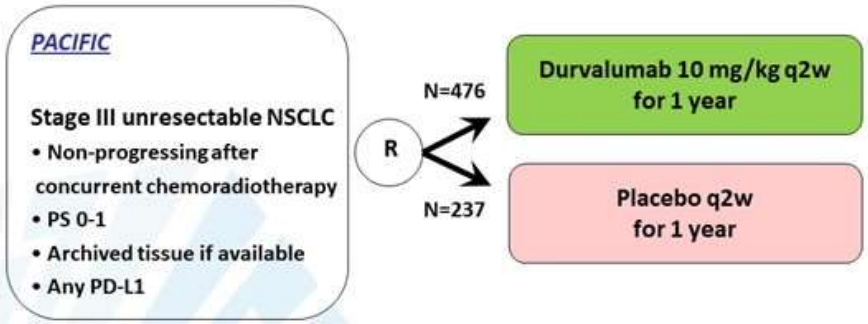
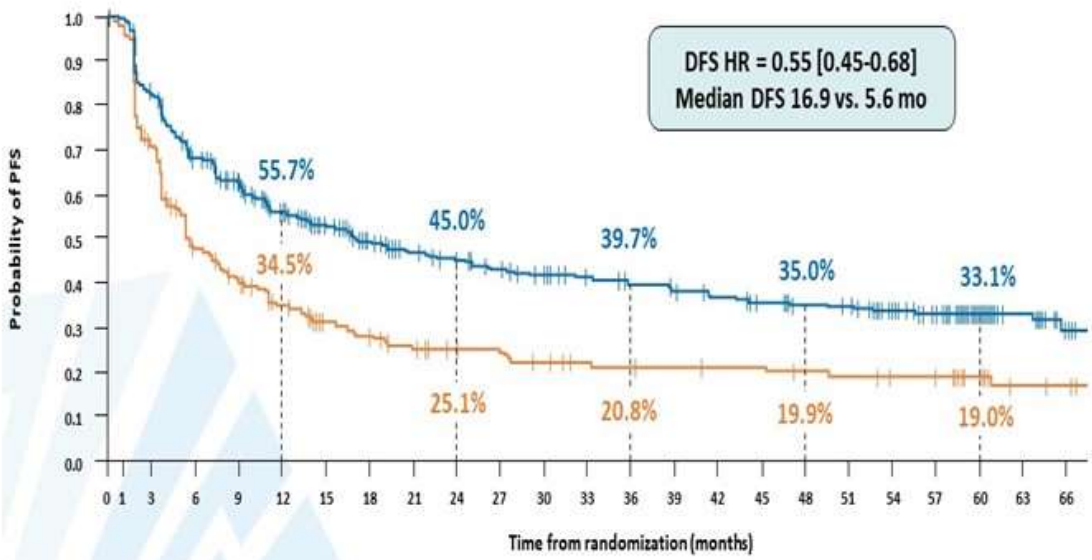
NSCLC, non-small cell lung cancer.

Unresectable stage III NSCLC immunotherapy

> pattern of DFS in PACIFIC study





DFS, disease-free survival; HR, hazard ratio; mo, month; NSCLC, non-small cell lung cancer; PFS, progression-free survival; PS, performance status.

Spigel D, et al. *J Clin Oncol* 2021;39(suppl 15): 8511-8511; Spigel D, et al. *J Clin Oncol* 2022;40:1301-11.

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Unresectable stage III NSCLC immunotherapy
> duration of ICI consolidation? Shorter?

➢ Not addressed in any of the current or ongoing trials

- In PACIFIC
  - 45% of the relapses are within first year, gradual plateau thereafter
  - Only 40% of the patients received 12 months of Durvalumab
- In a post-hoc analysis of a ph2 trial with consolidation Pembrolizumab, no detriment was seen with a shorter duration of ICI

➢ Trial designed to look at a shorter duration of ICI consolidation (<u>6 months</u>)
  - Patients in response or stable after cCRT: either Nivo 480 mg q4w *or* Nivo 240 mg q2w + Ipi 1 mg/kg q2w

cCRT, concomitant chemo-radiotherapy; ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; q2w, every 2 weeks; q4w, every 4 weeks.

