Optimal Indications of Rechallenge with Immune Checkpoint inhibitors

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- Data on rechallenge in clinical trials
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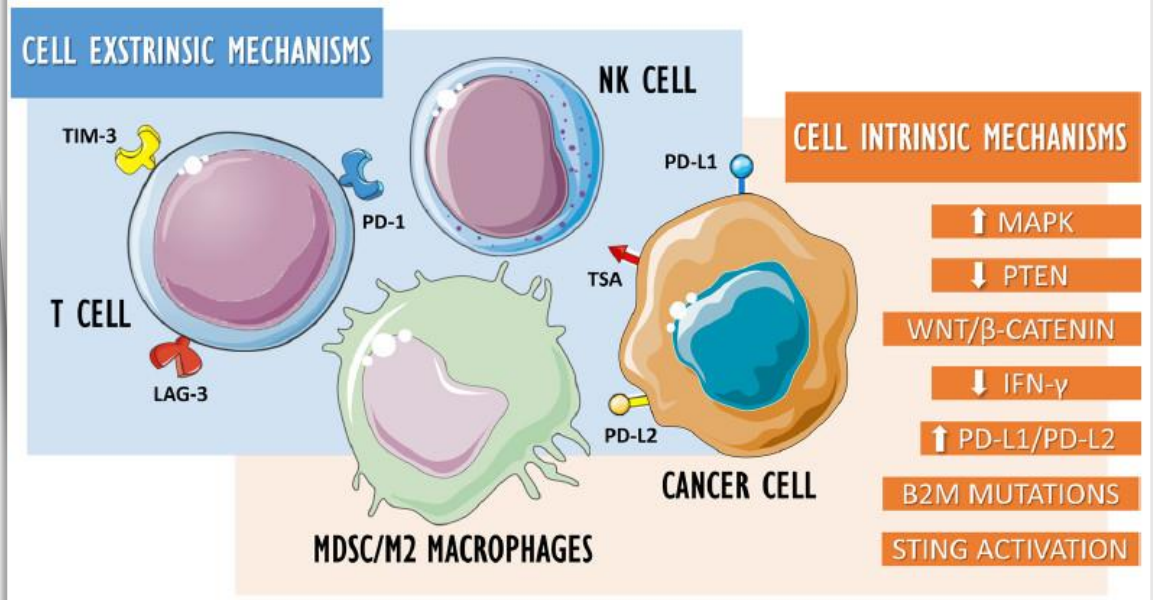
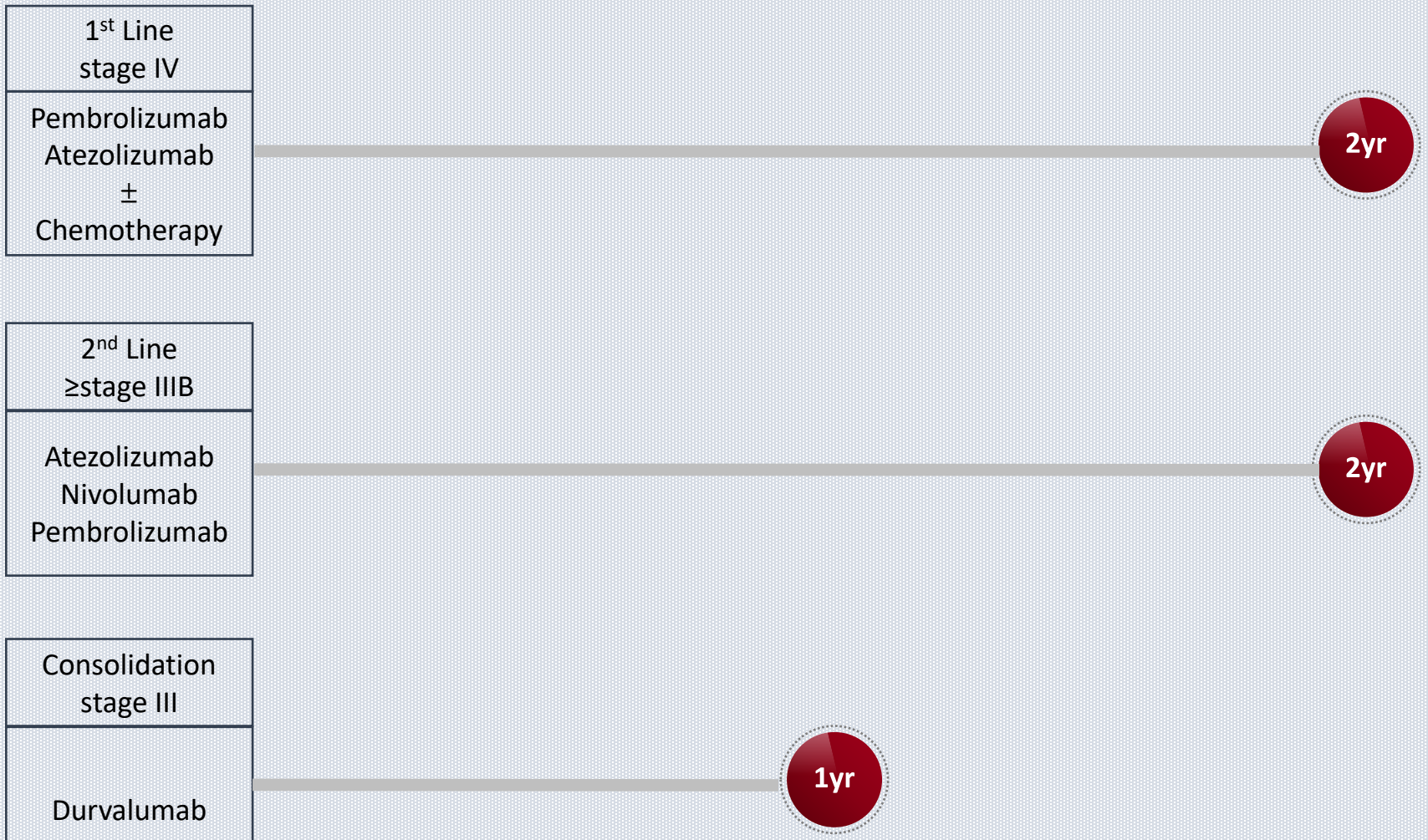


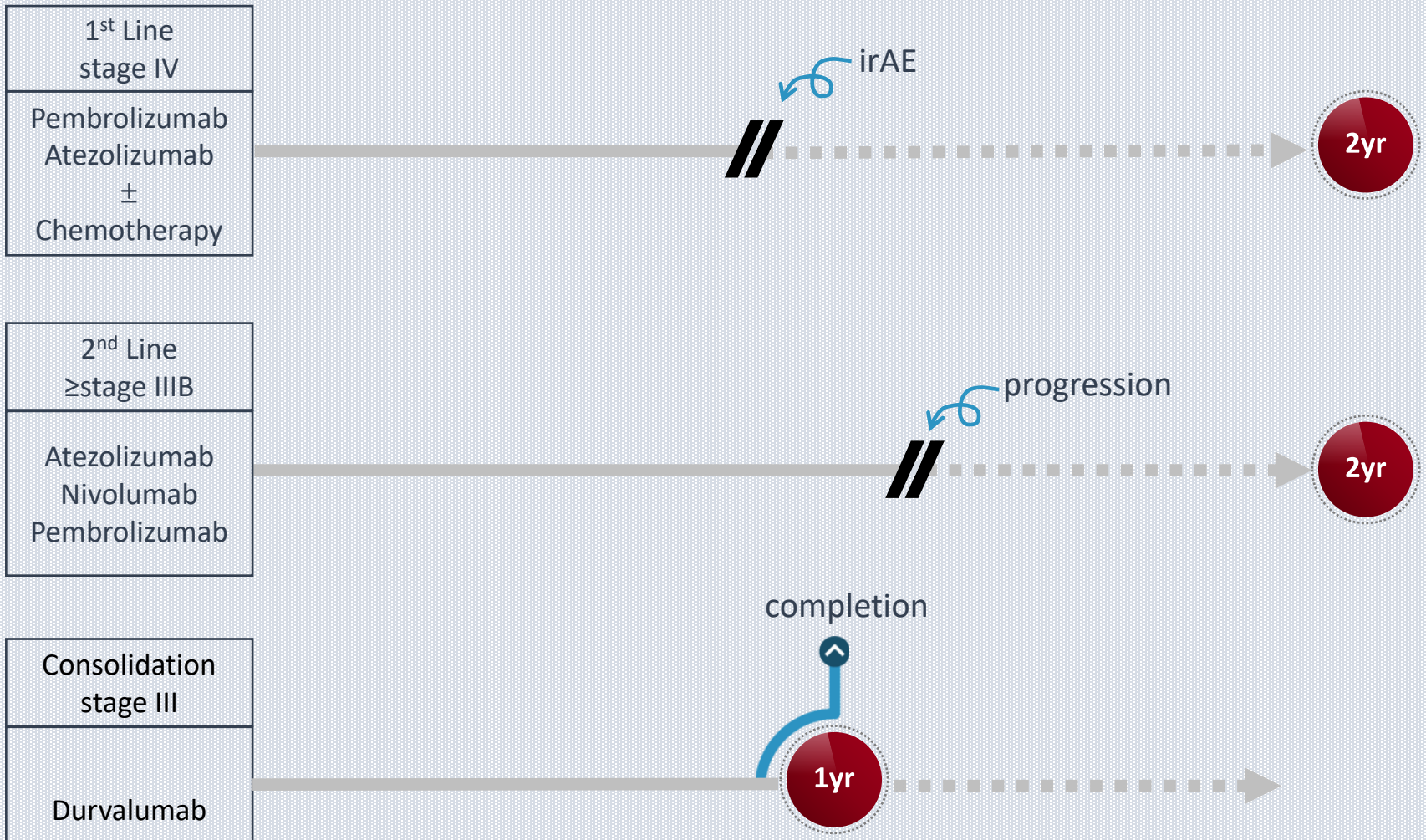
Critical Reviews in Oncology / Hematology 169 (2022) 103538

Immunotherapy on the patients with NSCLC

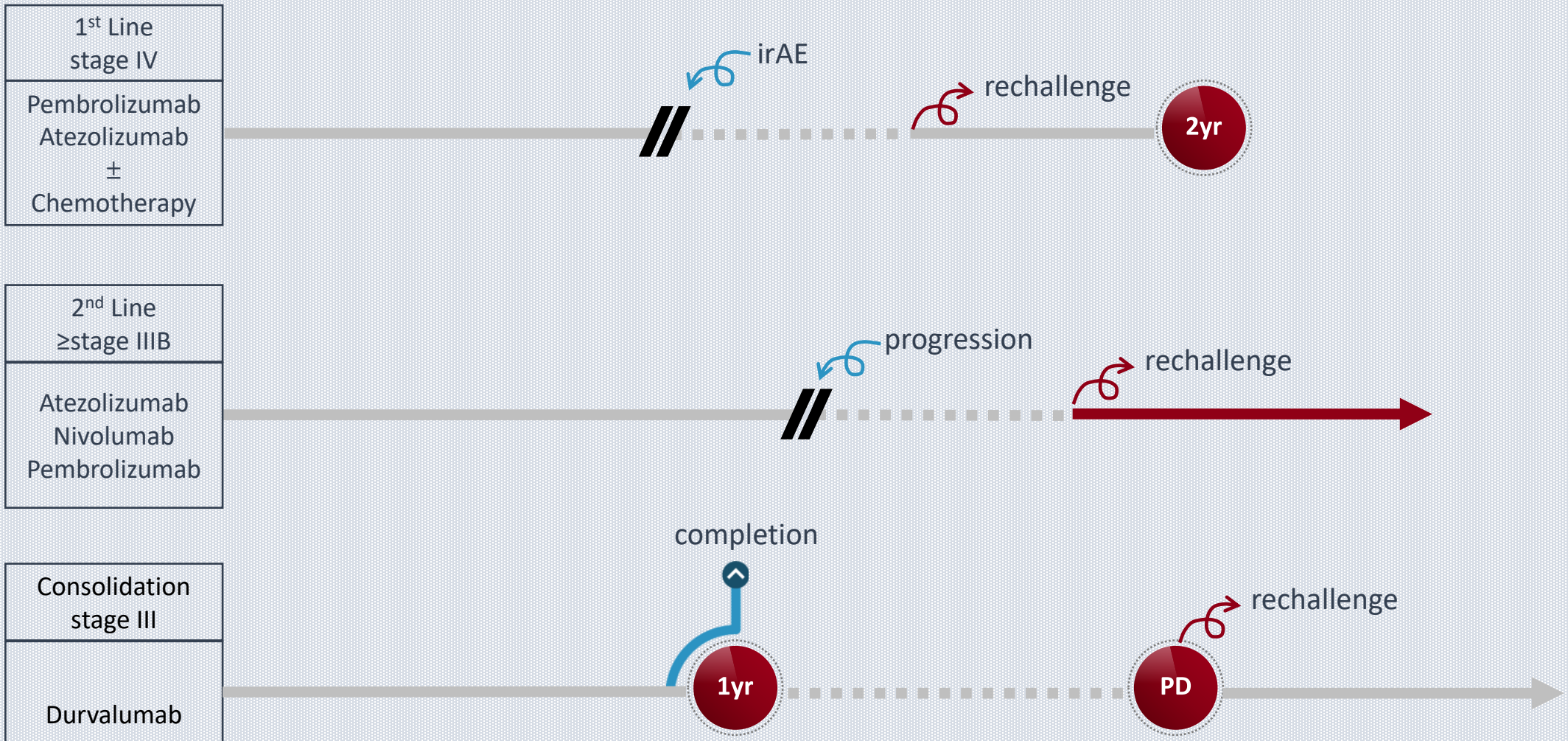
KU MEDICINE KOREA UNIVERSITY MEDICINE



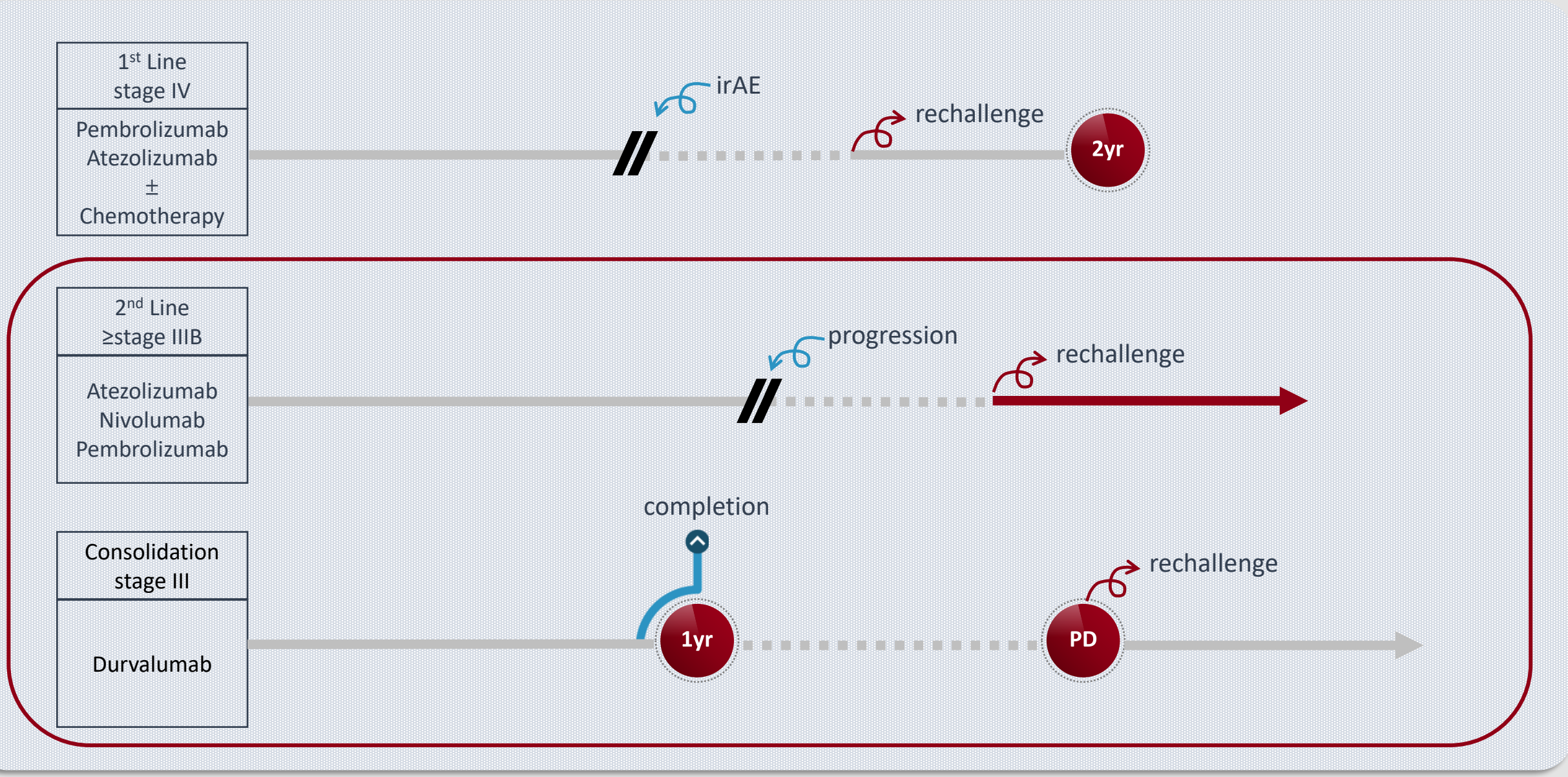
Discontinuation of Immunotherapy



Situations of rechallenge with immunotherapy



Situations of rechallenge with immunotherapy



NCCN version 3.2022

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE – SUBSEQUENT

ADENOCARCINOMA, LARGE CELL, NSCLC NOS (PS 0–2)

Preferred (no previous IO):

Systemic immune checkpoint inhibitors[e]

- Nivolumab (category 1)
- Pembrolizumab (category 1)[q]
- Atezolizumab (category 1)

Other Recommended (no previous IO or previous IO):[r]

- Docetaxel
- Pemetrexed
- Gemcitabine
- Ramucirumab/docetaxel
- Albumin-bound paclitaxel

SQUAMOUS CELL CARCINOMA (PS 0–2)

Preferred (no previous IO):

Systemic immune checkpoint inhibitors[e]

- Nivolumab (category 1)
- Pembrolizumab (category 1)[q]
- Atezolizumab (category 1)

Other Recommended (no previous IO or previous IO):[r]

- Docetaxel
- Gemcitabine
- Ramucirumab/docetaxel
- Albumin-bound paclitaxel

[e] If progression on PD-1/PD-L1 inhibitor, using a PD-1/PD-L1 inhibitor is not recommended.

[q] Pembrolizumab is approved for patients with NSCLC tumors with PD-L1 expression levels ≥1%, as determined by an FDA-approved test.

[r] If not previously given.

보험 급여 기준

연번	항암요법	투여대상
4	pembrolizumab[주1]	PD-L1 발현 양성(발현 비율 ≧ 50%[주3])이면서, EGFR 또는 ALK 변이가 없는 진행성 (stage IV) ※ 선행화학요법/수술후보조요법, 근치적항암화학방사선요법 치료 종료 후 6개월 이후 재발한 경우 포함 ※ 관해공고요법으로 durvalumab 치료 실패 시 급여 불가함
	(제2022-38호: 2022.3.1)	
5	pembrolizumab[주1] + pemetrexed + platinum	EGFR 또는 ALK 변이가 없는 전이성 비편평상피세포 ※ 선행화학요법/수술후보조요법, 근치적항암화학방사선요법 치료 종료 후 6개월 이후 재발한 경우 포함 ※ 관해공고요법으로 durvalumab 치료 실패 시 급여 불가함 ※ platinum은 초기 4주기 병용 투여 이후 투여하지 아니함 ※ pemetrexed는 최대 2년까지 급여 인정함
	(제2022-38호: 2022.3.1)	
6	pembrolizumab[주1] + paclitaxel + carboplatin	전이성 편평상피세포 ※ 선행화학요법/수술후보조요법, 근치적항암화학방사선요법 치료 종료 후 6개월 이후 재발한 경우 포함 ※ 관해공고요법으로 durvalumab 치료 실패 시 급여 불가함 ※ paclitaxel과 carboplatin은 초기 4주기 병용 투여 이후 투여하지 아니함
	(제2022-38호: 2022.3.1)	
7	atezolizumab[주1]	PD-L1 발현 양성(발현비율 TC3 또는 IC3[주7])이면서, EGFR 또는 ALK 변이가 없는 전이성 ※ 선행화학요법/수술후보조요법, 근치적항암화학방사선요법 치료 종료 후 6개월 이후 재발한 경우 포함 ※ 관해공고요법으로 durvalumab 치료 실패 시 급여 불가함
	(제2022-113호: 2022.5.1)	

- Durvalumab 치료 실패시 기간 명시 확인
  → 6개월

- Durvalumab 치료 반응 있었던 환자
  - durvalumab (12개월) 투약 종료 시점 CT와 6개월 뒤 CT상 SD 가 확인된 환자
  - 이후 시간이 경과되어 PD-L1 발현 양성이면서, EGFR 또는 ALK 변이가 없는 진행성(stage IV) pembrolizumab 투여 대상에 합당한 경우 1차로 pembrolizumab 보험 급여 투약 가능 ?
  - 이후 시간이 경과되어 PD-L1 발현 음성이면서, EGFR 또는 ALK 변이가 없는 진행성(stage IV) pembrolizumab + cytotoxic CTx 투여 대상에 합당한 경우 1차로 pembrolizumab 보험 급여 투약 가능 ?

Clinical trials
(PD after completion of prior ICI treatment)

Clinical trials of Immunotherapy

KN 010	Mono	NSCLC	II/III	≥2nd	≥1%	35cycles or 2yrs
KN 024	Mono	NSCLC	III	1st	≥50%	35cycles or 2yrs
KN 042	Mono	NSCLC	III	1st	≥1%	35cycles or 2yrs
KN 189	Pemetrexed+Platinum	nonsqcc NSCLC	III	1st	≥1% (<1%)	35cycles or 2yrs
KN 407	Paclitaxel+Carboplatin	Sqcc NSCLC	III	1st	≥1% (<1%)	35cycles or 2yrs
CM 017	Mono	Sqcc NSCLC	III	≥2nd	—	until PD/toxicity
CM 057	Mono	nonSqcc NSCLC	III	≥2nd	—	until PD/toxicity
CM 063	Mono	Sqcc NSCLC	II	≥3rd	≥5% (<5%)	until PD/toxicity
CM 026	Mono	NSCLC	III	1st	≥1%	until PD/toxicity
POPLAR	Mono	NSCLC	II	≥2nd	—	until PD/toxicity
OAK	Mono	NSCLC	III	≥2nd	—	until PD/toxicity
IMp 110	Mono	NSCLC	III	1st	≥1%	until PD/toxicity
IMp 130	Paclitaxel+Carboplatin	nonSqcc NSCLC	III	1st	—	until PD/toxicity
IMp 131	ACP or ABCP	nonSqcc NSCLC	III	1st	—	until PD/toxicity
IMp 132	Pemetrexed+Platinum	nonSqcc NSCLC	III	1st	—	until PD/toxicity
PACIFIC	mono	NSCLC	III	consolidation	—	1yr

Data on rechallenge in clinical trials

KN 010	Mono	NSCLC	II/III	≥2nd	≥1%	35cycles or 2yrs
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OAK	Mono	NSCLC	III	≥2nd	—	until PD/toxicity
IMp 110	Mono	NSCLC	III	1st	≥1%	until PD/toxicity
IMp 130	Paclitaxel+Carboplatin	nonSqcc NSCLC	III	1st	—	until PD/toxicity
IMp 131	ACP or ABCP	nonSqcc NSCLC	III	1st	—	until PD/toxicity
IMp 132	Pemetrexed+Platinum	nonSqcc NSCLC	III	1st	—	until PD/toxicity
PACIFIC	mono	NSCLC	III	consolidation	—	1yr

KEYNOTE-010

Data cutoff date: April 8, 2020
m Time from randomization: 67.4 months (60.0-77.9)

Key Eligibility

(N=1034)

- Histologically or cytologically confirmed stage IV NSCLC
- Measurable disease and progression per RECIST v1.1 after chemotherapy[a]
- ECOG PS 0-1
- PD-L1 TPS ≥1%
- No active brain metastasis or autoimmune disease