Durm G, et al. Cancer 2020;126:4353-61; Durm G, et al. *J Clin Oncol* 2022;40(suppl):Abstr 8509.

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Unresectable stage III NSCLC immunotherapy

> duration of ICI consolidation? Shorter?

	Nivolumab Alone (N= 52)	Nivolumab/Ipilimumab (N= 47)
Median F/u, months (range)	27.7 (2-44.2)	29.2 (3.2-46.8)
Progression Free Survival*		
18- Month (95% CI)	63.7 (47.3-76.2)	67.6 (51.4-79.5)
P-value	<0.1	<0.1
Median, months (95% CI)	25.8 (16.5-NR)	25.4 (18.6-NR)
Overall Survival		
18- Month (95% CI)	82.7 (69.2-90.6)	85.7 (72.3-92.9)
24- Month (95% CI)	77.7 (63.1-87.1)	80.6 (65.8-89.5)
Median, months (95% CI)	NR (NR-NR)	NR (28.1-NR)

PACIFIC

48%

	Nivolumab Alone (N=54)	Nivolumab/Ipilimumab (N=51)
Any Treatment-Related AE (TRAE), n (%)	39 (72.2)	41 (80.4)
Any Grade ≥3 AE, n (%)*	21 (38.9)	27 (52.9)
Any Grade ≥3 TRAE, n (%)	10 (18.5)	14 (27.5)
TRAE Occurring in ≥ 10% Pts, n (%)		
Fatigue	17 (31.5)	16 (31.4)
Dyspnea	8 (14.8)	10 (19.6)
Rash	9 (16.7)	8 (15.7)
Hypothyroidism	7 (13)	8 (15.7)
Diarrhea	4 (7.4)	10 (19.6)
Pruritus	5 (9.3)	9 (17.7)
Arthralgia	2 (3.7)	6 (11.8)
Nausea	2 (3.7)	6 (11.8)
Pneumonitis		
Grade ≥2	12 (22.2)	16 (31.4)
Grade 3 (no Gr 4/5 pneumonitis)	5 (9.3)	9 (17.6)
Median time to Gr ≥2 Pneum, mo. (range)	11.9 (4.1-36.6)	7.3 (1.3-36.9)

3.4%

ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; TRAE, treatment-related adverse event.
Durm G, et al. *J Clin Oncol* 2022;40(suppl):Abstr 8509.