Randomized 1:1:1

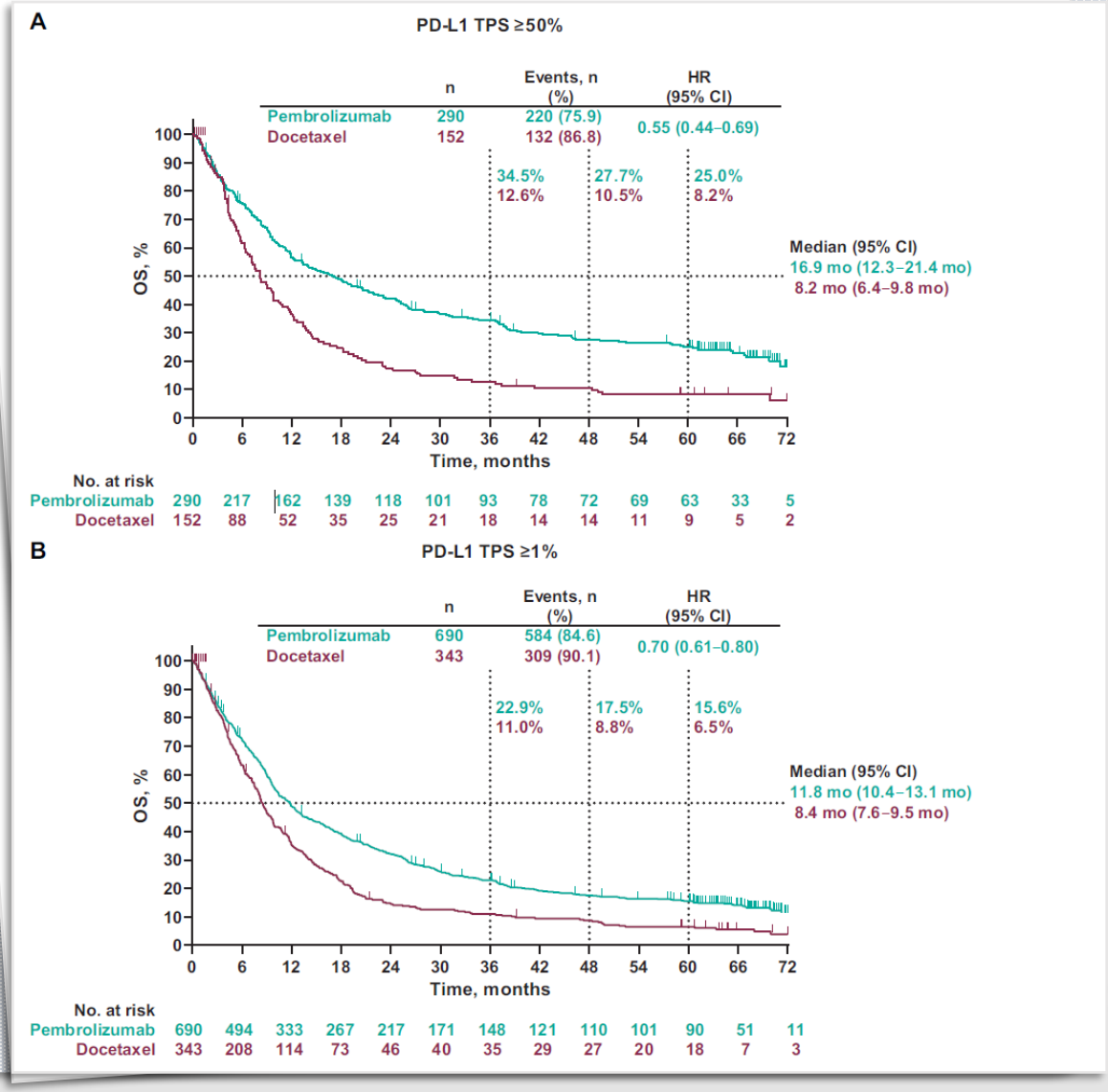
Stratification

- ECOG PS 0 vs 1
- PD-L1 TPS[b] ≥50% vs 1%-49%
- East Asian vs non–East Asian site

Pembrolizumab 2 mg/kg IV Q3W, 24 months (n=345)

Pembrolizumab 10 mg/kg IV Q3W, 24 months (n=346)

Docetaxel 75 mg/m² Q3W per local guidance (n=343)



JTO.16(10);1718-32

KEYNOTE-010

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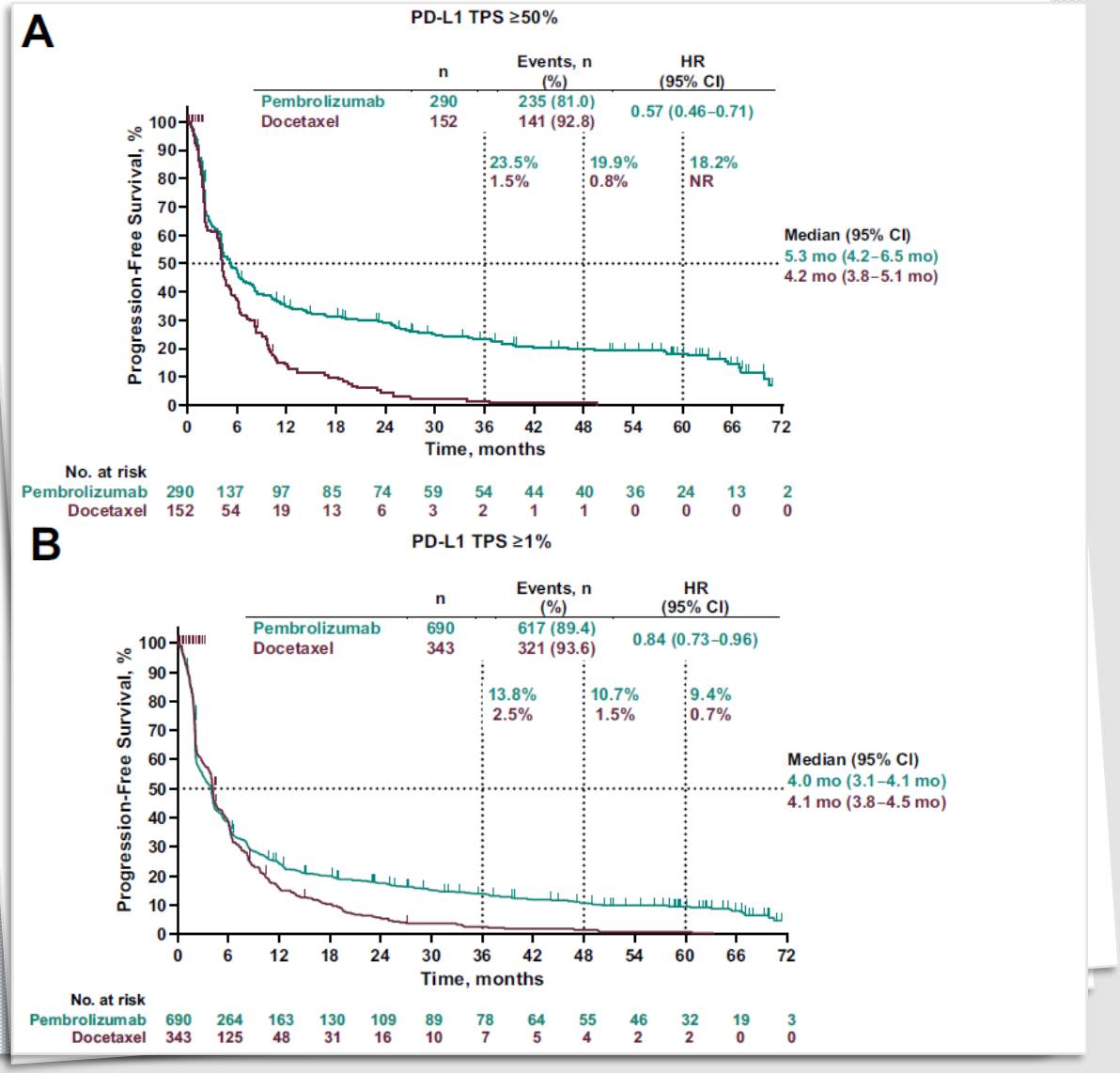
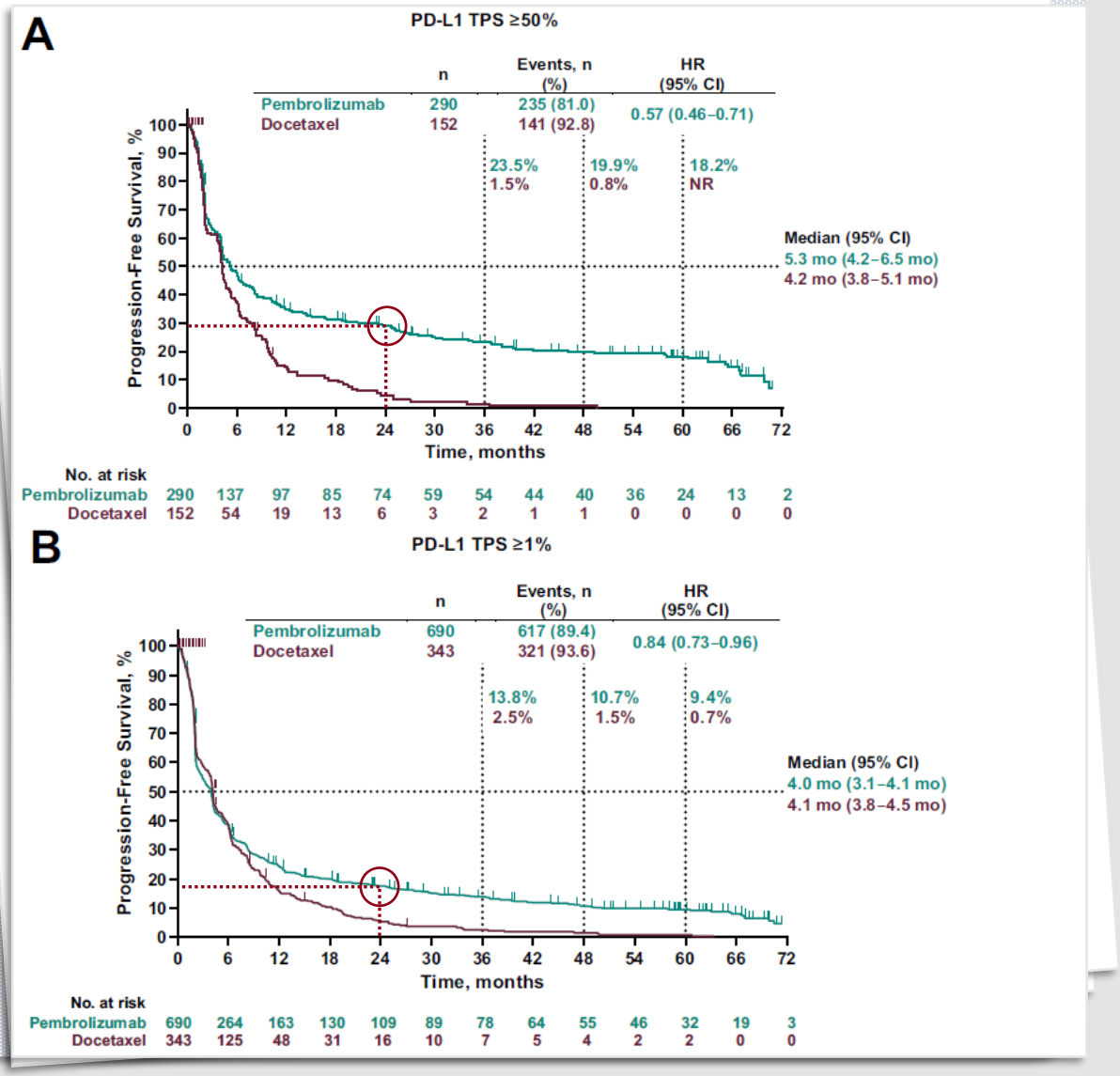


JTO.16(10);1718-32

KEYNOTE-010

- **Characteristics (n=79) of patients who completed 35 cycles** m Time from randomization: 68.1 months (60.5-74.5)
  - PD-L1 TPS, ≥50%: 58(73.4%), 1-49%: 21(26.6%)
  - current/former smoker: 72 (91.1%)
- **ORR**
  - 98.7% (CR: 19.0%)
- **OS after completing 35 cycles**
  - mOS: NR
  - 12months: 98.7% (95%CI, 91.1-99.8)
  - 24months: 86.3% (95%CI, 72.7-93.4)
  - 36months: 83.0% (~5yr from randomization)
- **PFS after completing 35 cycles**
  - 12months: 72.5% (95%CI, 59.9-81.8)
  - 24months: 57.7% (95%CI, 41.2-71.0)
  - 48.4% were alive without disease progression



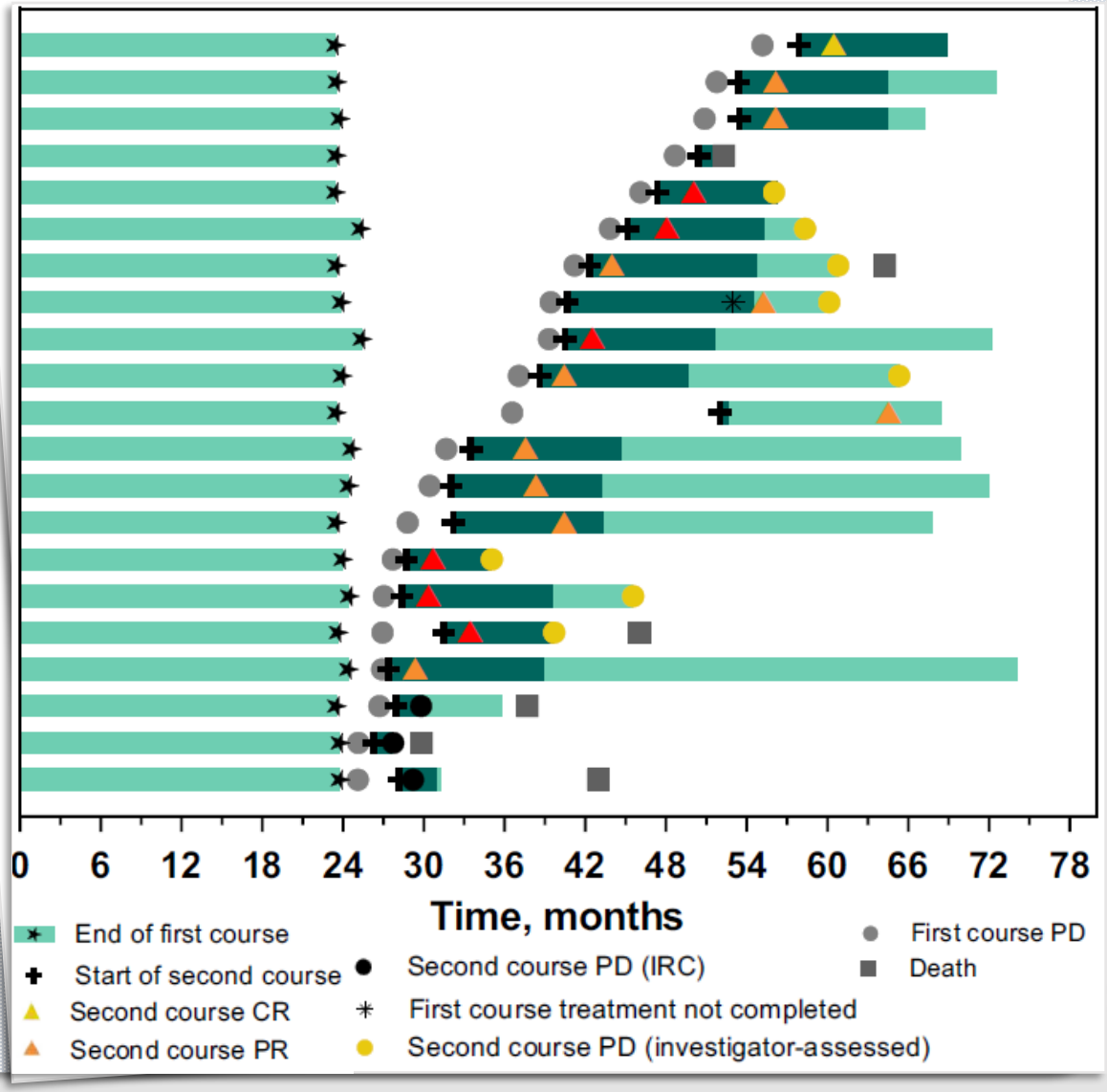
JTO.16(10);1718-32

Rechallenge with pembrolizumab in KEYNOTE-010

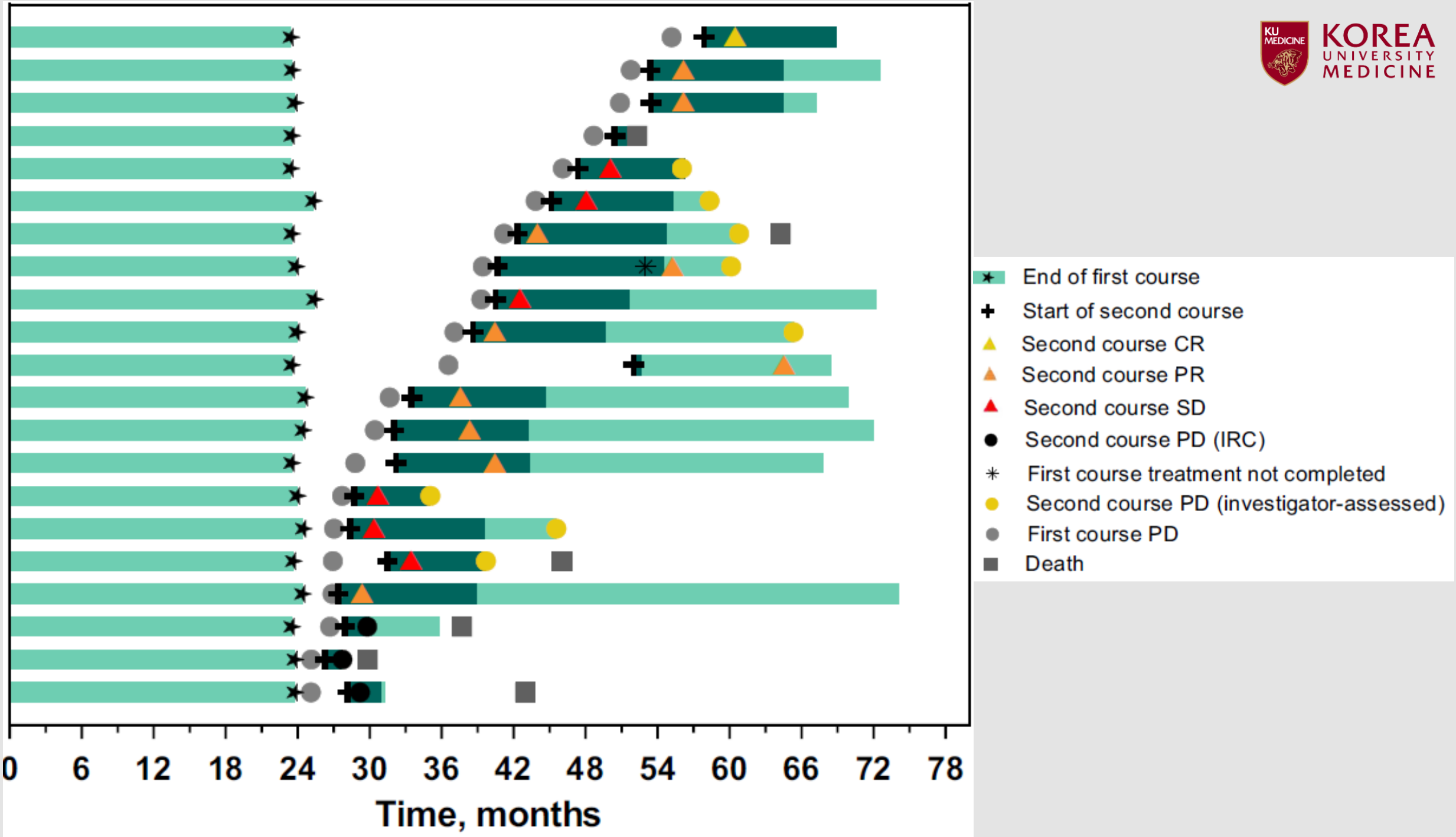
- **Indication**
  - completion of 35 cycles or 2 years of pembrolizumab
  - stopping after archieving CR and receiving ≥6 months of treatment
  - not administrated other anticancer therapy
- **2nd course pembrolizumab**
  - up to 17 cycles or 1 year
  - 21 subjects received 2nd course pembrolizumab
  - 71.4% were alive at data cutoff date
  - all Gr AE: 10 (47.6%), Gr3 AE: 2 (pneumonitis, LFT)

Best objective response, n(%)

ORR	11 (52.3)
CR	1 (4.7)
PR	10 (47.6)
SD	6 (28.7)
PD	3 (14.3)
No assess	1 (4.8)



1. JTO.16(10);1718-32, 2. Herbst RS, Garon EB, Kim DW, et al. Poster presented at: IASLC World Conference on Lung Cancer (WCLC); January 28-31, 2021; Virtual.


End of first course
Start of second course
Second course CR
Second course PR
Second course SD
Second course PD (IRC)
First course treatment not completed
Second course PD (investigator-assessed)
First course PD
Death
0
6
12
18
24
30
36
42
48
54
60
66
72
78
Time, months

KEYNOTE-024

Data cutoff date: June 1, 2020
m Time from randomization: 59.9 months (55.1-68.4)

Patients (N=305):

- Histologically or cytologically confirmed stage IV NSCLC
- No activating *EGFR* mutation or *ALK* translocation
- No prior systemic treatment
- Measurable disease
- Life expectancy of at least 3 months
- PD-L1 TPS ≥50%
- ECOG PS 0–1
- No untreated brain metastases
- No active autoimmune disease requiring systemic therapy

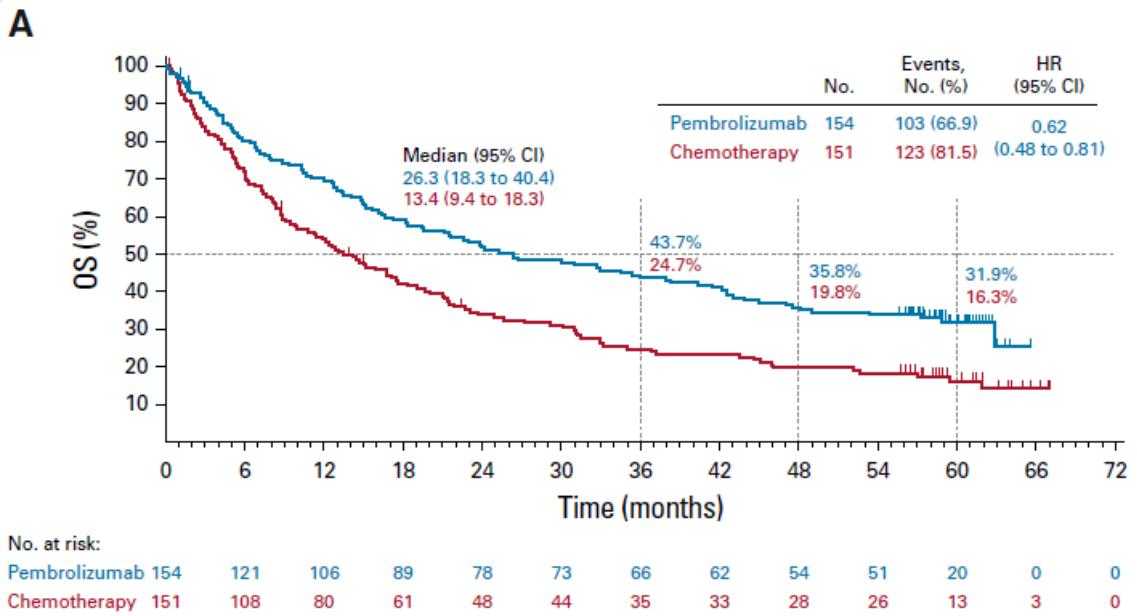
R 1:1

35 cycles (2 years)

Pembrolizumab 200 mg IV Q3W

4–6 cycles

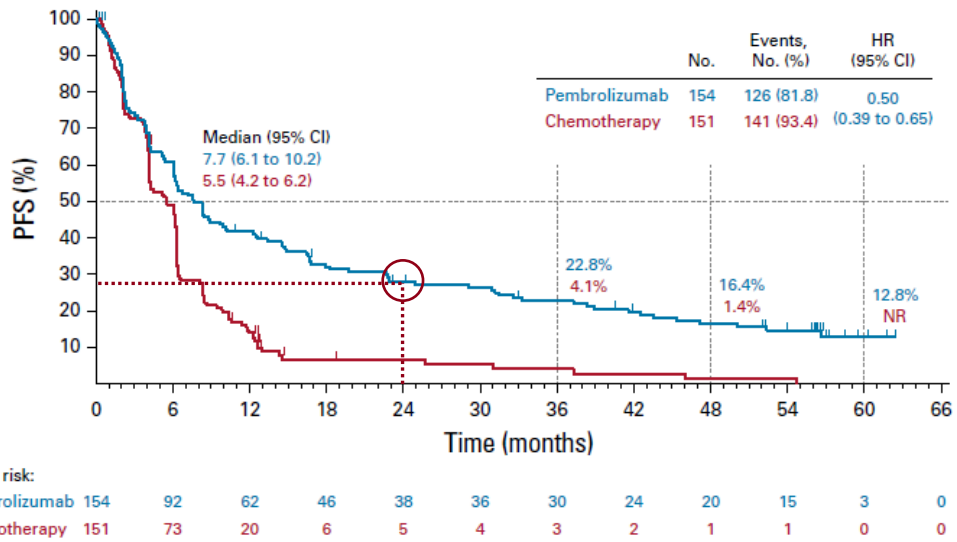
Platinum-doublet chemotherapy Q3W[a,b]

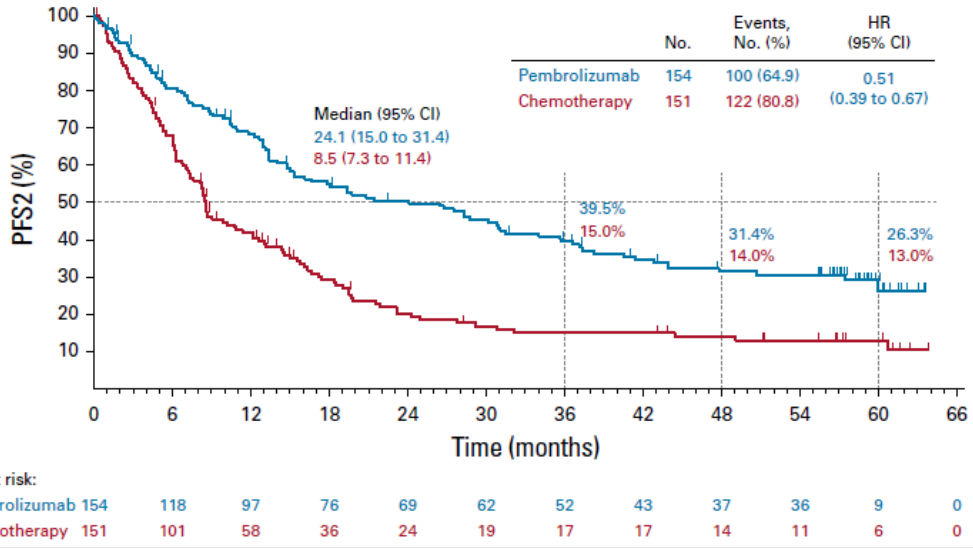


J Clin Oncol 39:2339-2349.

KEYNOTE-024

- **Characteristics of patients who completed 35 cycles**
  - 39 of 151 (25.8%)
- **ORR**
  - 82.1% (CR: 10.3%)
- **OS rate at 3yrs**
  - 81.4% (95%CI, 64.7-90.7)
- **PFS**
  - 18 of 39 (46.2%) alive without PD or subsequent therapy
- **Treatment related AE**
  - all Gr: 87.2%
  - Gr 3-4: 15.4%





J Clin Oncol 39:2339-2349.

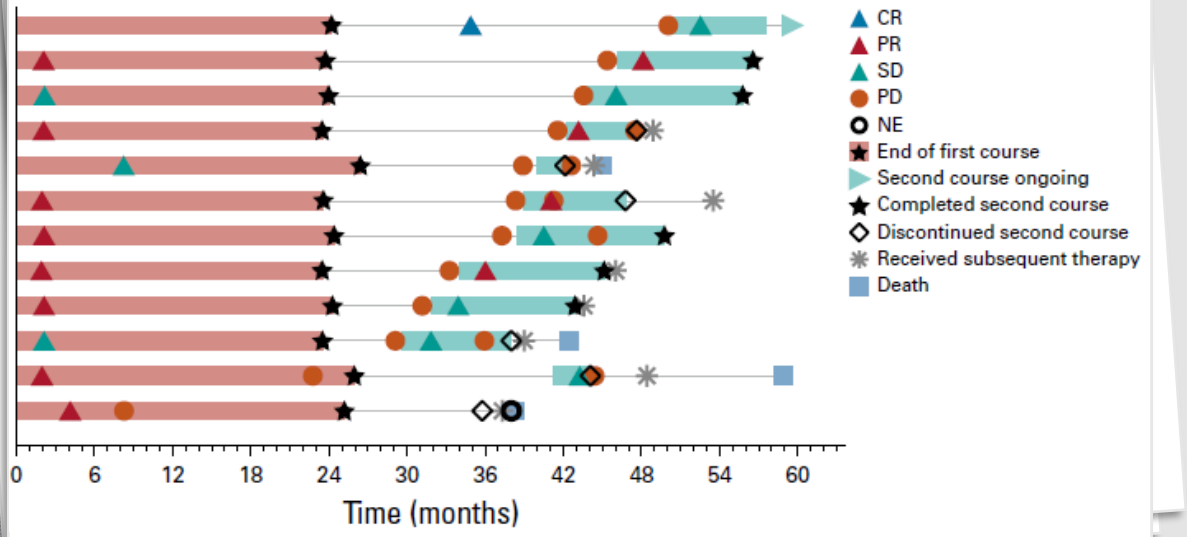
Rechallenge with pembrolizumab in KEYNOTE-024

- **Indication**
  - completion of 35 cycles or 2 years of pembrolizumab
  - stopping after archieving CR with receiving ≥6 months of treatment and and additional 2 cycles of pembrolizumab after CR
  - not administrated anticancer therapy since last dose of pembrolizumab

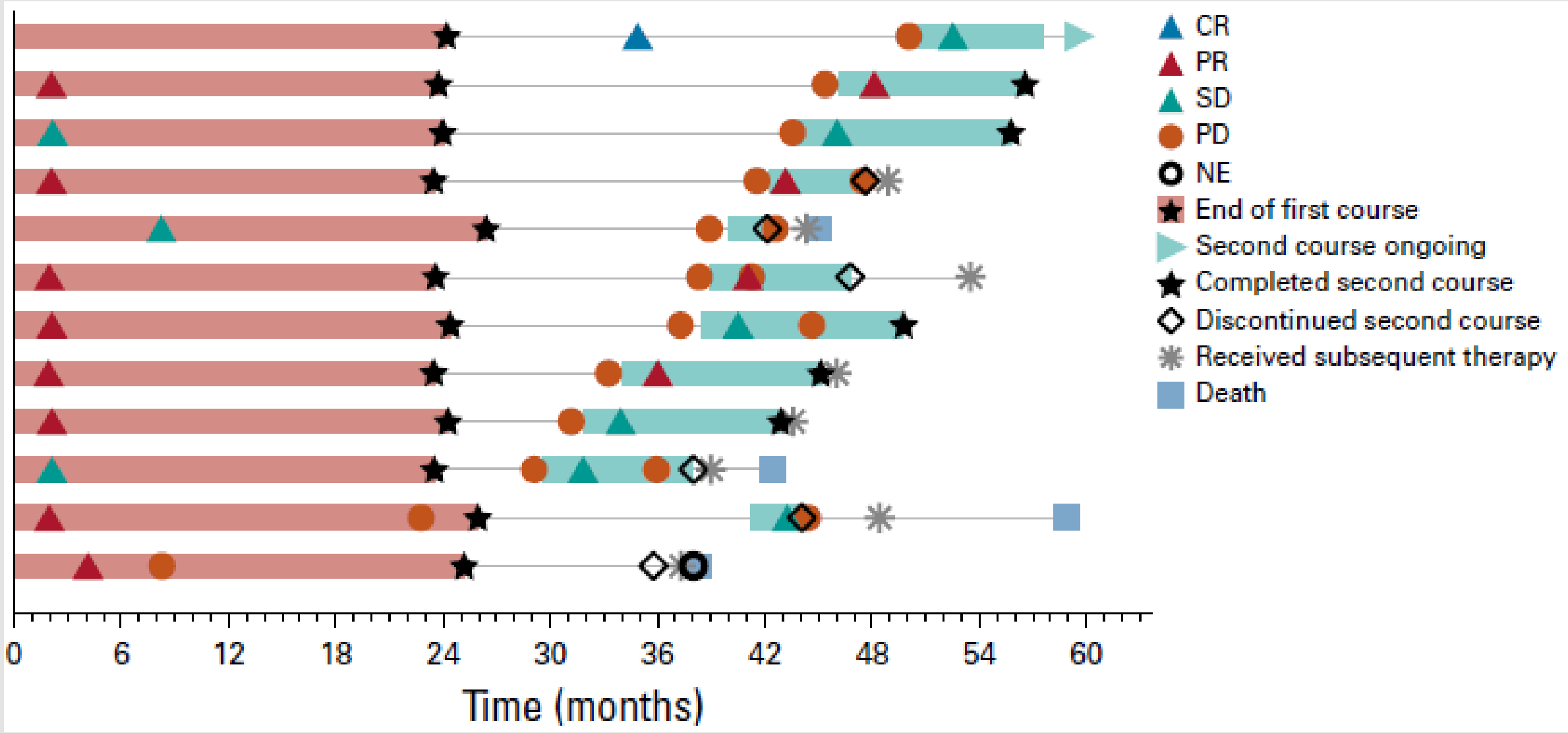
- **2nd course pembrolizumab**
  - up to 17 cycles or 1 year
  - 12 subjects received 2nd course pembrolizumab
  - alive at data cutoff: 8 (67%)
  - 5 (41.7%) were alive without PD
  - all Gr AE (1-2): 5 (41.7%)
  - ≥Gr 3: none

Best objective response, n(%)

ORR	4 (33.3)
CR	0 (0)
PR	4(33.3)
SD	6 (50)
PD	1 (8.3)
No assess	1 (8.3)



1. JTO.16(10);1718-32, 2. Herbst RS, Garon EB, Kim DW, et al. Poster presented at: IASLC World Conference on Lung Cancer (WCLC); January 28-31, 2021; Virtual.


CR
PR
SD
PD
NE
End of first course
Second course ongoing
Completed second course
Discontinued second course
Received subsequent therapy
Death
0
6
12
18
24
30
36
42
48
54
60
Time (months)

KEYNOTE-042

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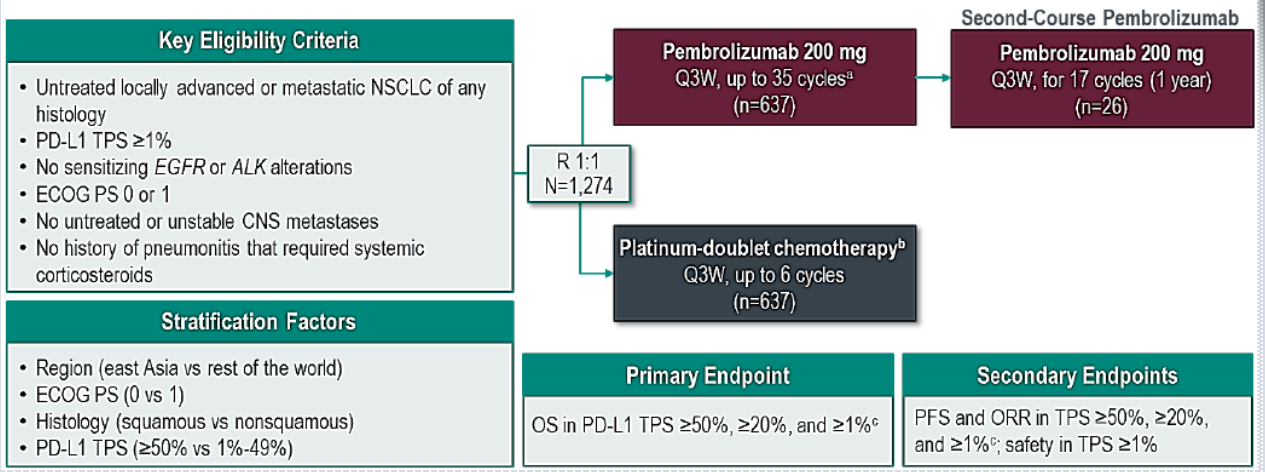
KEYNOTE-042 Study Design (Data Cutoff Date: February 21, 2020)[9]



- **Indication of 2nd course of pembrolizumab**
  - completion of 35 cycles or 2 years of pembrolizumab with SD or better
  - stopping after archieving CR
  - 26 subjects received 2nd course pembrolizumab (Data Cutoff Date: February 21, 2020)

	Completed 35 Cycles (2 Years) of Pembrolizumab (n=102)	Initiated Second Course Pembrolizumab (n=26)
Age, median (IQR), years	62.0 (33-81)	60.5 (49-75)
Sex, male, n (%)	73 (71.6)	17 (65.4)
Enrolled in East Asia,[a] n (%)	26 (25.5)	8 (30.8)
ECOG PS 1,[a] n (%)	50 (49.0)	12 (46.2)
Squamous histology,[a] n (%)	26 (25.5)	12 (46.2)
PD-L1 TPS,[a,b] n (%)		
≥50%	66 (64.7)	17 (65.4)
20%-49%	14 (13.7)	4 (15.4)
1%-19%	22 (21.6)	5 (19.2)
Current/former smoker, n (%)	83 (81.3)	19 (73.1)
Prior therapy, n (%)		
Neoadjuvant therapy	0	0
Adjuvant therapy	3 (2.9)	0
Radiotherapy	17 (16.7)	3 (11.5)

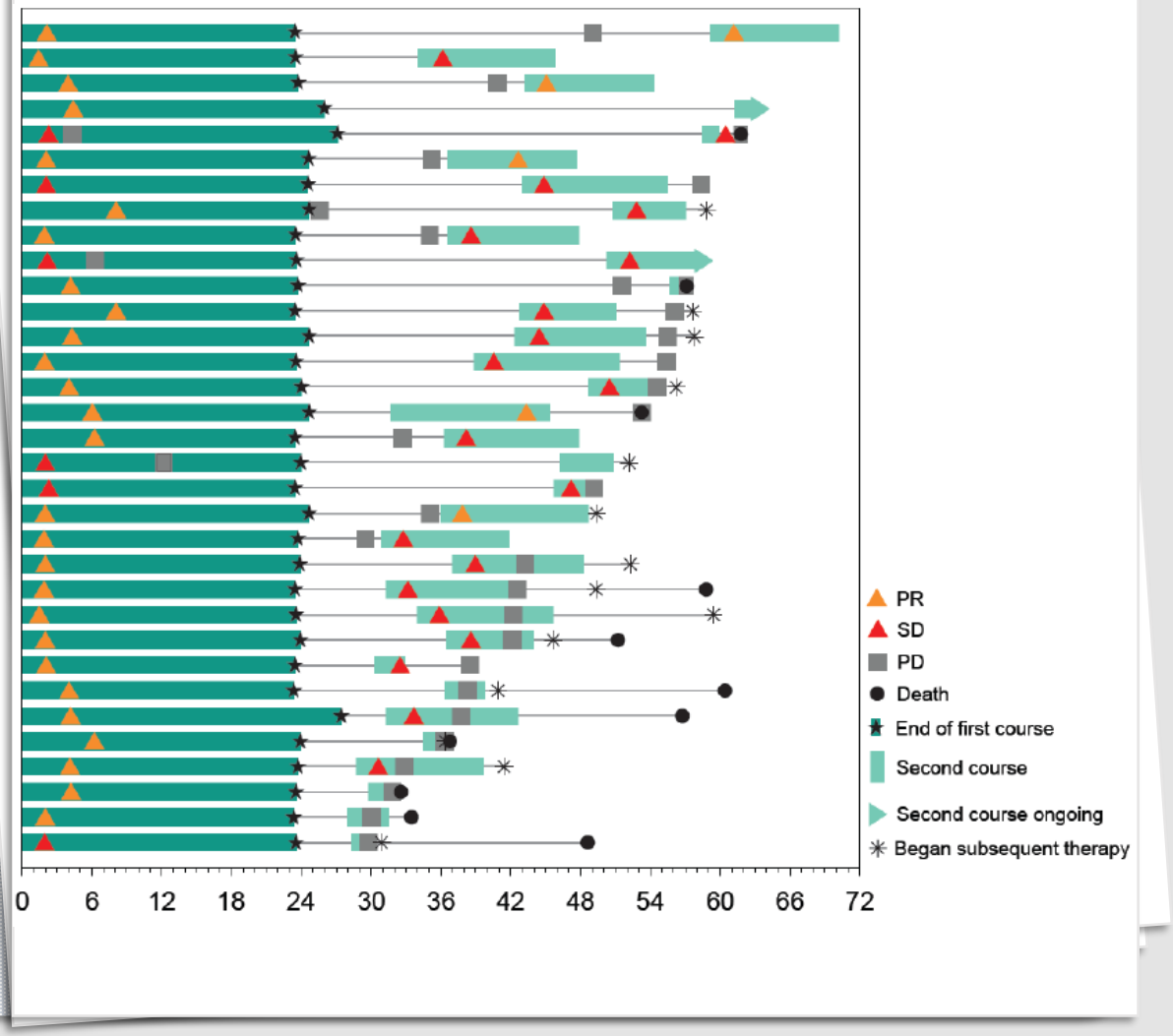
1. J Clin Oncol 39:2339-2349. 2. de Castro Jr G, Kudaba I, Wu Y-L, et al. Poster presented at: the 36th Annual Meeting of the Society for Immunotherapy of Cancer (SITC); 2021

Rechallenge with pembrolizumab in KEYNOTE-042

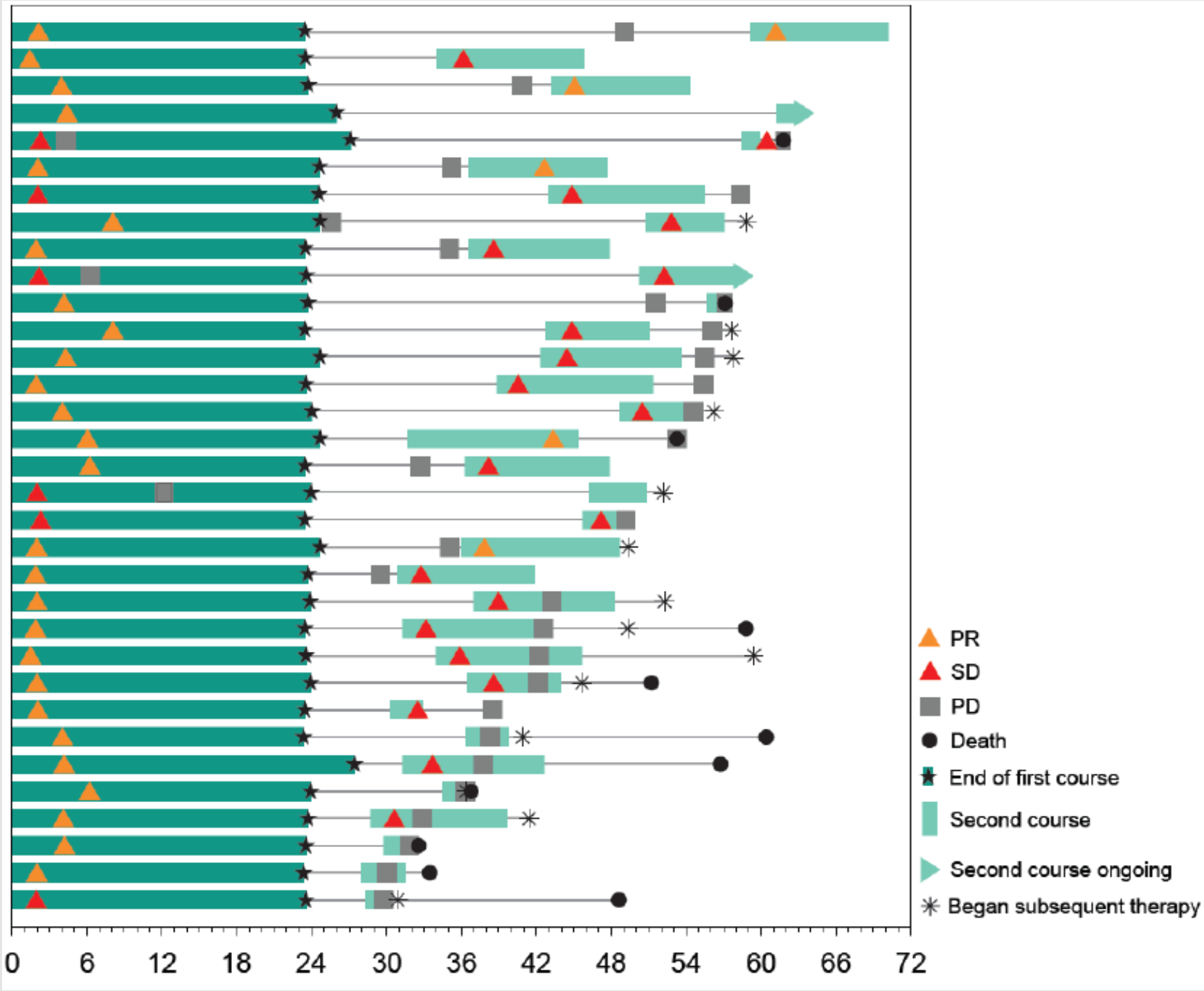
- **2nd course pembrolizumab**
  - up to 17 cycles or 1 year
  - 33 subjects received 2nd course pembrolizumab (Data Cutoff Date: April 28, 2021)
  - At data cutoff, 2 subjects (6.1%) remained on second-course pembrolizumab
  - Seventeen subjects (51.5%) had completed 17 cycles of second-course pembrolizumab

Best objective response, n(%); total 33

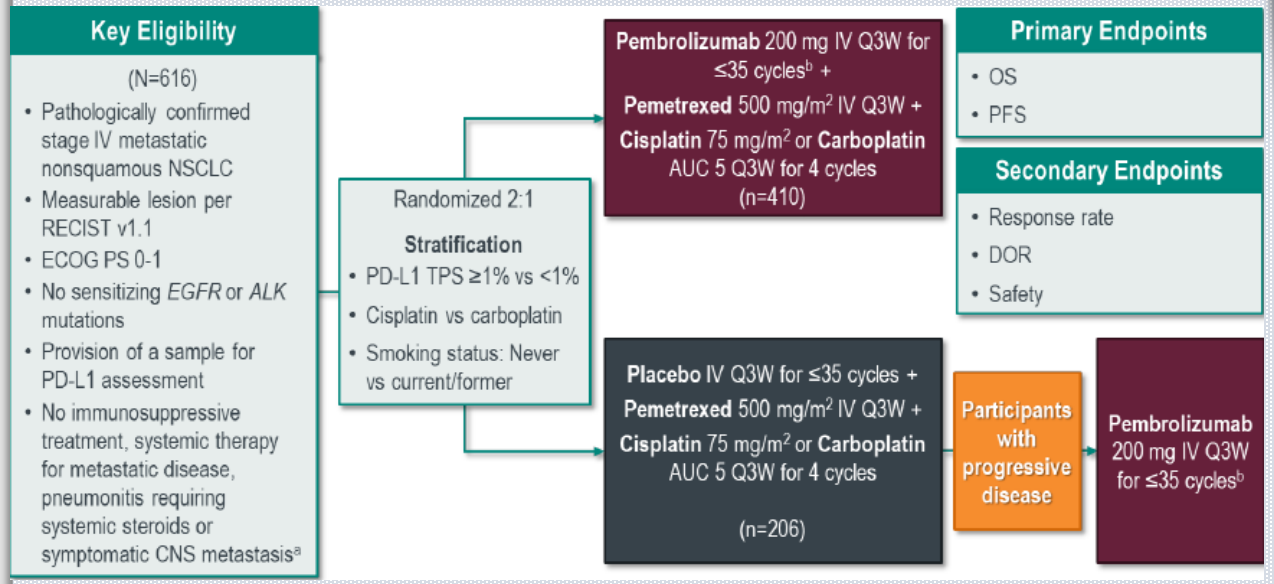
ORR	5 (15.2)
CR	0
PR	5 (15.2)
SD	20 (60.6)
PD	6 (18.2)
No assess	2 (6.0)



1. J Clin Oncol 39:2339-2349. 2. de Castro Jr G, Kudaba I, Wu Y-L, et al. Poster presented at: the 36th Annual Meeting of the Society for Immunotherapy of Cancer (SITC); 2021


0
6
12
18
24
30
36
42
48
54
60
66
72
PR
SD
PD
Death
End of first course
Second course
Second course ongoing
Began subsequent therapy

KEYNOTE-189



- **Indication of 2nd course of pembrolizumab**
  - completion of 35 cycles or 2 years of pembrolizumab
  - stopping after archieving CR and received ≥ 8 cycles of treatment
  - not administrated anticancer therapy since last dose of pembrolizumab
- **2nd course pembrolizumab**
  - up to 17 cycles or 1 year
  - 45/56 (80.4%) subjects who completed 35 cycles (2 years) of pembrolizumab therapy were alive
  - 7 subjects started second course pembrolizumab
  - 2: SD, 2: PD, 3: not assessed

1. J Clin Oncol 38:1505-1517. 2. Gray JE, Rodriguez-Abreu D, Powell SF, et al. Oral presented at: IASLC WCLC Annual Meeting; January 28-31, 2021; Virtual Meeting.