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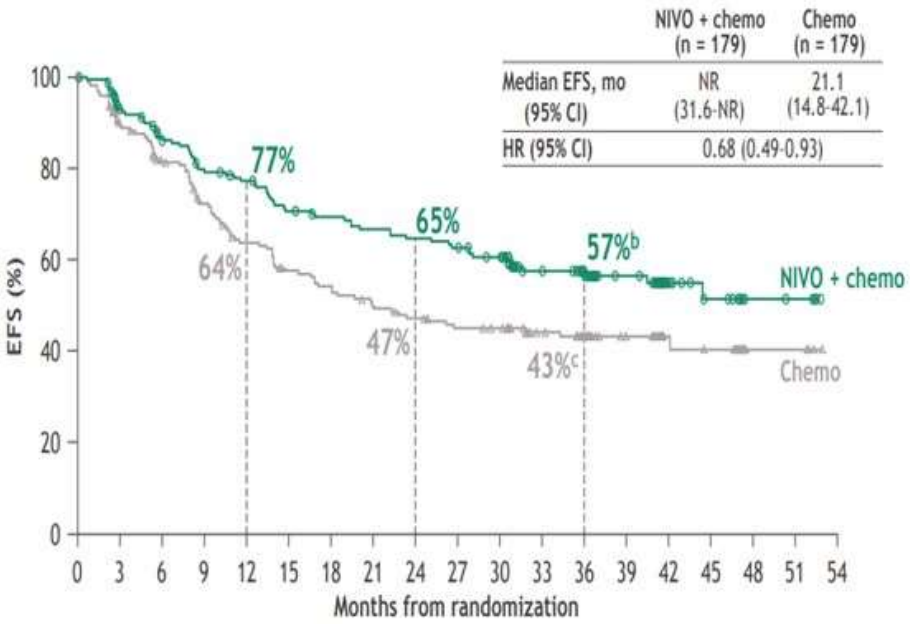
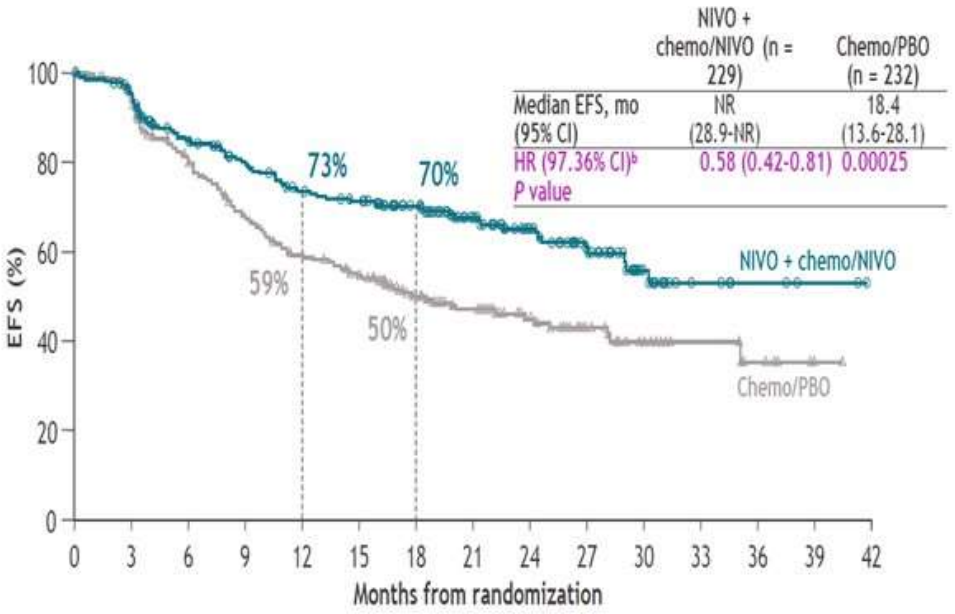
Resectable stage II-IIIB NSCLC immunotherapy

> *neoadjuvant* 3 cycles ICI+ChT vs. *perioperative* 3 cycles + postop ICI up to 1 year

CM-816: 3 cycles chemo+ICI neoadjuvant only



CM-77T: 3 cycles chemo-ICI neoadjuvant + postop ICI up to 1Y



EFS, event-free survival; HR, hazard ratio; ICI, immune checkpoint inhibitor; NR, not reached; NSCLC, non-small cell lung cancer.
Forde P, et al. Neoadjuvant nivolumab (N) + platinum-doublet chemotherapy (C) for resectable NSCLC: 3-y update from CheckMate 816. Presented at: 2023 European Lung Cancer Congress; March 29-April 1, 2023; Copenhagen, Denmark. Abstract 840; Cascone T, et al. *Ann Oncol* 2023;34:S1295 (abstr LBA1). Study 77T results is provided for scientific purpose; the study is still under review by the EU HA.

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NSCLC immunotherapy

> duration of treatment

Optimal duration at present uncertain

- **Metastatic NSCLC**
  - **Quite substantial circumstantial evidence to stop at 2 years, in consultation with the patient**
- **Non-metastatic NSCLC**
  - **Quite substantial data on duration of 1 year**
  - **Shorter courses may be reasonable**
  - **Role of biomarkers, although not ready for primetime**
    - **Pathological response in resection specimen**
    - **Response on imaging (CT, FDG-PET)**
    - **Clearance of ctDNA**

CT, computed tomography; ctDNA, circulating tumour DNA; FDG-PET, fluorodeoxyglucose (FDG)-positron emission tomography; NSCLC, non-small cell lung cancer.

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