PACIFIC

Data cutoff date: JAN 11, 2021

Patients with Stage III unresectable NSCLC who have not progressed following platinum-based concurrent CRT

Patients randomized = 713[a]

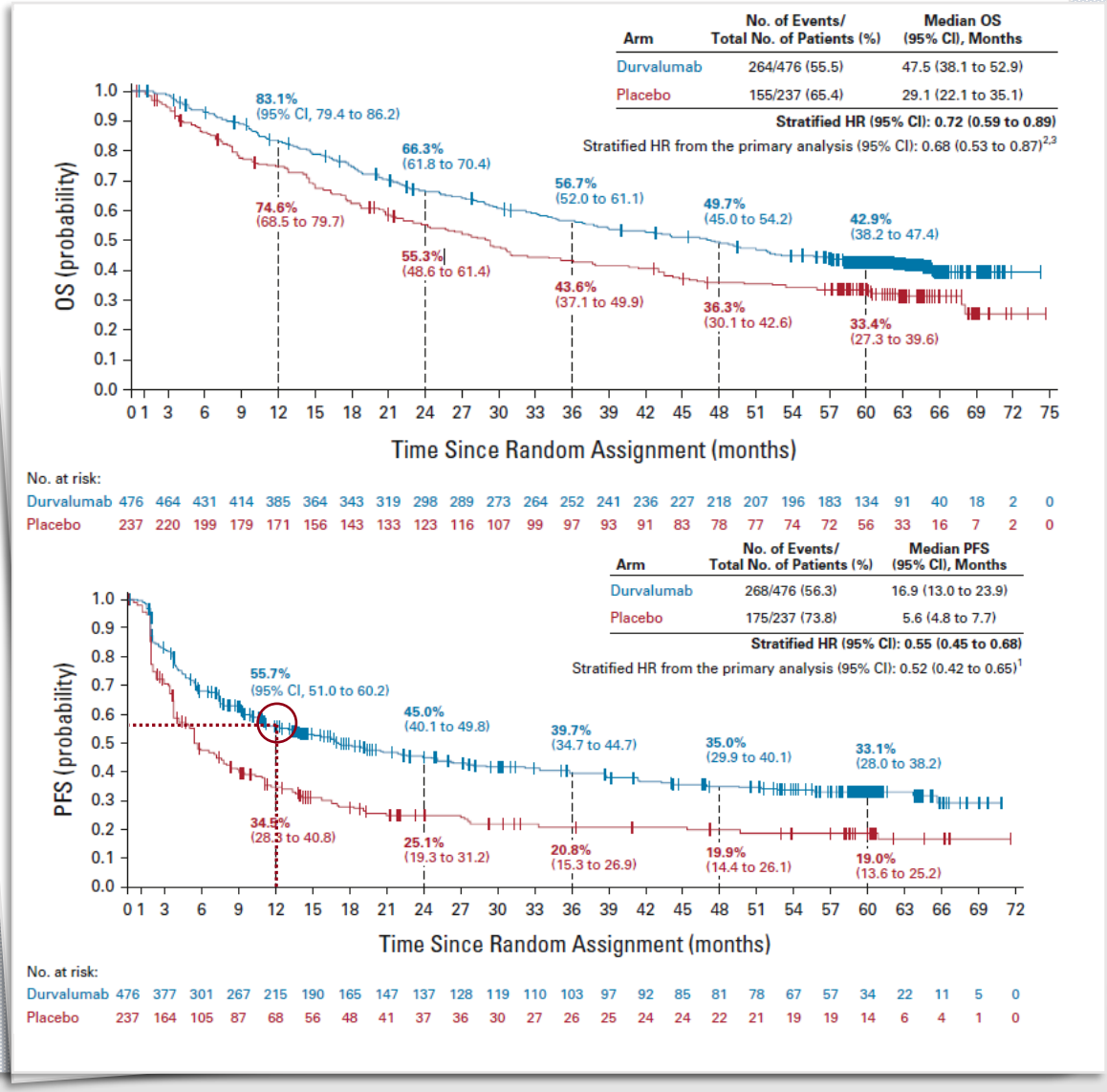
Randomization 2:1
1–42 days post-concurrent CRT

- **Durvalumab IV 10 mg/kg q2w up to 12 months n=476**
- **Placebo IV q2w up to 12 months n=237**

Stratification factors

1. **Age at randomization** (<65 vs ≥65 years of age)
2. **Sex** (male vs female)
3. **Smoking history** (smoker vs non-smoker)

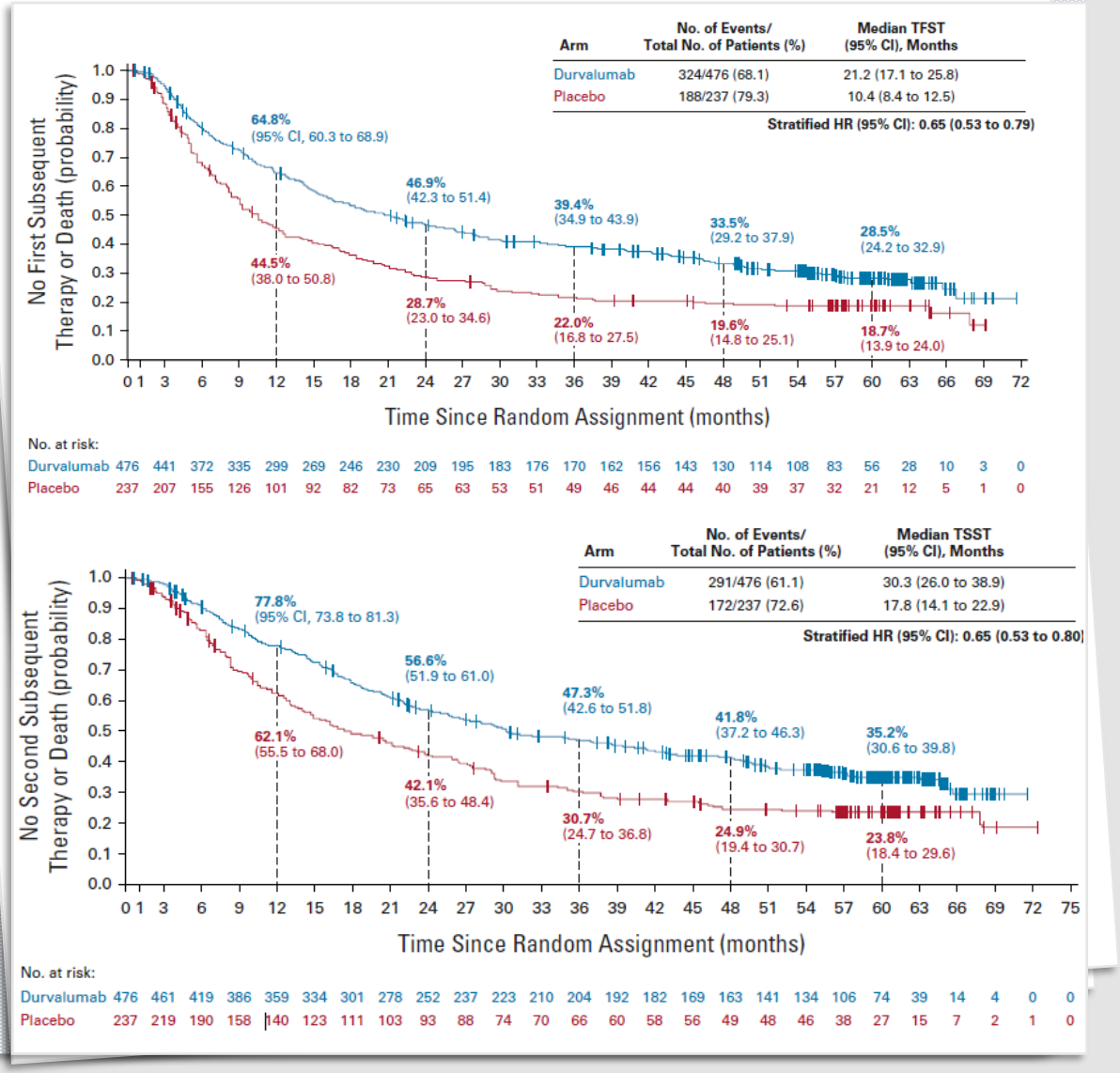
Pts must have received at least two cycles of chemotherapy
Definitive CCRT 54-66Gy
mean lung dose <20 Gy
the V20 (the volume of lung parenchyma that received 20 Gy or more) was less than 35%



JCO 40:1301-1311

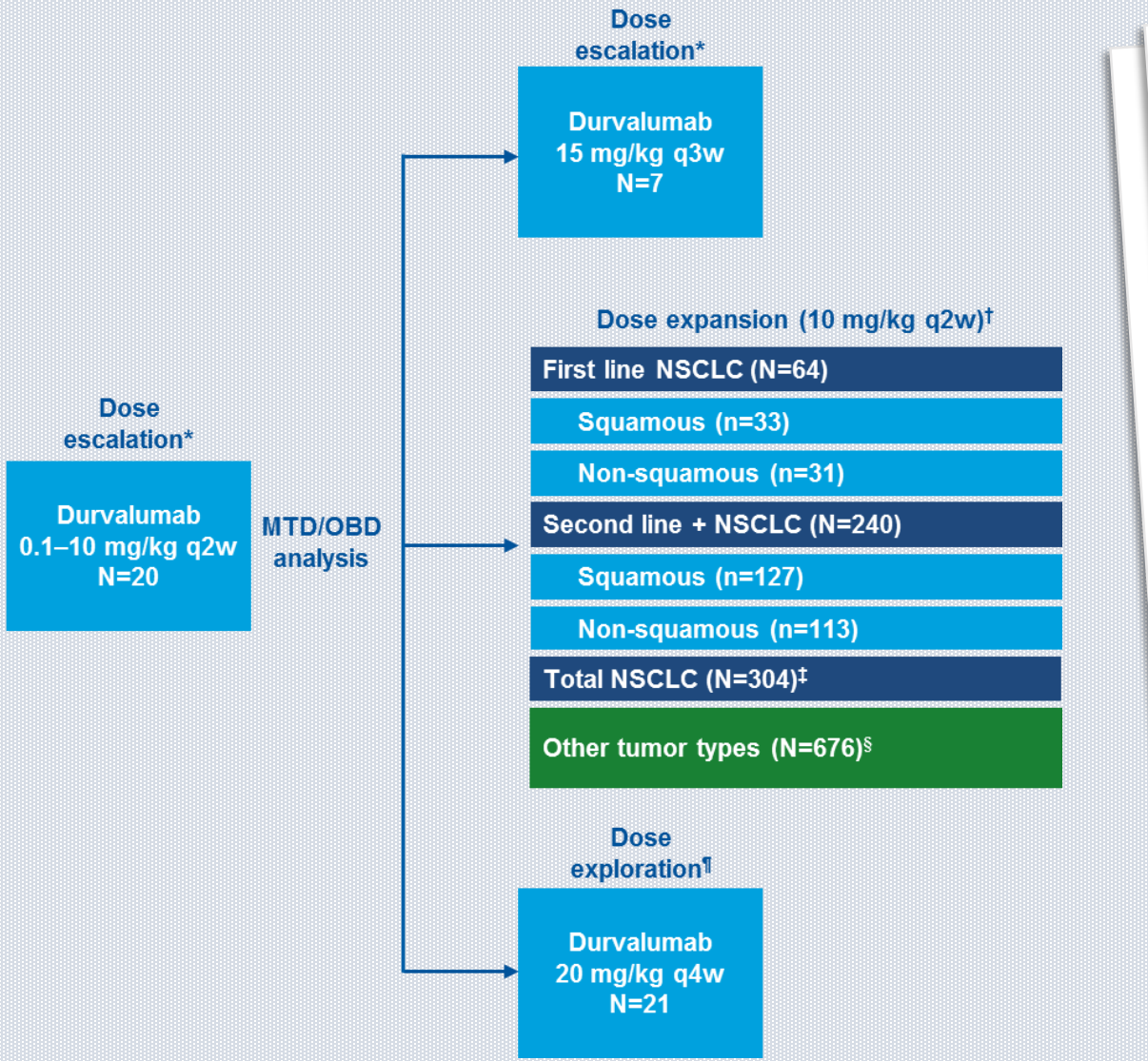
Rechallenge with durvalumab in PACIFIC trial

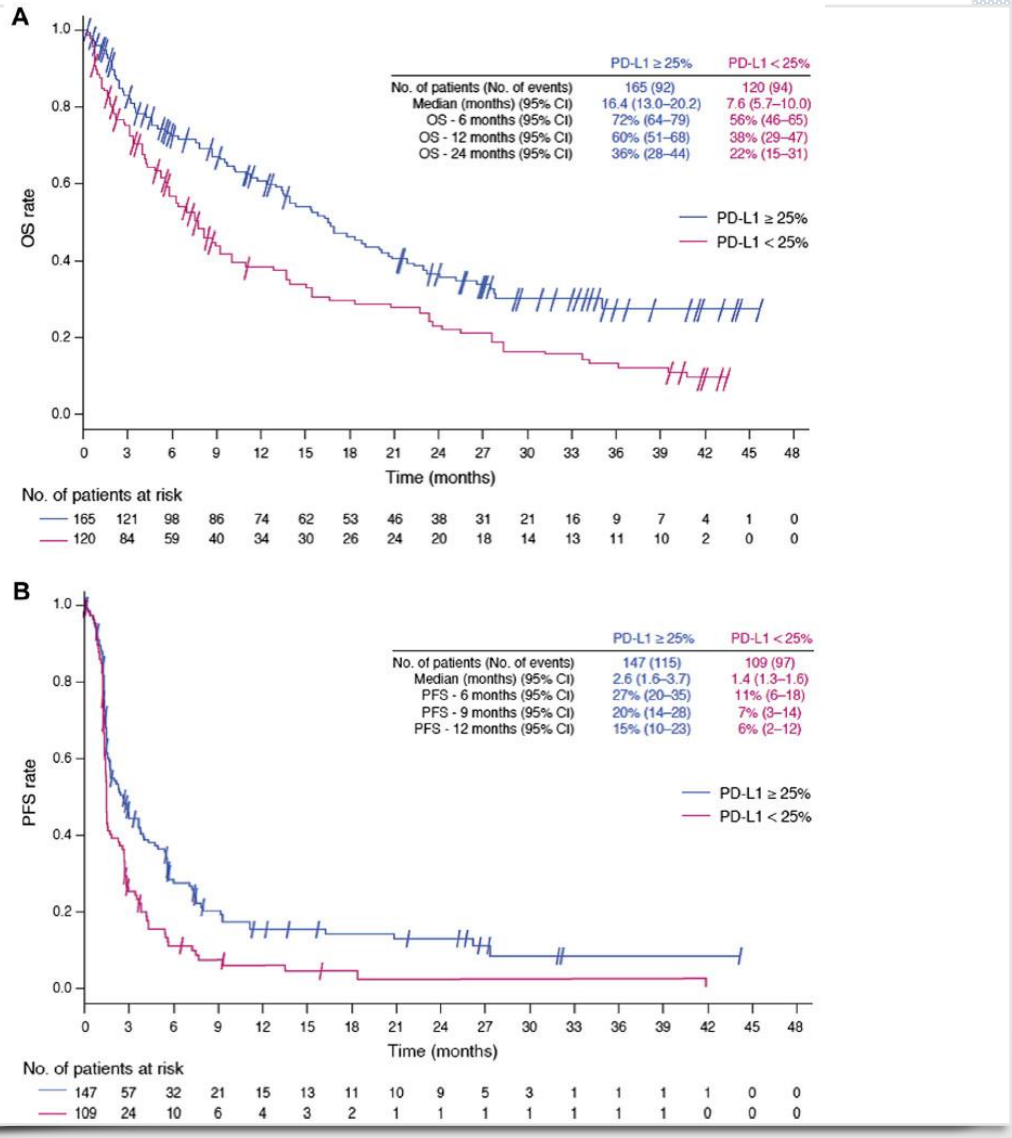
- **Indication**
  - completion of 12 months of durvalumab
  - disease control state at the end of the 12 months
  - not administrated anticancer therapy
- **2nd course durvalumab**
  - 34 of 476 (7.1%) patients in the durvalumab arm received retreatment
  - 4 of 34 (11.8%) completed 12 months of retreatment
  - 23 of 34 (67.6%) discontinued
  - 7 of 34 (20.6%) were ongoing retreatment
  - Median time to 2nd progression (from random)
    - 48.0 months (95% CI, 38.9 to 64.6)
  - Alive and without a second progression at 2, 4, and 5 years
    - 100% (95% CI, 100 to 100),
    - 50.9% (95% CI, 32.8 to 66.5)
    - 34.0% (95% CI, 18.0 to 50.6)



JCO 40:1301-1311

NCT01693562 (study 1108 Phase I/II)





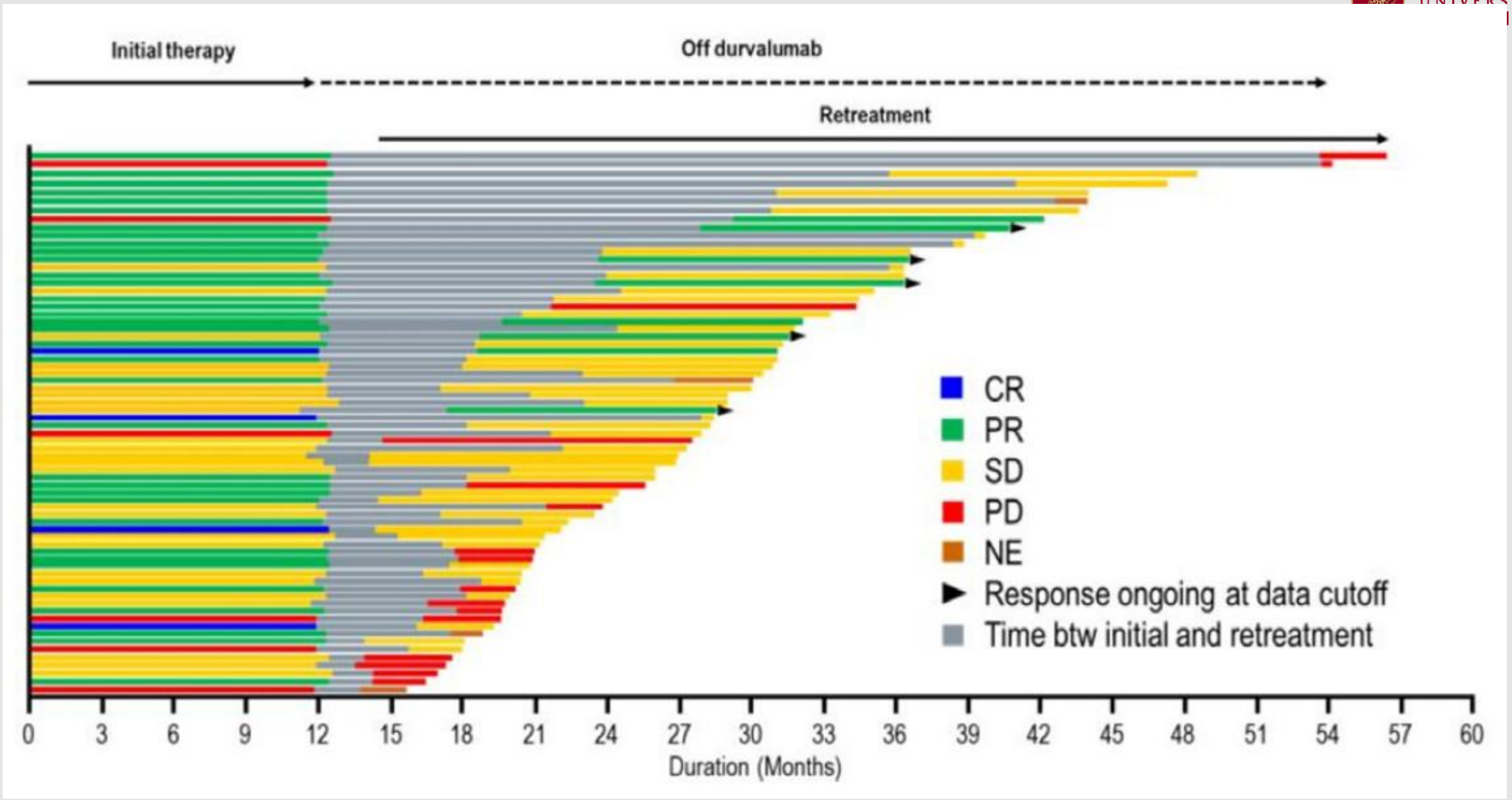
JTO 14(10):1794-1806

Rechallenge with durvalumab

- **Indication**
  - completion of 12 months of durvalumab
  - disease control state at the end of the 12 months
  - not administrated anticancer therapy
- **2nd course durvalumab**
  - 70 patients in the durvalumab arm received retreatment
  - up to 1 year
  - 21 of 70 (30.0%) were patients with NSCLC

Response	Initial treatment (n=70)	Retreatment (n=70)
Best overall response, n (%)		
Complete response	4 (5.7)	0
Partial response	35 (50.0)	8 (11.4)
Stable disease	25 (35.7)	42 (60.0)
Unconfirmed partial response	2 (2.9)	2 (2.9)
Disease progression	6 (8.6)	16 (22.9)
Non-evaluable	0	4 (5.7)
Median time to response, months	2.7	4.3
Median duration of response, months	14.8	16.5
DCR ≥24 weeks, %	82.9	47.1
PFS rate at 12 months, %	71.0	34.2
Median OS, months	48.9	23.8

Immunother Cancer 2020;8:e000650


Initial therapy
Off durvalumab
Retreatment
CR
PR
SD
PD
NE
Response ongoing at data cutoff
Time btw initial and retreatment
0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48 51 54 57 60
Duration (Months)

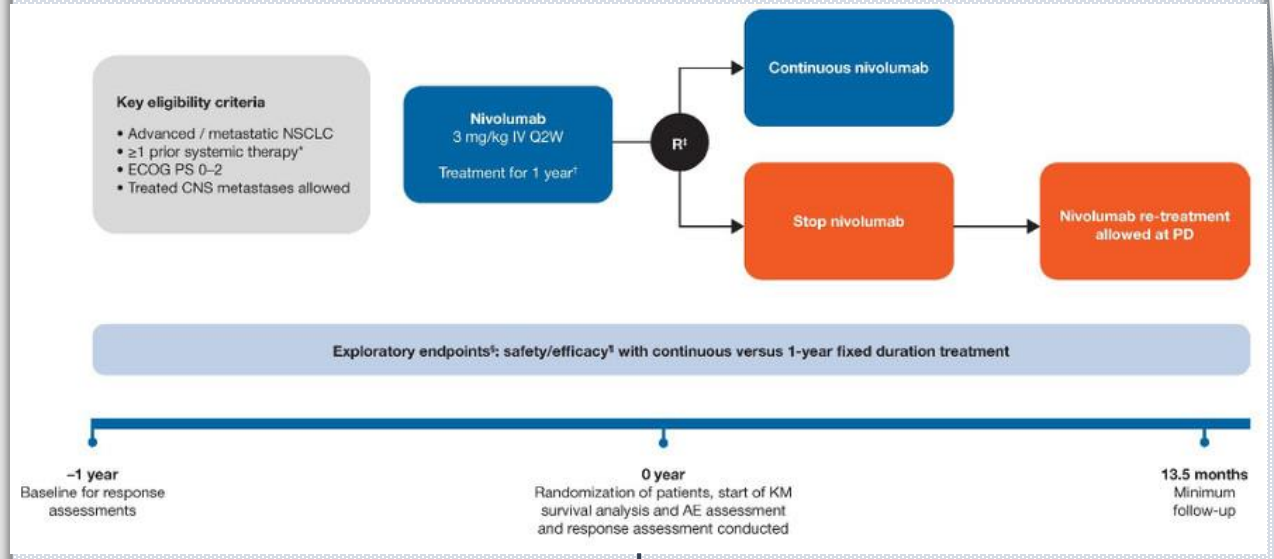
Rechallenge with durvalumab

Response	NSCLC n=21
Best overall response (BOR2), n (%)	
Complete response	0
Partial response	3 (14.3)
Stable disease	8 (38.1)
Unconfirmed partial response	1 (4.8)
Progressive disease	8 (38.1)
Non-evaluable	2 (9.5)
Objective response rate (ORR2), n (%)	3 (14.3)
Median time to response, months	5.6
Median duration of response (range), months	13.4 (7.2 to 25.1+)
DCR2, n (%)	11 (52.4)
DCR2 ≥24 weeks, n (%)	7 (33.3)
PFS2 rate at 12 months, %	31.0
Median PFS2, months	2.7
Median OS2, months	16.3

Tumor	NSCLC**	
PD-L1 status	High (n=12)	Low/neg (n=7)
Best overall response, n (%)		
Complete response	0	0
Partial response	2 (16.7)	1 (14.3)
Stable disease	5 (41.7)	3 (42.9)
Unconfirmed partial response	1 (8.3)	0
Progressive disease	4 (33.3)	2 (28.6)
Non-evaluable	1 (8.3)	1 (14.3)
Objective response rate, n (%)	2 (16.7)	1 (14.3)
Median time to response, months	3.4	8.3†
Median duration of response, months	NR	7.2†
DCR2 ≥24 weeks, n (%)	6 (50.0)	1 (14.3)

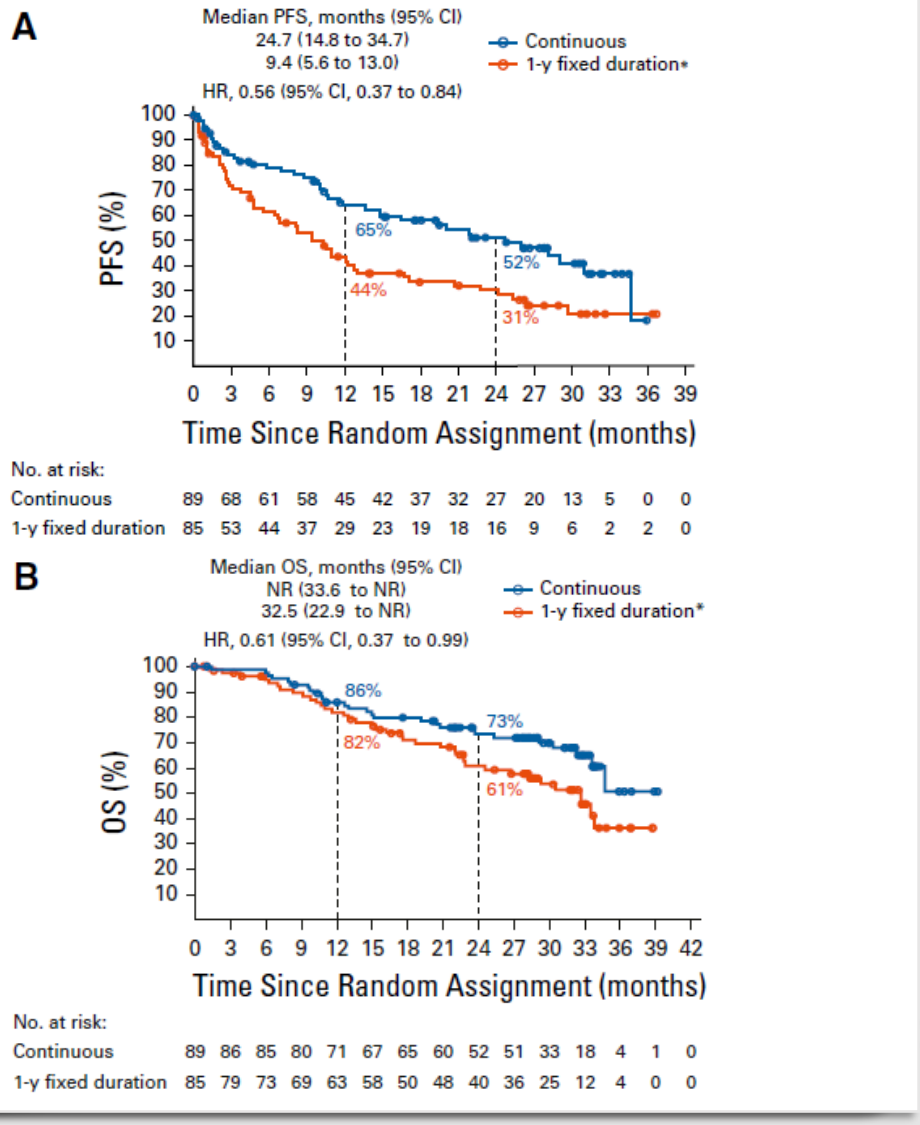
Immunother Cancer 2020;8:e000650

CHECKMATE-153 (III/IV)



continuous treatment (n=89)

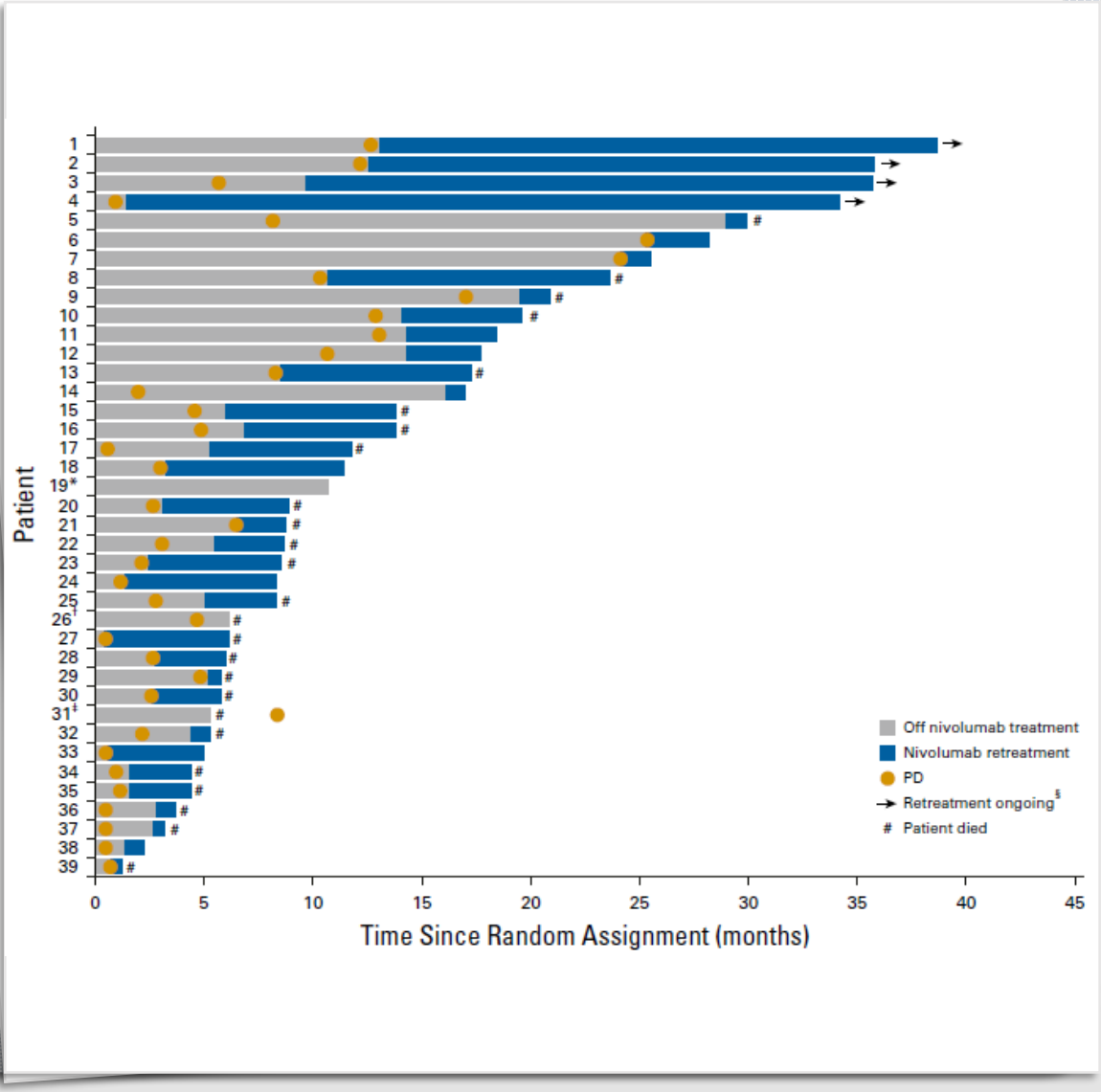
1-yr fixed-duration treatment (n=86)



J Clin Oncol 38:3863-3873.

Rechallenge with nivolumab in CHECKMATE-153

- **Indication**
  - completion of 1 year of nivolumab
  - disease control state at the end of the 1 year
  - not administrated anticancer therapy
- **nivolumab retreatment**
  - 39 of 47 (83.0%) received retreatment
  - median time between discontinuation and progression leading to retreatment was 10.3 months
  - median duration of nivolumab was 3.8 months (range 0.1–17.5 months)
  - 4 of 39 (10.2%) were ongoing retreatment
  - 14 of 39 (35.9%) were alive



J Clin Oncol 38:3863-3873.

WJOG9616L

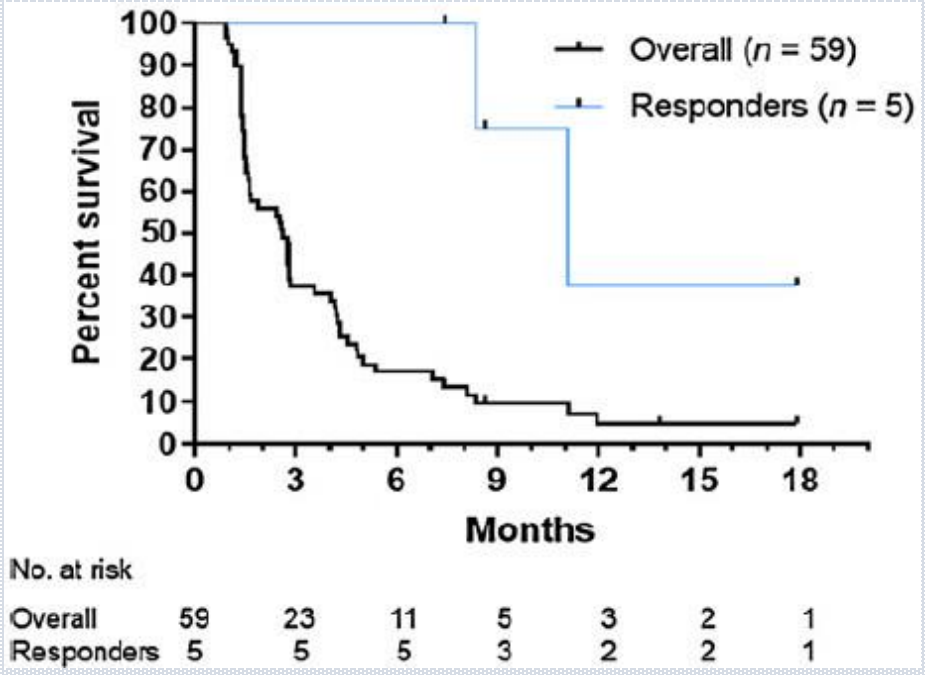
- **study design**
  - open-label, multi-institutional, single-arm phase II study
  - previously received at least one systemic anticancer treatment including ICI
  - clinical benefit from prior ICI-containing regimen preceding progression (CR, PR, or SD ≥ 6 months)
  - ICI-free interval ≥ 60 days
- **Endpoints**
  - primary endpoint: ORR
  - secondary endpoint: PFS, OS, AE
- **Biomarker ananlysis**
  - PD-L1, CD8+ lymphocyte, circulating tumor cells

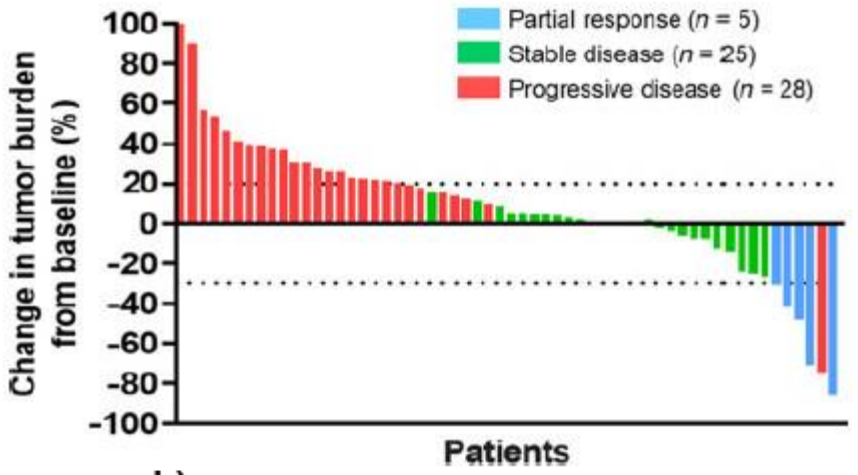
	n **= 59**
Age	
Median (range)	70 (38–81)
Sex, *n* (%)	
Male/Female	43 (73)/16 (27)
Smoking status, *n* (%)	
Never/(ex-) smoker	10 (17)/49 (83)
ECOG performance status, *n* (%)	
0/1	22 (37)/37 (63)
Histology, *n* (%)	
Non-Sq/Sq	38 (64)/21 (36)
EGFR WT/MT/unknown	30 (51)/2 (3)/6 (10)
ALK WT/MT/unknown	30 (51)/0/8 (14)
Clinical stage at registration, *n* (%)	
IIIB-C/IV/postoperative relapse	6 (10)/38 (64)/15 (25)
Prior chemotherapy lines, median (range)	3 (1–6)
Prior radiotherapy, *n* (%)	
Yes/No	32 (54)/27 (46)
PD-L1 expression (TPS); < 50%/≥50%/unknown, *n* (%)	
At diagnosis	20 (34)/17 (29)/22 (37)
At registration	8 (14)/1 (1)/50 (85)
Types of prior ICI, *n* (%)	
Monotherapy (Nivo/Pembro/Durva/Atezo)	30 (51)/21 (36)/2 (3)/1 (1)
ICI +cytotoxic chemotherapy	5 (9)
Best response of prior ICI, *n* (%)	
CR/PR/SD ≥ 6 months	2 (3)/39 (66)/18 (31)
Duration of prior ICI, median (range), months	8.1 (0.8–37.0)
ICI-free interval, median (range), months	9.2 (2.4–29.4)
History of irAE that required discontinuation of prior ICI, *n* (%)	
Yes/No	20 (34)/39 (66)

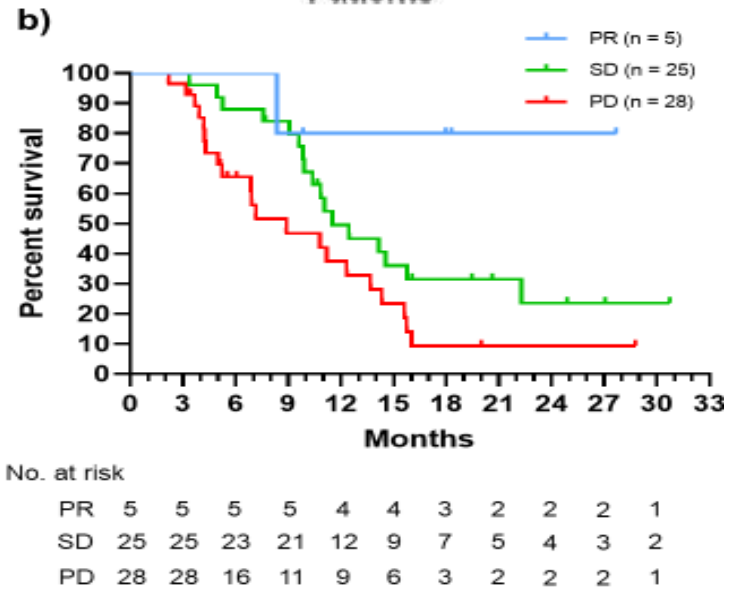
Clin Cancer Res 2022;XX:XX–XX

WJOG9616L

- **Results**
  - ORR: 8.5% (95% CI, 2.8-18.7)
    - PR: 5, SD: 25, PD: 28
  - mPFS: 2.6months (95% CI, 1.6–2.8)
  - PFS rate at 12 months: 4.8% (95% CI, 1.0–13.6)
  - mOS: 11.0 months (95% CI, 9.0–14.5)
  - OS rate at 12 months: 46.4% (95% CI, 32.8–59.0)



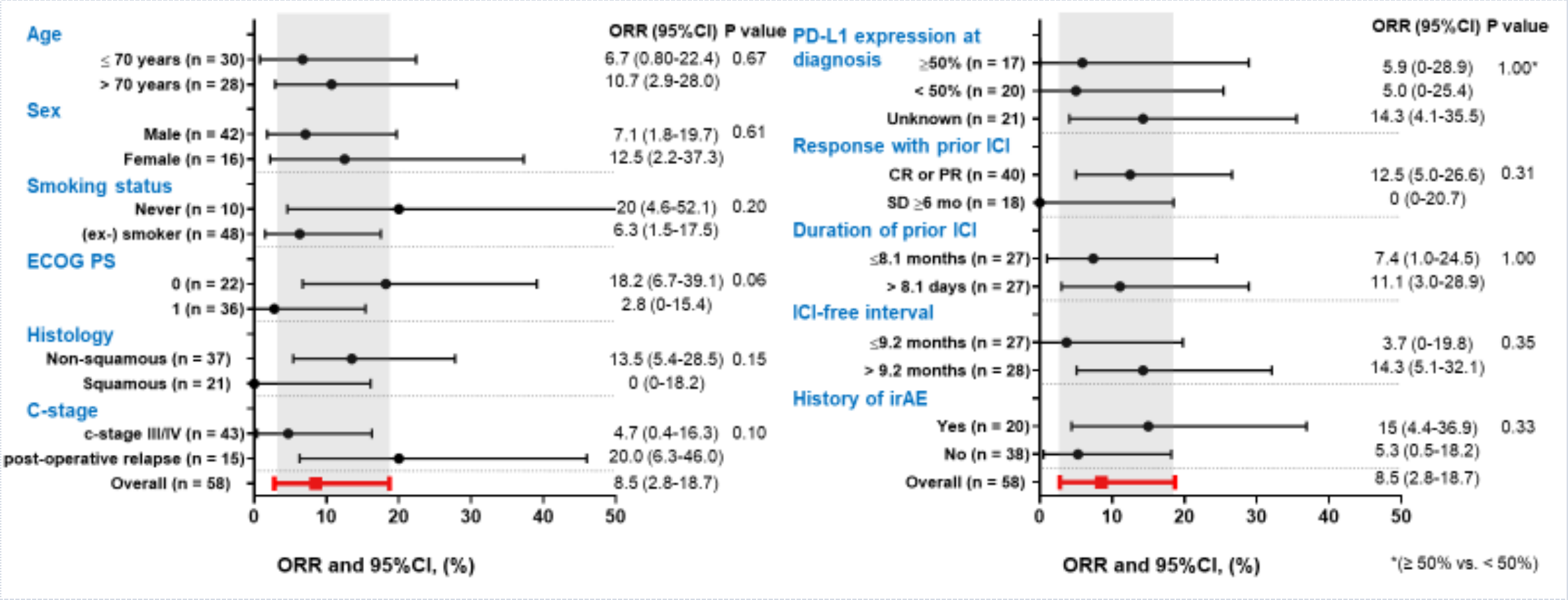




Clin Cancer Res 2022;XX:XX–XX ;epub

Predictive factor of response to nivolumab retreatment

- None of the clinical backgrounds significantly influenced ORR



Clin Cancer Res 2022;XX:XX–XX ;epub

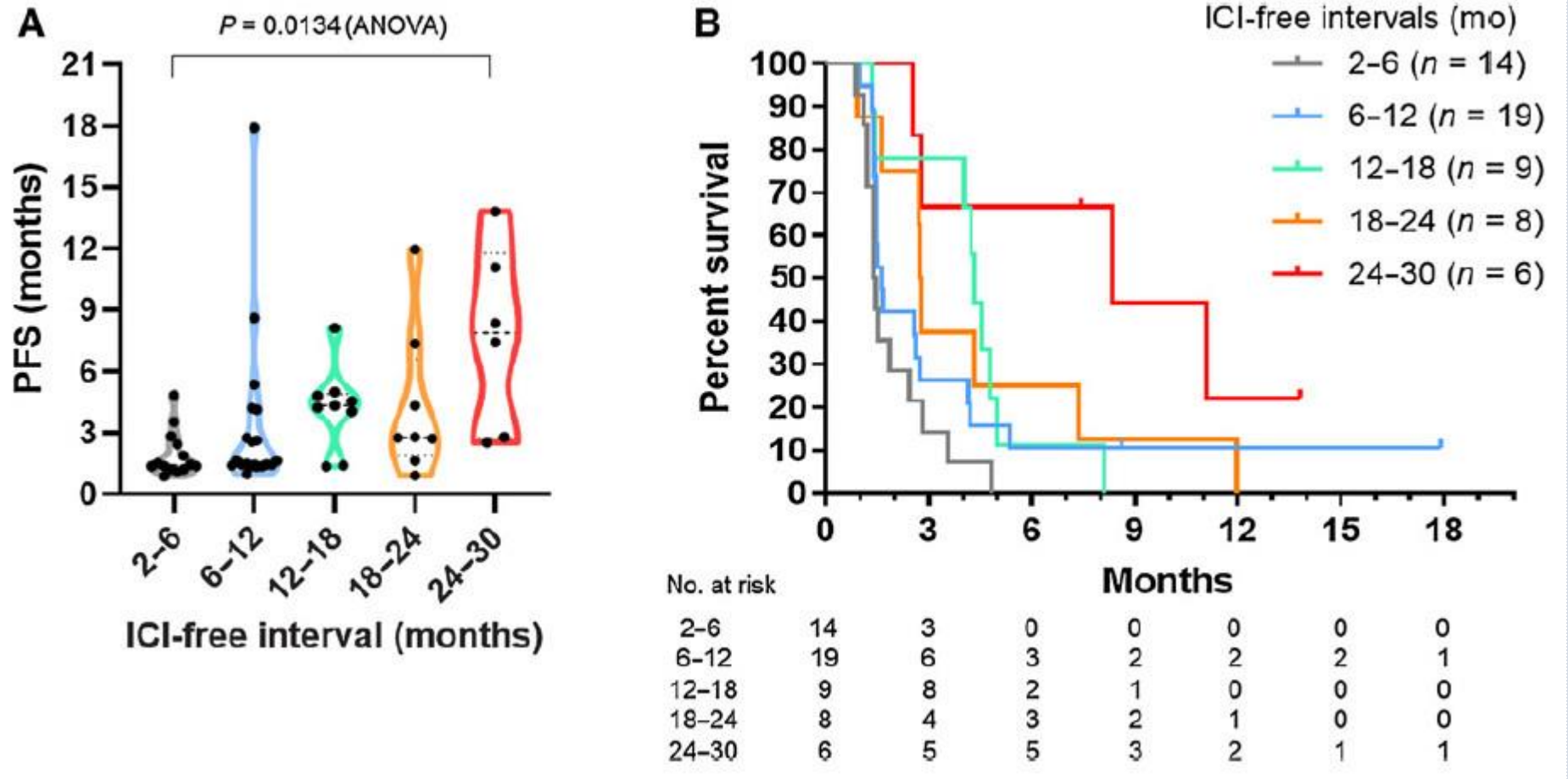
Predictive factor of response to nivolumab retreatment

- Cox-proportional hazard regression analysis for PFS

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age (≤70/>70)	1.10 (0.64–1.87)	0.73		
Sex (male/female)	1.25 (0.69–2.29)	0.47		
Smoking history (yes/no)	1.55 (0.75–3.18)	0.23		
ECOG PS (0/1)	0.73 (0.42–1.28)	0.28		
Histology (non-Sq/Sq)	0.45 (0.25–0.81)	0.01	0.57 (0.31–1.05)	0.07
Stage (III, IV/recurrence)	1.35 (0.72–2.53)	0.35		
PD-L1 expression at diagnosis (<50%/≥50%)	1.24 (0.89–1.70)	0.59		
Response with prior ICI (CR, PR/SD ≥ 6 months)	0.85 (0.48–1.49)	0.56		
Duration of prior ICI (≤8.1 months/>8.1 months)	1.83 (1.02–3.30)	0.04	1.27 (0.68–2.38)	0.46
ICI-free interval (≤9.2 months/>9.2 months)	2.61 (1.47–4.64)	0.001	2.02 (1.10–3.73)	0.02
History of irAE with prior ICI (yes/no)	0.51 (0.28–0.91)	0.02	0.69 (0.37–1.29)	0.24

Clin Cancer Res 2022;XX:XX–XX ;epub

Predictive factor of response to nivolumab retreatment



Clin Cancer Res 2022;XX:XX–XX ;epub

Predictive factor of response and adverse events

- **Biomarker**
  - Only 2 specimens were obtained: all responder
    1) TPS>90%, low CD8+
    2) low TPS, low CD8+
  - Changes in CTCs at 6 to 8 weeks: not predictive because most patients had lower CTC counts
- **AEs**
  - Grade 3: 9 events
  - Grade 4: 3 events
  - skin ds: 14 events, malaise: 12 events

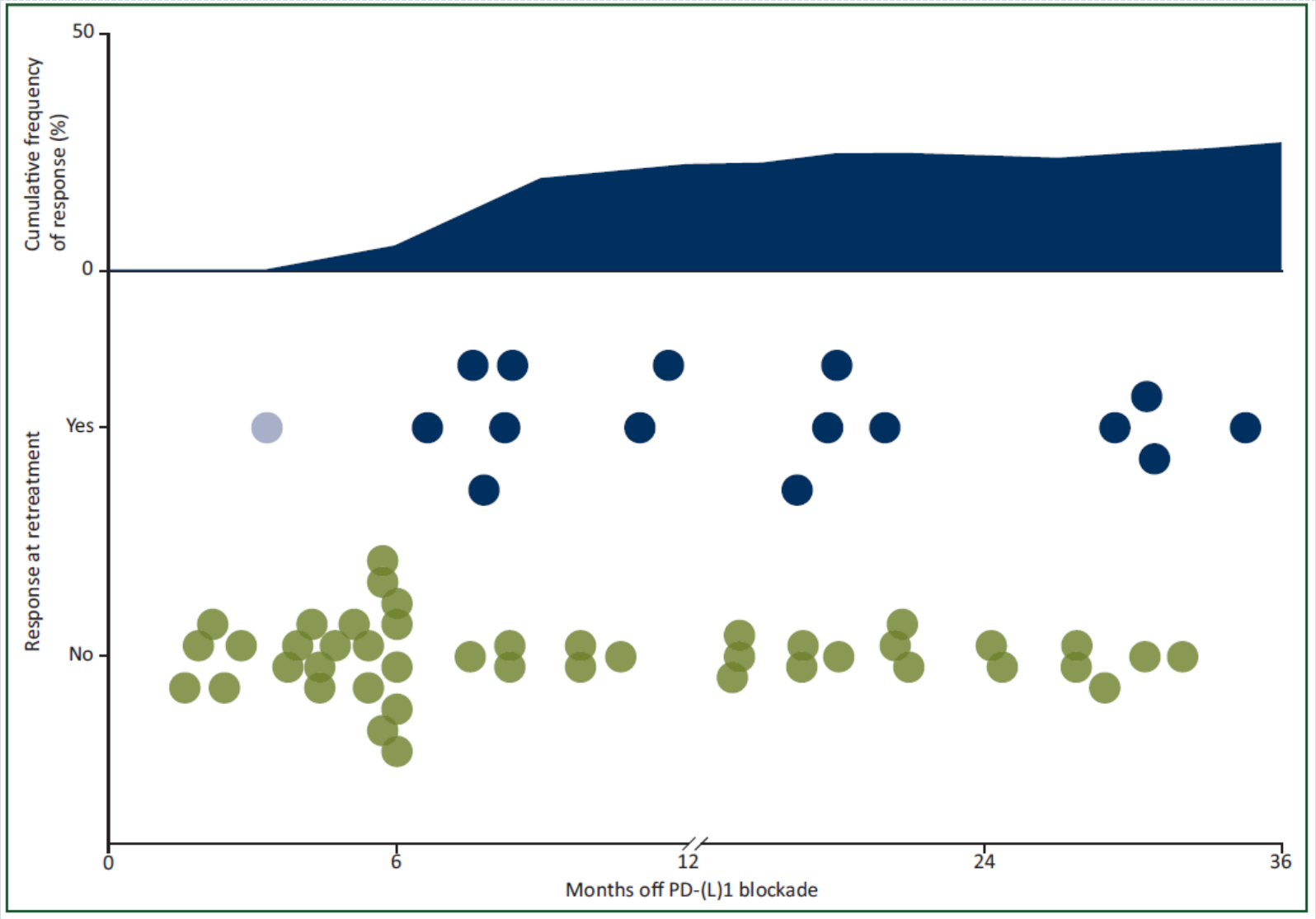
- **severe irAEs**
  - myocarditis (grade 4, n=1)
  - pancreatitis (grade 3, n=1)
  - vasculitis (grade 3, n=1)
  - adrenal insufficiency (grade 3, n=1)
  - Of 20 patients who discontinued prior ICI due to irAEs, 4 had severe irAEs by nivolumab retreatment

Clin Cancer Res 2022;XX:XX–XX ;epub

Clinical trials of rechallenge with ICI

Trials	Phase	Line	Duration of Tx	Indication of 2nd course ICI	N	ORR (%)	DCR (%)	PFS (months)
KN 010	II/III	≥2nd	35cycles or 2yrs	completed 1st course	21/79/690	52.4	81	
KN 024	III	1st	35cycles or 2yrs	completed 1st course	12/34/154	33.3	83.3	
KN 042	III	1st	35cycles or 2yrs	completed 1st course	33/102/637	15.2	75.8	
KN 189	III	1st	35cycles or 2yrs	completed 1st course	7/45/56	—	—	
CM 153	III/IV	≥2nd	1yr	completed 1st course	39/86	—	—	
PACIFIC	III	consolidation	1yr	completed 1st course	34/476	—	—	48 (from random)
NCT01693562	I/II		1yr	completed 1st course	21	14.3	52.4	2.7
WJOG9616L				CR, PR, or SD ≥ 6 months	59	8.5	50.8	2.6

Majority of retreatment responders (KN010, NCT01693562)

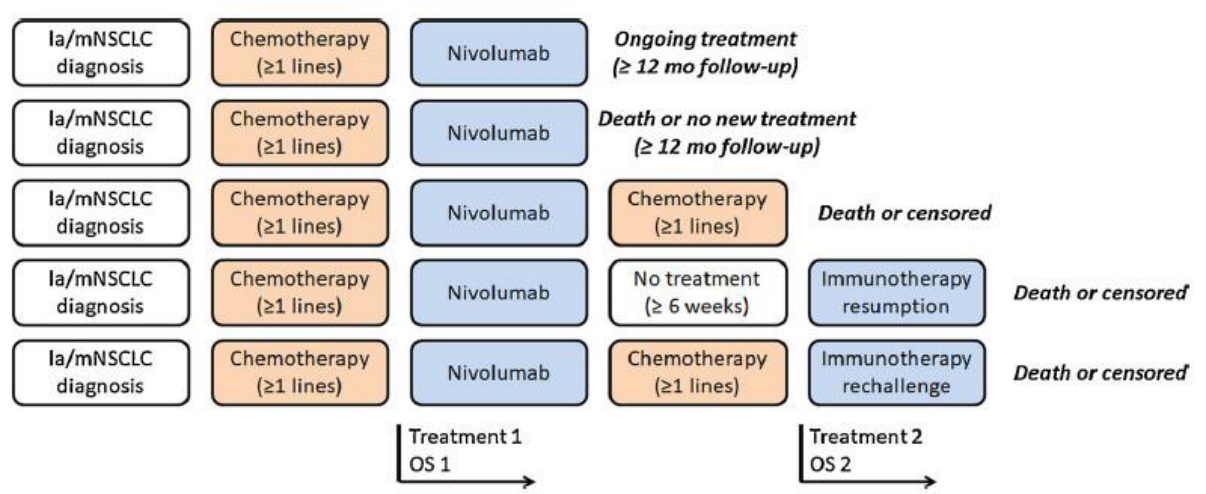


Ann Oncol. 2021 Dec;32(12):1597-1607

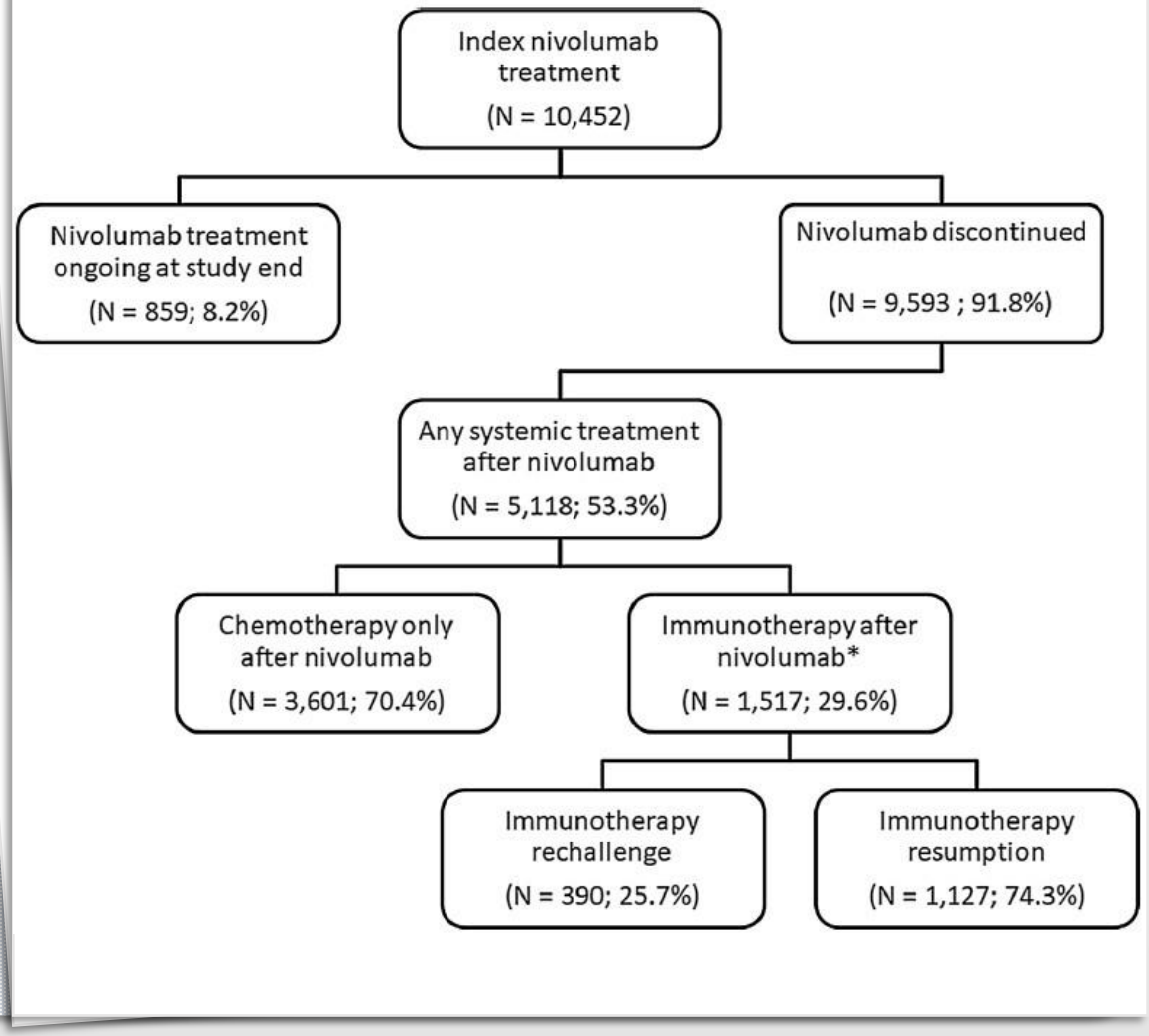
Real world studies
(PD during prior ICI treatment)

Immunotherapy rechallenge after nivolumab

- **A national data base analysis**
  - French National Hospital discharge database

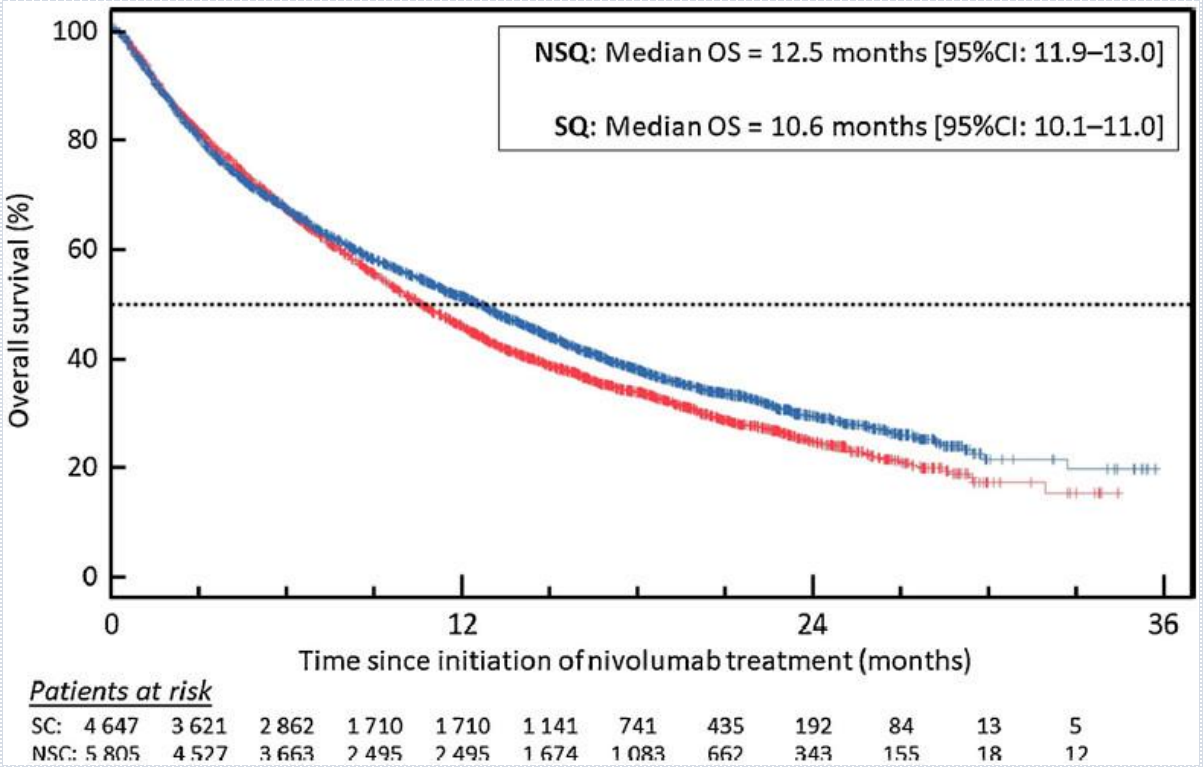


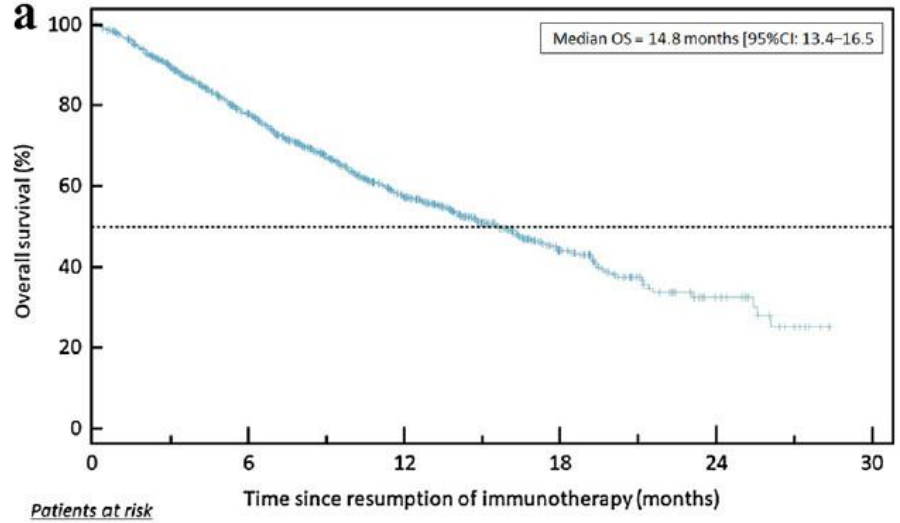
During the initial treatment course with nivolumab, the median treatment duration was 2.8 months

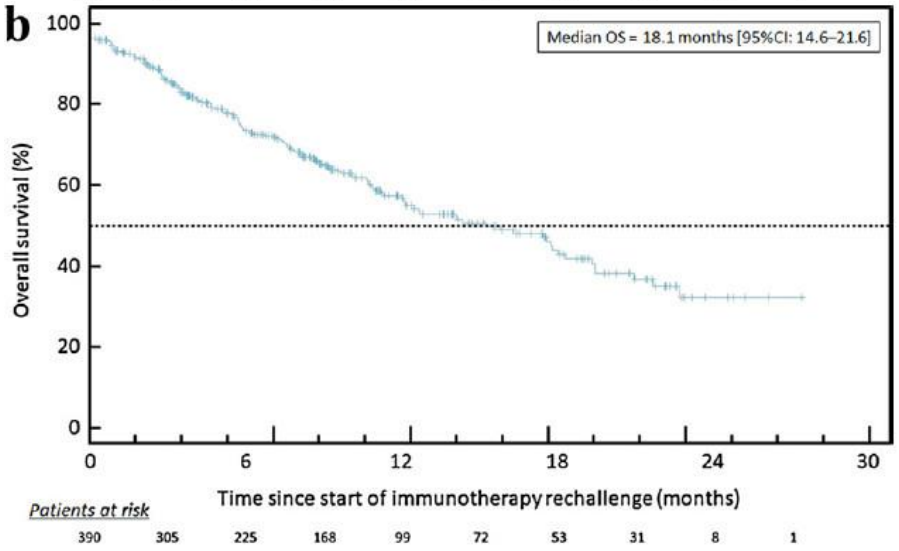


Lung Cancer 140 (2020) 99–106

Overall survival



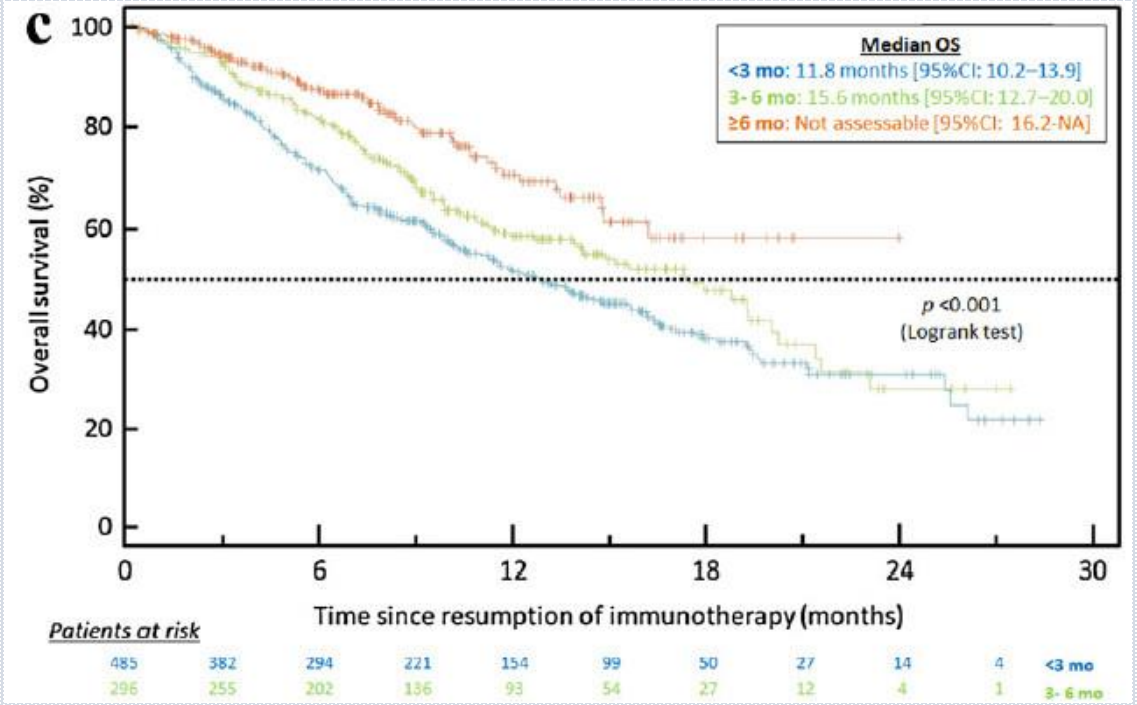


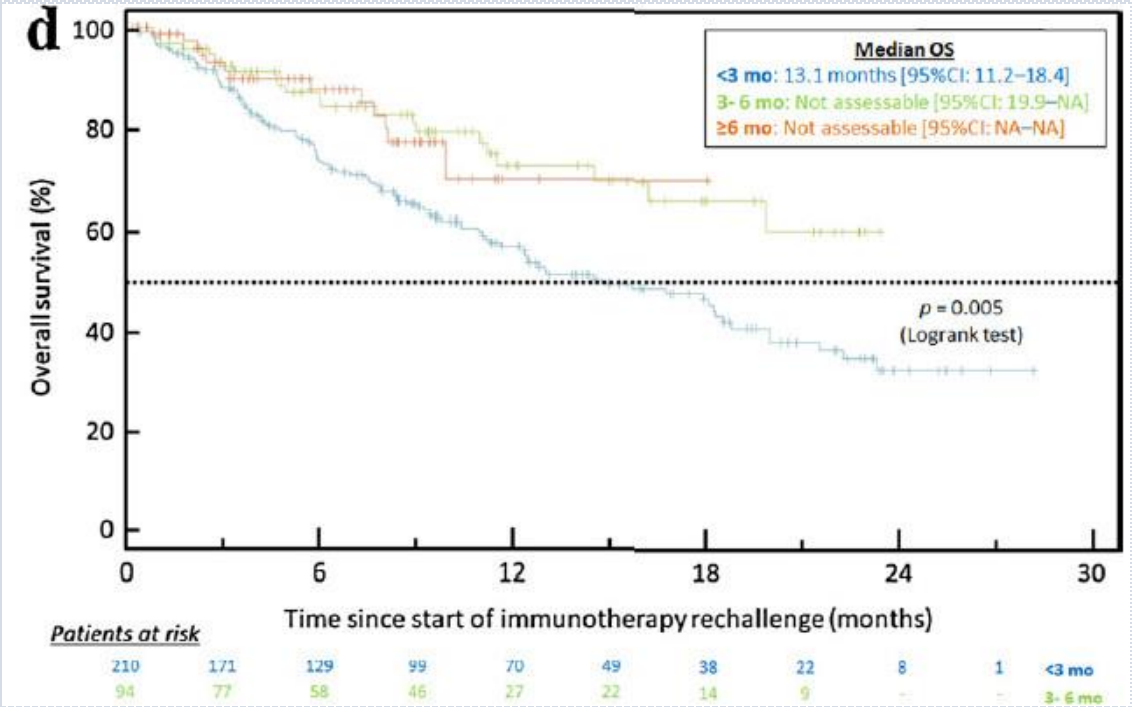


Lung Cancer 140 (2020) 99–106

Predictive factor of response to rechallenge

- **Duration of the initial nivolumab treatment**
  - the only meaningful variable of OS2 data (vs. CTx group)
  - IO resumption group
    - < 3months vs 3-6months: HR 0.56 (95% CI: 0.46–0.70)
    - < 3months vs ≥ 6months: HR 0.19 (95% CI: 0.46–0.70)
  - IO rechallenge group
    - < 3months vs 3-6months: HR 0.56 (95% CI: 0.22-0.56)
    - < 3months vs ≥ 6months: HR 0.19 (95% CI: 0.10-0.33)





Lung Cancer 140 (2020) 99–106

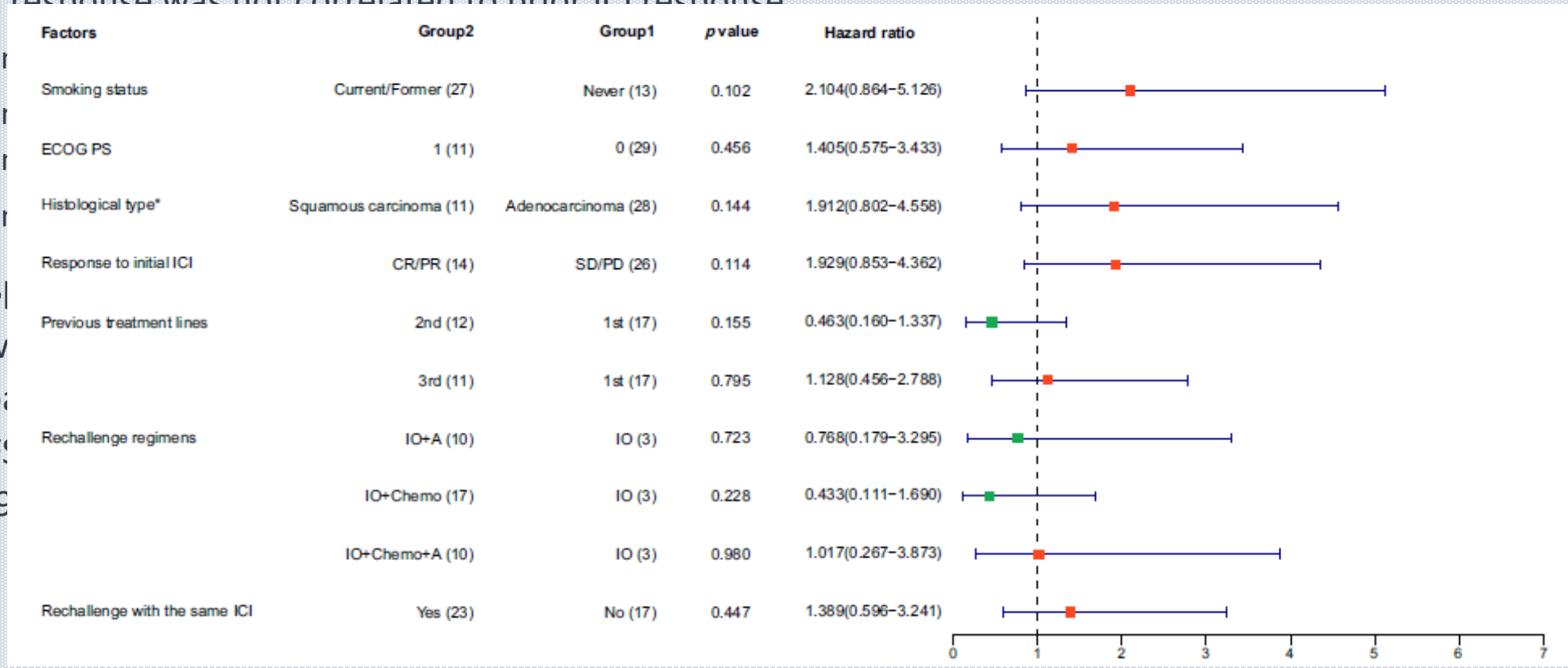
Other retrospective studies

- **Retrospective study from French National Cohort (n=144)**
  - discontinuation of ICI
    - toxicity, progession, clinical decision
  - best response was not correlated to prior ICI response
    - mPFS1: 13 months [95% CI 10-16.5], mPFS2: 4.4 months [95% CI 3-6.5]
    - mPFS2 was longer in patients discontinued because of clinical decision (6.5 months [95% CI 2.5-11.9]) or toxicity (5.8 months [95%CI 3.5-18]) compared to disease progression (2.9 months [95% CI 2.0-4.4]) (P =0.021)
    - mOS1: 3.3 years [95% CI 2.9-3.9], mOS2: 1.5 years [95%CI 1.0-2.1]
- **Retrospective study from Chinese Cohort (n=40)**
  - 33 were directly rechallenged and 7 recieved other threapy between two lines of ICI
  - 17 patients were rechallenged with another ICI
  - mPFS: 6.8months
  - PR: 9 (22.5%), SD: 25 (62.5%)

1. Journal of Thoracic Oncology Vol. 14 No. 10S 2. J Cancer Res Clin Oncol. 2022 Jan 4 online ahead of print

Other retrospective studies

- **Retrospective study from French National Cohort (n=144)**
  - discontinuation of ICI
    - toxicity, progession, clinical decision
  - best response was not correlated to prior ICI response
    -
    -
    -
    -
- **Retros**
  - 33 w
  - 17 pa
  - mPF
  - PR: 9



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1. Journal of Thoracic Oncology Vol. 14 No. 10S 2. J Cancer Res Clin Oncol. 2022 Jan 4 online ahead of print

Other retrospective studies

- **Switching administration (atezolizumab after anti-PD1 treatment)**
  - n=18
  - response of prior ICI
    - PR 7, SD 3
    - nivolumab: 9.5 (3-37) cycles, pembrolizumab: 10 (2-12) cycles
  - median number of cycle: 3 (range: 2-7)
  - SD: 7/18
  - mPFS2: 2.9 months
- **Switching administration (anti-PD1 after atezolizumab)**
  - n=15
  - response of prior ICI
    - PD 9, SD 4
    - mPFS: 2.8 (0.60-10.3), median cycle: 5 (1-15)
  - mPFS: nivolumab 1.9 months (0.43–3.0), pembrolizumab 2.8 months (0.47–13.4)
  - SD: nivolumab 1/7, pembrolizumab 3/8
  - PD: nivolumab 5/7, pembrolizumab 4/8

1. Anticancer research 39.7: 3917-3921. (Jul 2019) 2. Thoracic Cancer 11 (2020) 15–18

Other retrospective studies

Table 4 Prior reports about immune checkpoint inhibitor rechallenge in advanced non-small cell lung cancer

		First ICI				Second ICI			
Authors	N	Type of antibody	ORR (%)	DCR (%)	Median PFS (months)	Type of antibody	ORR (%)	DCR (%)	Median PFS (months)
Fujita *et al.*[11]	12	Anti-PD-1	58.3	75	6.2	Anti-PD-1	8.3	41.7	3.1
Niki *et al.*[12]	11	Anti-PD-1	45.5	63.6	4.9	Anti-PD-1	27.2	45.5	2.7
Watanabe *et al.*[13]	14	Anti-PD-1/ PD-L1	21.4	57.1	3.7	Anti-PD-1	7.1	21.4	1.6
Fujita *et al.*[14]	18	Anti-PD-1	NA	NA	NA	Anti-PD-L1	0	38.9	1.7
Fujita *et al.*[15]	15	Anti-PD-L1	0.0	33.3	2.8, 6.0	Anti-PD-1	0	26.7	1.9, 2.8
Katayama *et al.*[16]	35	Anti-PD-1/ PD-L1	34.3	68.6	3.9	Anti-PD-1/ PD-L1	2.9	45.7	2.7
Current cases	17	Anti-PD-1/ PD-L1	35.0	88.2	9.7	Anti-PD-1/ PD-L1	5.9	58.8	4.0

DCR, disease control rate; ICI, immune checkpoint inhibitor; ORR, overall response rate; PD-1, programmed death 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival.

Other retrospective studies

Table 4 Prior reports about immune checkpoint inhibitor rechallenge in advanced non-small cell lung cancer

		First ICI				Second ICI			
Authors	N	Type of antibody	ORR (%)	DCR (%)	Median PFS (months)	Type of antibody	ORR (%)	DCR (%)	Median PFS (months)
Fujita *et al.*					6.2	Anti-PD-1	8.3	41.7	3.1
Niki *et al.*[12]	11	Anti-PD-1	45.5	63.6	4.9	Anti-PD-1	27.2	45.5	2.7
Watanabe *et al.*[13]	14	Anti-PD-1/ PD-L1	21.4	57.1	3.7	Anti-PD-1	7.1	21.4	1.6
Fujita *et al.*[14]	18	Anti-PD-1	NA	NA	NA	Anti-PD-L1	0	38.9	1.7
Fujita *et al.*[15]	15	Anti-PD-L1	0.0	33.3	2.8, 6.0	Anti-PD-1	0	26.7	1.9, 2.8
Katayama *et al.*[16]	35	Anti-PD-1/ PD-L1	34.3	68.6	3.9	Anti-PD-1/ PD-L1	2.9	45.7	2.7
Current cases	17	Anti-PD-1/ PD-L1	35.0	88.2	9.7	Anti-PD-1/ PD-L1	5.9	58.8	4.0

DCR, disease control rate; ICI, immune checkpoint inhibitor; ORR, overall response rate; PD-1, programmed death 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival.

without description of the reason of rechallenge

Other retrospective studies

Table 4 Prior reports about immune checkpoint inhibitor rechallenge in advanced non-small cell lung cancer

		First ICI				Second ICI			
Authors	N	Type of antibody	ORR (%)	DCR (%)	Median PFS (months)	Type of antibody	ORR (%)	DCR (%)	Median PFS (months)
Fujita *et al.*[11]						Anti-PD-1	8.3	41.7	3.1
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DCR, disease control rate; ICI, immune checkpoint inhibitor; ORR, overall response rate; PD-1, programmed death 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival.

All patient discontinued the first ICI due to disease progression

6

Other retrospective studies

Table 4 Prior reports about immune checkpoint inhibitor rechallenge in advanced non-small cell lung cancer

		First ICI				Second ICI			
Authors	N	Type of antibody	ORR (%)	DCR (%)	Median PFS (months)	Type of antibody	ORR (%)	DCR (%)	Median PFS (months)
Fujita *et al.*[11]	12	Anti-PD-1	58.3	75	6.2	Anti-PD-1	8.3	41.7	3.1
Niki *et al.*[12]	11	Anti-PD-1	45.5	63.6	4.9	Anti-PD-1	27.2	45.5	2.7
Watanabe *et al.*[13]	14	Anti-PD-1/ PD-L1	21.4	57.1	3.7	Anti-PD-1	7.1	21.4	1.6
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DCR, disease control rate; ICI, immune checkpoint inhibitor; ORR, overall response rate; PD-1, programmed death 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival.

- PFS of the initial ICI treatment was 120 days (84-139 days)
- ICI-free interval was not associated with PFS & OS

보험 급여 기준

연번	항암요법	투여대상
4	pembrolizumab[주1]	PD-L1 발현 양성(발현 비율 ≧ 50%[주3])이면서, EGFR 또는 ALK 변이가 없는 진행성 (stage IV) ※ 선행화학요법/수술후보조요법, 근치적항암화학방사선요법 치료 종료 후 6개월 이후 재발한 경우 포함 ※ 관해공고요법으로 durvalumab 치료 실패 시 급여 불가함
	(제2022-38호: 2022.3.1)	
5	pembrolizumab[주1] + pemetrexed + platinum	EGFR 또는 ALK 변이가 없는 전이성 비편평상피세포 ※ 선행화학요법/수술후보조요법, 근치적항암화학방사선요법 치료 종료 후 6개월 이후 재발한 경우 포함 ※ 관해공고요법으로 durvalumab 치료 실패 시 급여 불가함 ※ platinum은 초기 4주기 병용 투여 이후 투여하지 아니함 ※ pemetrexed는 최대 2년까지 급여 인정함
	(제2022-38호: 2022.3.1)	
6	pembrolizumab[주1] + paclitaxel + carboplatin	전이성 편평상피세포 ※ 선행화학요법/수술후보조요법, 근치적항암화학방사선요법 치료 종료 후 6개월 이후 재발한 경우 포함 ※ 관해공고요법으로 durvalumab 치료 실패 시 급여 불가함 ※ paclitaxel과 carboplatin은 초기 4주기 병용 투여 이후 투여하지 아니함
	(제2022-38호: 2022.3.1)	
7	atezolizumab[주1]	PD-L1 발현 양성(발현비율 TC3 또는 IC3[주7])이면서, EGFR 또는 ALK 변이가 없는 전이성 ※ 선행화학요법/수술후보조요법, 근치적항암화학방사선요법 치료 종료 후 6개월 이후 재발한 경우 포함 ※ 관해공고요법으로 durvalumab 치료 실패 시 급여 불가함
	(제2022-113호: 2022.5.1)	

- Durvalumab 치료 실패시 기간 명시 확인
  → 6개월

- Durvalumab 치료 반응 있었던 환자
  - durvalumab (12개월) 투약 종료 시점 CT와 6개월 뒤 CT상 SD 가 확인된 환자
  - 이후 시간이 경과되어 PD-L1 발현 양성이면서, EGFR 또는 ALK 변이가 없는 진행성(stage IV) pembrolizumab 투여 대상에 합당한 경우 1차로 pembrolizumab 보험 급여 투약 가능 ?
  - 이후 시간이 경과되어 PD-L1 발현 음성이면서, EGFR 또는 ALK 변이가 없는 진행성(stage IV) pembrolizumab + cytotoxic CTx 투여 대상에 합당한 경우 1차로 pembrolizumab 보험 급여 투약 가능 ?

Summary

- Clinical data on rechallenge with immune check point inhibitors is not sufficient.
- ‘Some’ patients can respond to retreatment
- Completion of 1st line ICI treatment
- Clinical benefit from prior ICI
- ICI-free interval ≥ 6 months

Table 1. Criteria for acquired resistance to PD-(L)1 blockade in patients with NSCLC

1. Type of treatment: • Prior treatment with PD-(L)1 blockade is required. IO–IO combinations are allowed.
2. Depth of response: • Patients experience objective response on PD-(L)1 blockade. Stable disease is excluded.
3. Timing of progression: • No duration of response threshold is required. Confirmatory scans of progression after prior response are not required.
4. Continuity of treatment: • Progression occurs within 6 months of last PD-(L)1 blockade treatment. In patients with progression occurring >6 months since last treatment, PD-(L)1 blockade retreatment is required.

Ann Oncol. 2021 Dec;32(12):1597-1607

Rechallenge after immune-related adverse events

Guidelines of irAEs

KU MEDICINE KOREA UNIVERSITY MEDICINE

ASCO special articles

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: ASCO Guideline Update

Bryan J. Schneider, MD[1]; Jarushka Naidoo, MI
Milan Anadkat, MD[7]; Michael B. Atkins, MD[8];
Marianne J. Davies, DNP[11]; Marc S. Ernstoff,
Jennifer S. Mammen, MD, PhD[15]; Aung Naing
Cristina A. Reichner, MD[18]; Carole Seigel, ME
Maria Suarez-Almazor, MD[6]; Umang Swami, I
Jeffrey S. Weber, MD, PhD[25]; Pauline Funcha

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

CLINICAL PRACTICE GUIDELINES

Annals of Oncology 28 (Supplement 4): i119–i142, 2017
doi:10.1093/annonc/mdx225

Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

J. B. A. G. Haanen[1], F. Carbonnel[2], C. Robert[3], K. M. Kerr
the ESMO Guidelines Committee*

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Management of Immunotherapy-Related Toxicities

Version 1.2022 — February 28, 2022

Grade of adverse events

- **CTCAE**

	Symptom	Management
Grade 1	asymptom or mild	observation
Grade 2	limiting instrumental ADL	minimal, local or noninvasive intervention
Grade 3	disabling or limiting self care ADL	hospitalization
Grade 4	life-threatening	urgent intervention
Grade 5	death	

- **irAEs**
  - similar to CTCAE
  - organ-specific consideration
  - Grade 1: continuation of immunotherapy
  - Grade 2: withholding of immunotherapy
  - Grade 3-4: (permanent) discontinuation of immunotherapy

Principles of immunotherapy rechallenge

- **General principles**
  - Exercise caution & Close follow-up
  - If toxicity returns, permanently discontinue class of immnuotherapy
  - Consideration may be given to other class of immunotherapy
  - Immunotherapy should be continued for grade 1 toxicities, except for some neurologic,hematologic, and cardiac toxicities
  - Grade 4 toxicities warrant permanent discontinuation of ICPis, except for endocrinopathies
  - Resumption of immunotherapy following grade 2 irAEs can be considered on resolution to ≤ grade 1
  - Consult with organ-specific specialists prior to resumption of immunotherapy

- Rechallenge after discontinuing ICI for irAE ≥ grade 2
  - 39% experienced another ≥ grade 2 irAE
  - 70% had the same irAE at recurrence

J ImmunoTher Cancer (2020) 8(2):e001622

- Rechallenge was associated with about 25–30% of thesame irAEs experienced previously

JAMA Oncol. 2020;6(6):865-871.

- In the recurrence group, the average time for the first irAE was shorter (9 weeks) compared to the non-recurrent group (15weeks).

Cancers (2022) 14 (4):955

NCCN Guidelines Version 1.2022, J Clin Oncol 39:4073-4126

Immune-related adverse events

- irAE occurrence after rechallenge
  - VigiBase

Figure 2. Rate of Recurrence According to the Initial Immune-Related Adverse Event

Adverse drug reaction	No. of cases	Recurrence rate (95% CI), %
Diabetes	13	0 (0-27)
Neurologic	17	6 (0-29)
Uveitis	11	9 (0-40)
Adrenal	40	12 (5-27)
Pancreatitis	13	15 (3-43)
Thyroiditis	60	17 (9-28)
Hypophysitis	23	26 (12-47)
Hepatitis	31	29 (16-47)
Hematologic	10	30 (10-61)
Pneumonitis	101	34 (25-43)
Colitis	123	37 (29-45)
Skin	16	38 (18-61)
Arthritis	29	45 (28-62)

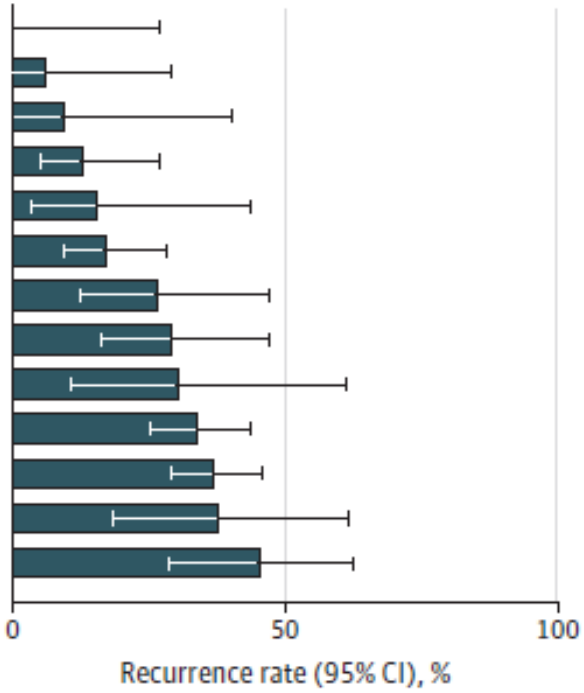


Table 2. Factors Associated With the Recurrence of the Same Immune-Related Adverse Event

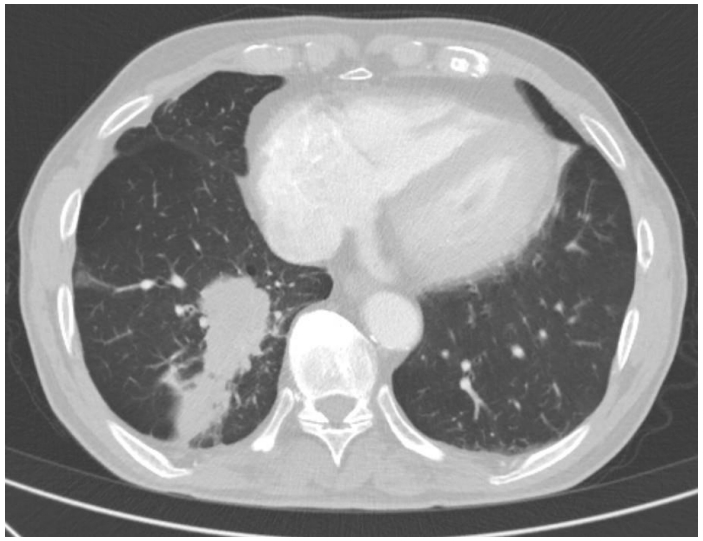
Initial irAE	No. (%) Recurrence after ICI rechallenge (n = 130)	No. (%) No recurrence after ICI rechallenge (n = 322)	Reporting OR (95% CI) Univariate analysis	Reporting OR (95% CI) Multivariate analysis
ICI				
Anti-PD-1 or anti-PD-L1 alone	105 (80.8)	265 (82.3)	0.9 (0.54-1.52)	NA
Anti-CTLA-4 alone	7 (5.4)	15 (4.7)	1.16 (0.46-2.93)	3.5 (1.05-11.64)
Combination therapy	18 (13.8)	42 (13.0)	1.07 (0.59-1.94)	NA
Type of initial irAE[a]				
Adrenal	5 (3.8)	35 (10.9)	0.33 (0.13-0.86)	NA
Arthritis	13 (10.0)	16 (5.0)	2.12 (0.99-4.55)	NA
Colitis	47 (36.2)	78 (24.2)	1.77 (1.14-2.75)	2.99 (1.60-5.59)
Diabetes	0	13 (4.0)	NA	NA
Hematological	3 (2.3)	7 (2.2)	1.06 (0.27-4.18)	NA
Hepatitis	11 (8.5)	22 (6.8)	1.26 (0.59-2.68)	3.38 (1.31-8.74)
Hypophysitis	6 (4.6)	17 (5.3)	0.87 (0.33-2.25)	NA
Mucositis	2 (1.5)	3 (0.9)	1.66 (0.27-10.06)	NA
Myocarditis	0	3 (0.9)	NA	
Myositis	2 (1.5)	7 (2.2)	0.7 (0.14-3.43)	NA
Nephritis	4 (3.1)	4 (1.2)	2.52 (0.62-10.25)	4.92 (0.94-25.64)
Neurological	3 (2.3)	16 (5.0)	0.45 (0.13-1.58)	NA
Pancreatitis	3 (2.3)	11 (3.4)	0.67 (0.18-2.43)	NA
Pneumonitis	36 (27.7)	67 (20.8)	1.46 (0.91-2.33)	2.26 (1.18-4.32)
Skin	6 (4.6)	10 (3.1)	1.51 (0.54-4.24)	3.21 (0.81-12.75)
Thyroiditis	11 (8.5)	50 (15.5)	0.5 (0.25-1.00)	0.37 (0.12-1.16)
Uveitis	1 (0.8)	10 (3.1)	0.24 (0.03-1.91)	NA
Vasculitis	1 (0.8)	0	NA	NA
Initial irAE				
Serious	118 (90.8)	297 (92.2)	0.83 (0.40-1.70)	NA
Fatal	8 (6.2)	13 (4.0)	1.56 (0.63-3.85)	NA

JAMA Oncol. 2020;6(6):865-871.

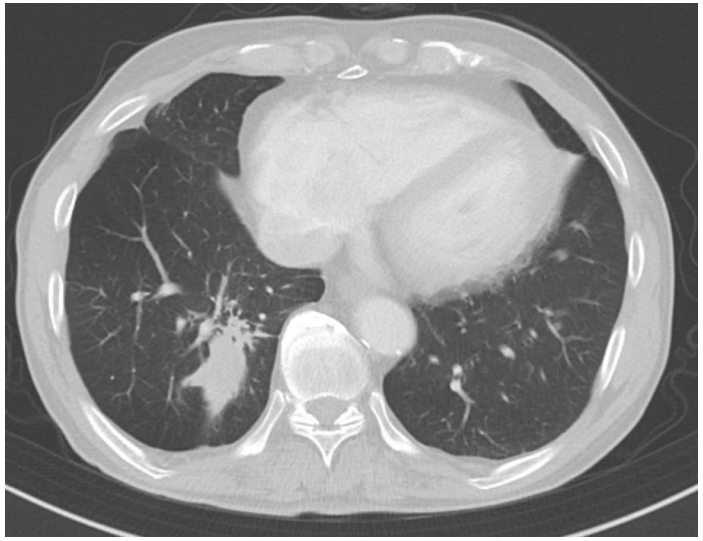
CASE #1

- **M/78**
- **current smoker: 25PY**
- **Hemoptysis**
- **NSCLC (Sqcc, RLL, T4N3M1a)**
- **1L4C gemcitabine, carboplatin (2019/6/20~2019/9/4)**
- **2L pembrolizumab (2019/10/21~)**
- **bilirubin(total)**
  - 1.09mg/dL → 1.82 (Nov/2019) → 2.83(Jan/2020; 5th cycle) (upper normal : 1.4 mg/dL)
  - AST/ALT 22/63 IU/L, direct bilirubin 0.31 mg/dL

baseline of
2L pembrolizumab



Jan/2020



CASE #1

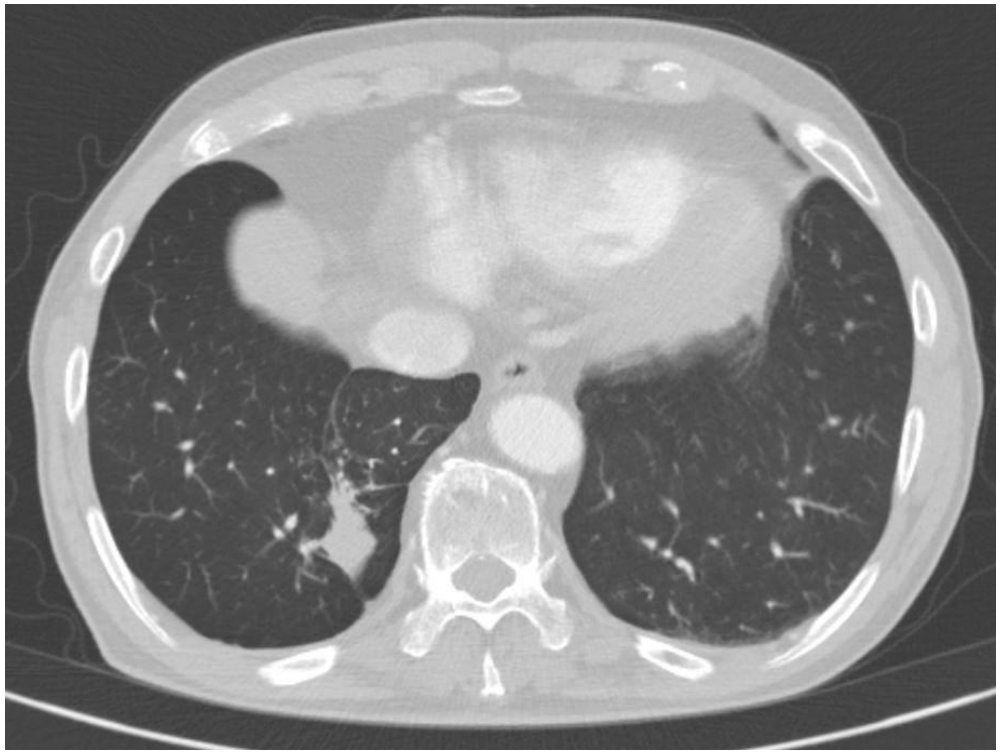
- **ASCO**
  - Grade 1: Asymptomatic (AST or ALT > ULN to 3.0 X ULN and/or total bilirubin > ULN to 1.5 X ULN)
  - Grade 2: Asymptomatic (AST or ALT > 3.0 to ≤5 ULN and/or total bilirubin >1.5 to ≤ 3 X ULN)
  - Grade 3: AST or ALT 5-20 X ULN and/or total bilirubin 3-10 X ULN, OR symptomatic liver dysfunction; fibrosis by biopsy; compensated cirrhosis; and reactivation of chronic hepatitis
  - Grade 4: AST or ALT > 20 X ULN and/or total bilirubin . 10 X ULN OR decompensated liver function (eg, ascites, coagulopathy, encephalopathy, and coma)

- Hold ICPi temporarily
- Patients should be advised to stop unnecessary medications and any known hepatotoxic drugs. Temporarily hold other potentially hepatotoxic oncologic agents
- For grade 2 hepatic toxicity, may administer steroid (0.5-1 mg/kg/d prednisone) or equivalent if no improvement is seen after 3-5 days
- Increase frequency of monitoring to every 3 days
- If inadequate improvement after 3 days, consider adding mycophenolate mofetil
- May initiate steroid taper when symptoms improve to ≤ G1 and may resume ICPi treatment when steroid ≤ 10 mg/d. Taper over at least 1 month.
- Consider hepatology consult for G2 and above
- May resume if recover to ≤ G1 on prednisone ≤ 10 mg/d

CASE #1

- **Treatment**
  - Holding pembrolizumab without steroid
  - Rechallenge :bilirubin: 1.91mg/dL
  - follow up: bilirubin 2.08~2.54
  - eosinophil : 1000/μL
- **Progress**
  - at 2yrs: PR

  → 200mg/5~6 week
  - Bilirubin: within normal range
  - eosinophil: within normal range



Organ-specific considerations

Carido-vascular	• Grade 1 myocarditis: Consider resuming on resolution of symptoms. • Permanent discontinuation is warranted in the setting of grade 2–4 myocarditis.
Endocrine	• Thyroid: No discontinuation required for hypothyroidism. For symptomatic hyperthyroidism resembling Graves-like disease, consider holding immunotherapy and resuming after workup is complete and there is evidence for improvement in symptoms and TFTs. • Hypophysitis manifested by deficiency of ACTH, TSH, and/or gonad-stimulating hormones, but without symptomatic pituitary swelling: Immunotherapy may continue while replacement endocrine therapy is regulated. • Hypophysitis accompanied by symptoms of pituitary swelling (eg, headache, vision disturbance, and/or neurologic dysfunction): Hold immunotherapy until resolution of symptoms after steroid therapy; consider resumption of immunotherapy after symptoms related to mass effect are resolved. • T1DM with DKA: Consider resuming once DKA has been corrected and glucose level has stabilized. • Primary adrenal insufficiency: After appropriate replacement endocrine therapy is instituted, immunotherapy may continue.
Eye	• Grade 2-4 irAE: Hold immunotherapy per guideline; consider resumption of immunotherapy in consultation with ophthalmology on resolution to ≤ grade 1.
GI	• PD-1/PD-L1 agents: After grade 2–3 colitis, consider resumption of immunotherapy after symptoms have resolved to ≤ grade 1. In rare circumstances in which the patient cannot completely taper off steroids and sympto ms are unresolved, immunotherapy may be resumed while patient is still on ≤10 mg prednisone equivalent daily. Consider concurrent vedolizumab on resumption of PD-1/PD-L1. • CTLA-4 agents: Discontinue if irAE is serious or life-threatening. Do not make up doses missed due to irAE and/or required steroid treatment.
Kidney	• Hold immunotherapy per guidelines; on resolution to ≤ grade 1, consider resuming concomitant with or without steroid if creatinine is stable. • After restarting immunotherapy, monitor creatinine every 2–3 weeks or more frequently as clinically indicated. If creatinine remains stable, consider longer durations between creatinine checks. • Consider permanent discontinuation in the setting of severe (grade 3–4) proteinuria. • For resolved G2 and/or G3 renal irAE, may consider re-challenge if clinically indicated, at least after ≥2 months of holding ICI therapy.
Liver	• Transaminitis without elevated bilirubin: Following a grade 2 irAE, consider resumption of immunotherapy after ALT/AST return to baseline and steroids, if used, have been tapered to ≤10 mg prednisone equivalent daily. • For grade 3 hepatitis, if on CTLA-4 combined with PD-1/PD-L1, restart with just PD-1/PD-L1 inhibitor. • Permanent discontinuation is warranted in the setting of severe or life-threatening (grade 4) hepatitis.
Lung	• Progressive grade 1 pneumonitis requiring a hold: Consider resuming on radiographic evidence of improvement. • Grade 2: Resume once pneumonitis has resolved to ≤ grade 1 and patient is off steroids. Resume once pneumonitis has resolved to ≤ grade 1 and patient is on a corticosteroid dose of ≤10 mg/day of prednisone. • Permanent discontinuation is warranted in the setting of severe (grade 3–4) pneumonitis.
Musculoskeletal	• Inflammatory arthritis (moderate to severe irAE requiring hold): Resume on stabilization, or adequate management of symptoms. Permanent discontinuation may be warranted for severe inflammatory arthritis that significantly impairs ADLs and quality of life.
Nervous System	• Myasthenia gravis: Permanently discontinue immunotherapy after grade 2–4 AE. • GBS: Permanently discontinue immunotherapy for any grade GBS. • Peripheral neuropathy: Following hold for grade 1–2 AE, consider resuming if symptoms resolve to ≤ grade 1 or if patient has well-controlled isolated painful sensory neuropathy. • Aseptic meningitis: Consider resuming following mild to moderate AE if symptoms resolve to grade 0. • Encephalitis: Permanent discontinuation is warranted in the setting of moderate to severe encephalitis (grade 2–4). • Transverse myelitis: Discontinuation of immunotherapy following any-grade transverse myelitis.
Pancreas	• Symptomatic grade ≤3 pancreatitis: Consider resumption of immunotherapy if no clinical/radiologic evidence of pancreatitis ± improvement in amylase/lipase. Consider consultation with relevant pancreatic specialist reg arding resumption. • Permanent discontinuation is warranted for severe (grade 4) pancreatitis.
Skin	• Maculopapular rash and/or pruritus: Consider resuming after symptoms have resolved to ≤ grade 1 (ie, once skin condition is mild/localized with only topical intervention indicated). • Permanent discontinuation of immunotherapy in the setting of severe or life-threatening bullous disease (grade 3–4), including all cases of SJS and TEN.

Organ-specific considerations

Carido-vascular	• Permanent discontinuation is warranted in the setting of grade 2–4 myocarditis.
Endocrine	• Thyroid: No discontinuation required for hypothyroidism. For symptomatic hyperthyroidism resembling Graves-like disease, consider holding immunotherapy and resuming after workup is complete and there is evidence for improvement in symptoms and TFTs. • Hypophysitis manifested by deficiency of ACTH, TSH, and/or gonad-stimulating hormones, but without symptomatic pituitary swelling: Immunotherapy may continue while replacement endocrine therapy is regulated. • Hypophysitis accompanied by symptoms of pituitary swelling (eg, headache, vision disturbance, and/or neurologic dysfunction): Hold immunotherapy until resolution of symptoms after steroid therapy; consider resumption of immunotherapy after symptoms related to mass effect are resolved. • T1DM with DKA: Consider resuming once DKA has been corrected and glucose level has stabilized. • Primary adrenal insufficiency: After appropriate replacement endocrine therapy is instituted, immunotherapy may continue.
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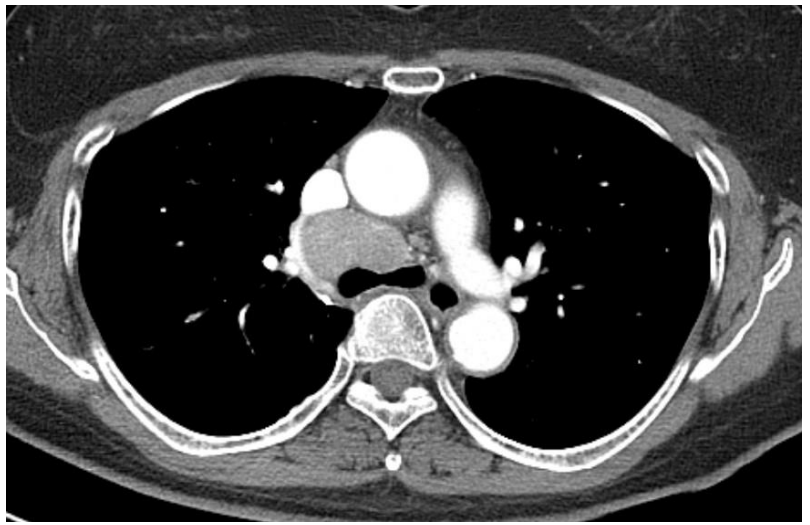
GI	• PD-1/PD-L1 agents: After grade 2–3 colitis, consider resumption of immunotherapy after symptoms have resolved to ≤ grade 1. In rare circumstances in which the patient cannot completely taper off steroids and symptoms are unresolved, immunotherapy may be resumed while patient is still on ≤10 mg prednisone equivalent daily. Consider concurrent vedolizumab on resumption of PD-1/PD-L1. • CTLA-4 agents: Discontinue if irAE is serious or life-threatening. Do not make up doses missed due to irAE and/or required steroid treatment.
Kidney	• Hold immunotherapy per guidelines; on resolution to ≤ grade 1, consider resuming concomitant with or without steroid if creatinine is stable. • After restarting immunotherapy, monitor creatinine every 2–3 weeks or more frequently as clinically indicated. If creatinine remains stable, consider longer durations between creatinine checks. • Consider permanent discontinuation in the setting of severe (grade 3–4) proteinuria. • For resolved G2 and/or G3 renal irAE, may consider re-challenge if clinically indicated, at least after ≥2 months of holding ICI therapy.
Liver	• Transaminitis without elevated bilirubin: Following a grade 2 irAE, consider resumption of immunotherapy after ALT/AST return to baseline and steroids, if used, have been tapered to ≤10 mg prednisone equivalent daily. • For grade 3 hepatitis, if on CTLA-4 combined with PD-1/PD-L1, restart with just PD-1/PD-L1 inhibitor. • Permanent discontinuation is warranted in the setting of severe or life-threatening (grade 4) hepatitis.
Lung	• Progressive grade 1 pneumonitis requiring a hold …ement. …eumonitis has resolved to ≤ grade 1 and patient is on a corticosteroid dose of ≤10 mg/day of prednisone.
Musculoskeletal	• Inflammatory arthritis (moderate to severe irAE requiring hold): Resume on stabilization, or adequate management of symptoms. Permanent discontinuation may be warranted for severe inflammatory arthritis that significantly impairs ADLs and quality of life.
Nervous System	• Myasthenia gravis: Permanently discontinue immunotherapy after grade 2–4 AE. • GBS: Permanently discontinue immunotherapy for any grade GBS • Encephalitis: Permanent discontinuation is warranted in the setting of grade 2–4 • Transverse myelitis: Discontinuation of immunotherapy following any-grade transverse myelitis.
Pancreas	…ncreatic specialist reg
Skin	• Maculopapular rash and/or pruritus: Consider resuming after symptoms have resolved to ≤ grade 1 (ie, once skin condition is mild/localized with only topical intervention indicated). • Permanent discontinuation of immunotherapy in the setting of severe or life-threatening bullous disease (grade 3–4), including all cases of SJS and TEN.

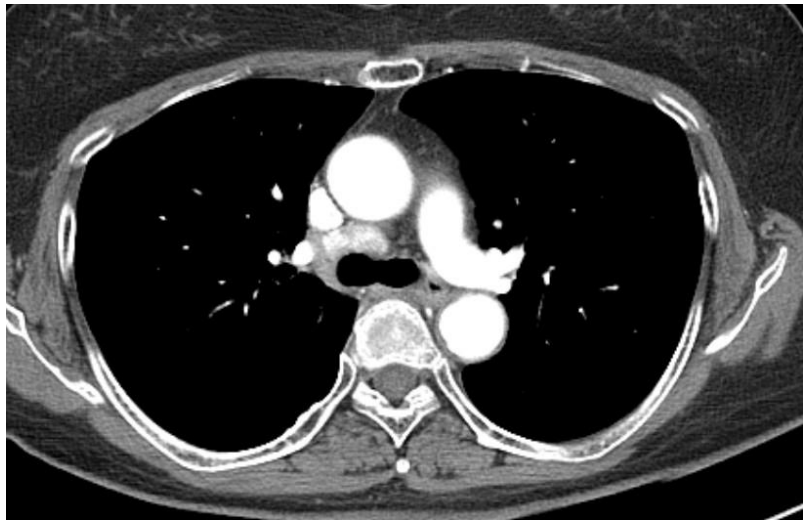
CASE #2

- **F/64, ex-smoker (10PY)**
- **NSCLC (adenocarcinoma, IIIB)**
- **EGFR/ALK/ROS1/BRAF-V600E -/-/-/-**
- **SP263 80%**
- **CCRT**
  - Paclitaxel, Carboplatin: 7C weekly
  - 6000cGy
  - 2019/9/9~2019/10/24
- **Durvalumab**
  - 2019/11/4~

baseline of CCRT



After CCRT



CASE #2

- **2019/12/24**
  - after 3rd cycle durvalumab
  - dyspnea mMRC2, cough
- **Pneumonitis**
  - hospitalization
  - antibiotics
  - BAL: gram/stain culture negative, respiratory virus negative, WBC 610 (lymphocyte 41%)
  - holding durvalumab: 2019/12/4~2020/1/2
  - methylprednisolone 1mg/kg 2weeks → 0.5mg/kg 2weeks and discontinuation

CASE #2

- **2019/12/24**
  - after 3rd cycle durvalumab
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- **Pneumonitis**
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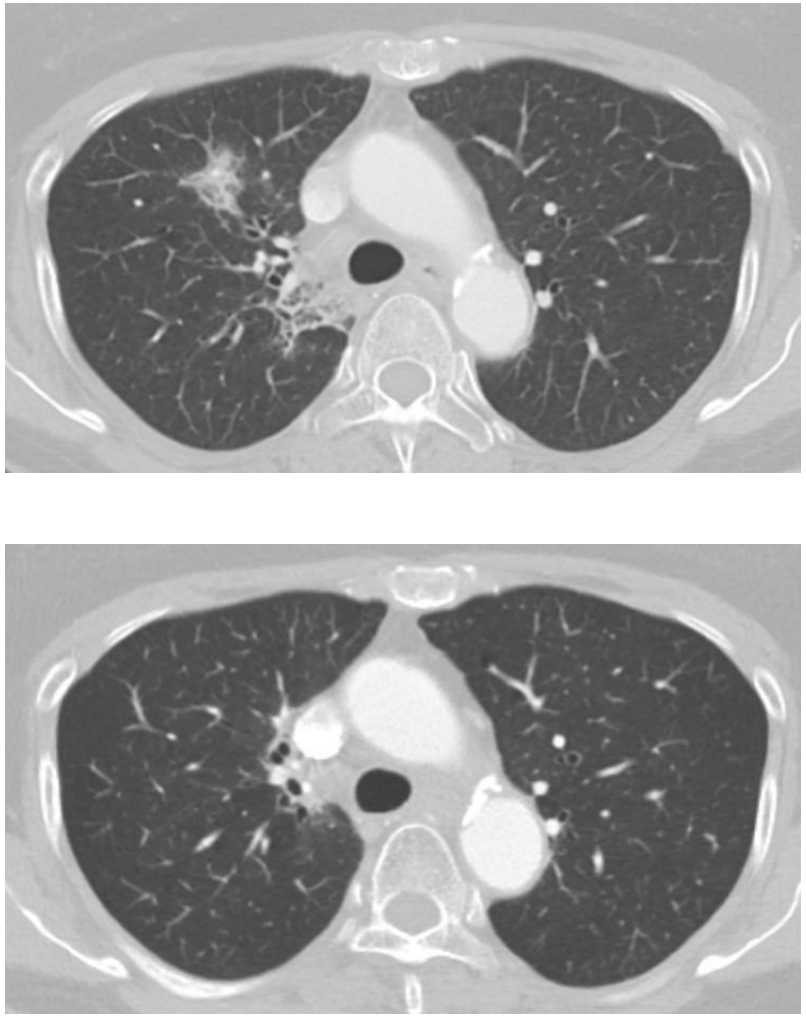
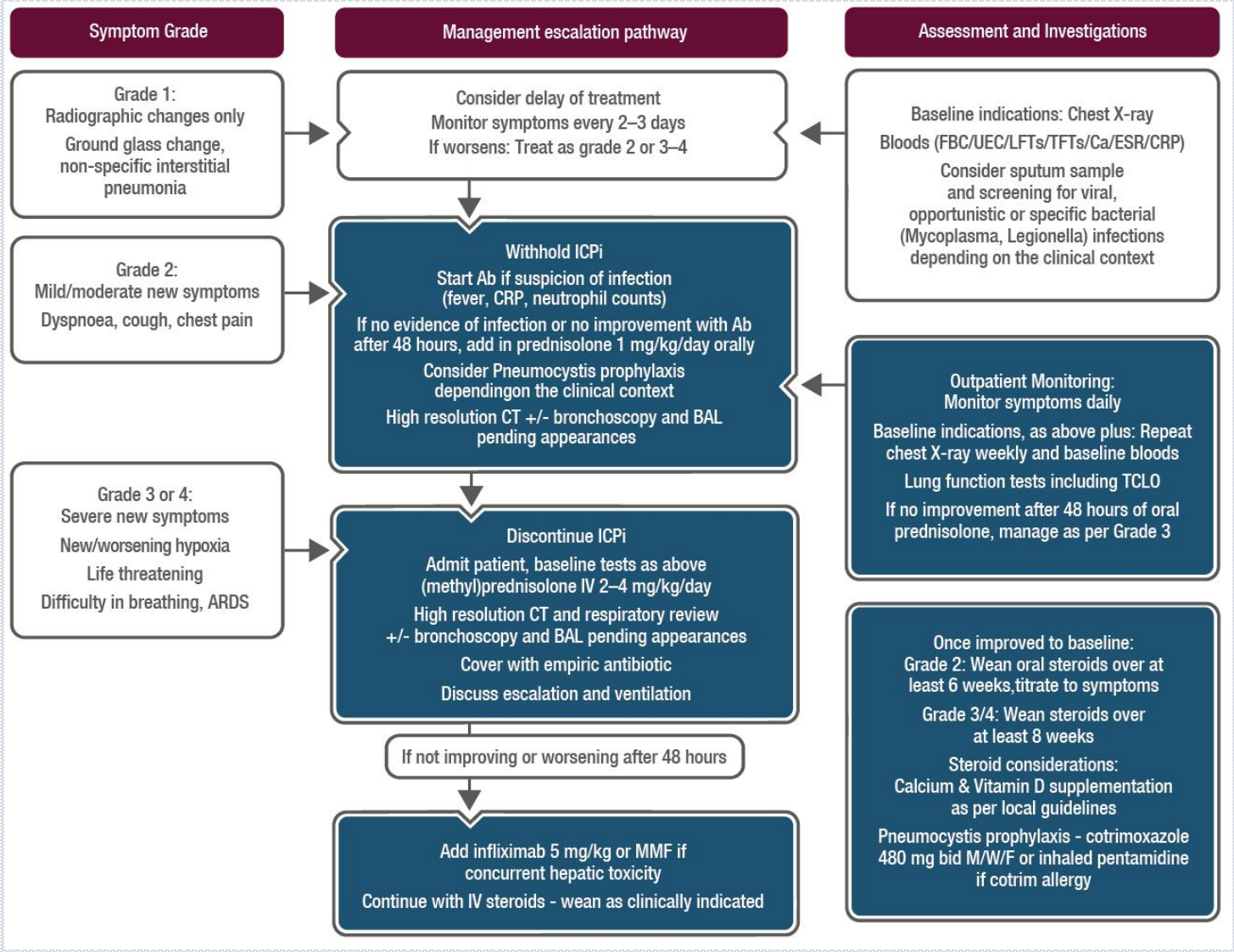
  - antibiotics
  - BAL: gram/stain culture negative, respiratory virus negative, WBC 610 (lymphocyte 41%)
  - holding durvalumab: 2019/12/4~2020/1/2
  - methylprednisolone 1mg/kg 2weeks → 0.5mg/kg 2weeks and discontinuation
  - completion of durvalumab at 1yr
- **Radiation pneumonitis vs. immontherapy related pneumonitis**



Pneumonitis



Annals of Oncology 28 (Supplement 4): i119–i142, 2017

Pneumonitis

TABLE 3. Lung Toxicities

3.1. Pneumonitis

Workup and evaluation

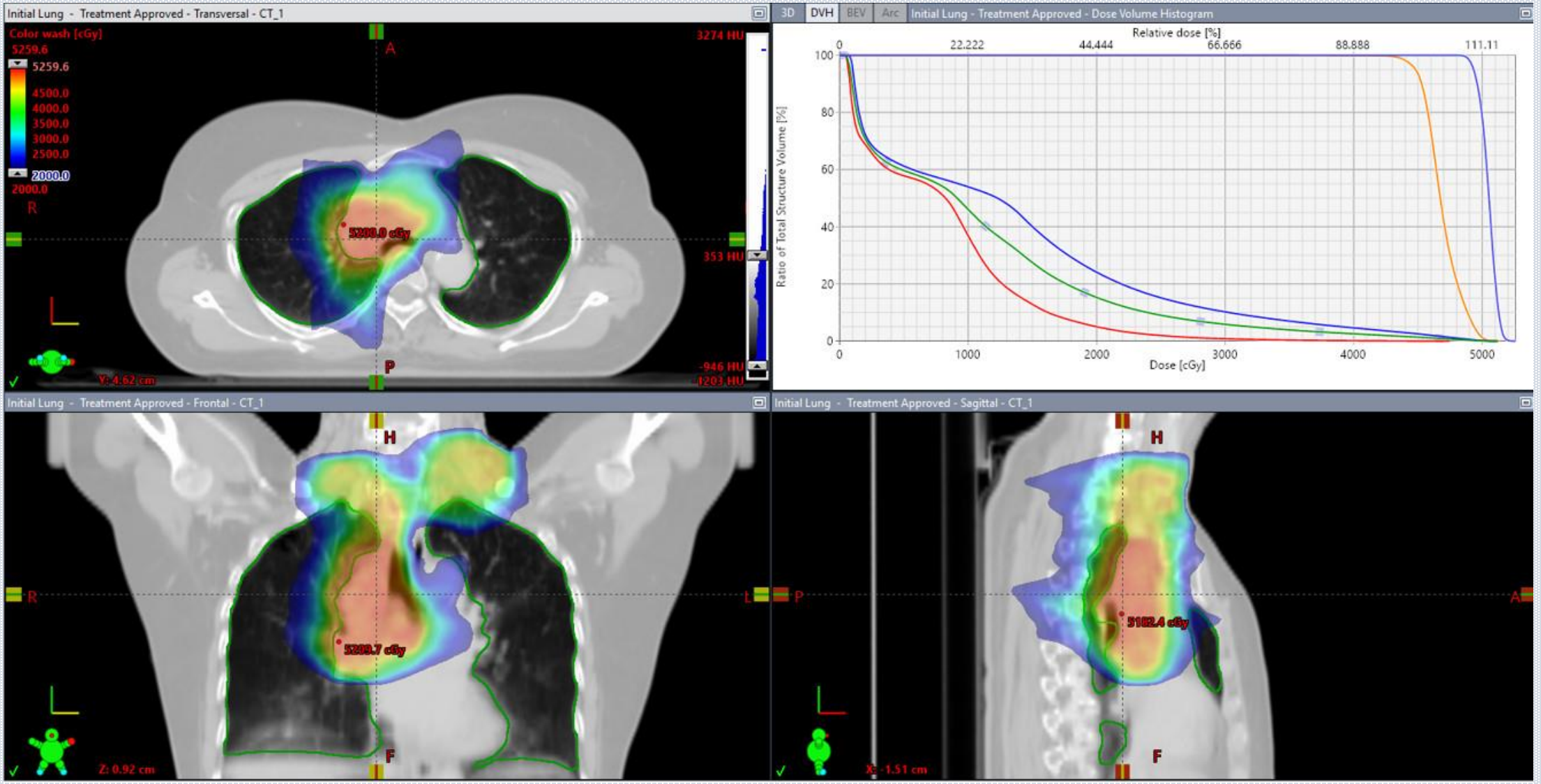
Should include the following: Pulse oximetry and CT chest[1,23] preferably with contrast if concerned for other etiologies such as pulmonary embolus.

For G2 or higher, may include the following infectious workup: nasal swab, sputum culture, and sensitivity, blood culture and sensitivity, urine culture, and sensitivity.

COVID-19 evaluation—per institutional guidelines where relevant.

Grading	Management
G1: Asymptomatic; confined to one lobe of the lung or < 25% of lung parenchyma; clinical or diagnostic observations only	Hold ICPi or proceed with close monitoring. Monitor patients weekly with history and physical examination, pulse oximetry; may also offer chest imaging (CXR, CT) if uncertain diagnosis and/or to follow progress. Repeat chest imaging in 3-4 weeks or sooner if patient becomes symptomatic. In patients who have had baseline testing, may offer a repeat spirometry or DLCO in 3-4 weeks. May resume ICPi with radiographic evidence of improvement or resolution if held. If no improvement, should treat as G2.
G2: Symptomatic; Involves more than one lobe of the lung or 25%-50% of lung parenchyma; medical intervention indicated; limiting instrumental ADL	Hold ICPi until clinical improvement to ≤ G1. Prednisone 1-2 mg/kg/d and taper over 4-6 weeks. Consider bronchoscopy with BAL ± transbronchial biopsy. Consider empiric antibiotics if infection remains in the differential diagnosis after workup. Monitor at least once per week with history and physical examination, pulse oximetry, consider radiologic imaging; if no clinical improvement after 48-72 hours of prednisone, treat as grade 3. Pulmonary and infectious disease consults if necessary.
G3: Severe symptoms; Hospitalization required: Involves all lung lobes or > 50% of lung parenchyma; limiting self-care ADL; oxygen indicated. G4: Life-threatening respiratory compromise; urgent intervention indicated (intubation)	Permanently discontinue ICPi. Empiric antibiotics may be considered. Methylprednisolone IV 1-2 mg/kg/d. If no improvement after 48 hours, may add immunosuppressive agent. Options include infliximab or mycophenolate mofetil IV or IVIG or cyclophosphamide (See Table A2 for dosing). Taper corticosteroids over 4-6 weeks[a] Pulmonary and infectious disease consults if necessary. May consider bronchoscopy with BAL ± transbronchial biopsy if patient can tolerate.

CASE #2

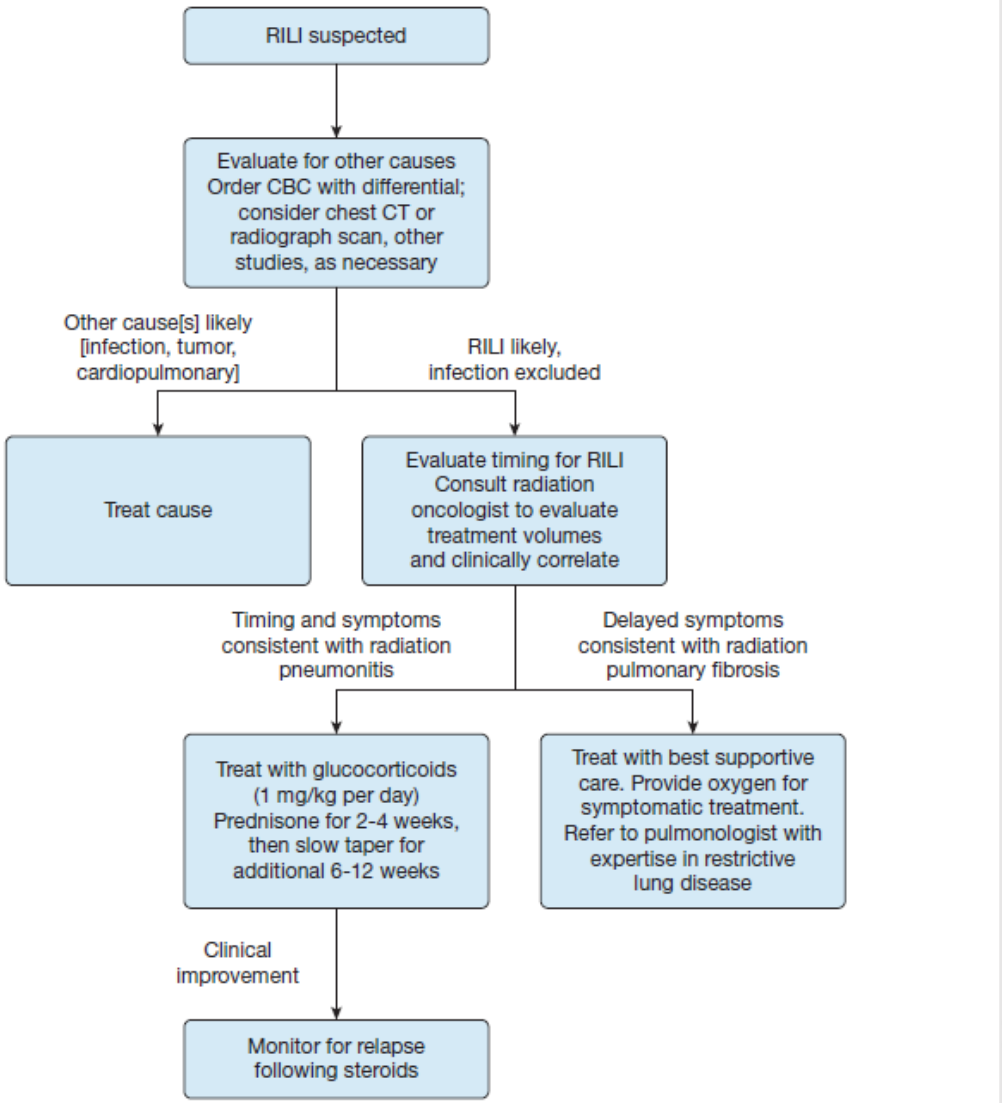

Initial Lung - Treatment Approved - Transversal - CT_1
Color wash [cGy]
5259.6
5259.6
4500.0
4000.0
3500.0
3000.0
2500.0
2000.0
2000.0
3274 HU
353 HU
-946 HU
-1203 HU
5208.0 cGy
A
P
R
Y: 4.62 cm
3D
DVH
BEV
Arc
Initial Lung - Treatment Approved - Dose Volume Histogram
Relative dose [%]
0
22.222
44.444
66.666
88.888
111.11
100
80
60
40
20
0
Ratio of Total Structure Volume [%]
0
1000
2000
3000
4000
5000
Dose [cGy]
Initial Lung - Treatment Approved - Frontal - CT_1
H
F
R
L
5219.7 cGy
Z: 0.92 cm
Initial Lung - Treatment Approved - Sagittal - CT_1
H
F
P
A
5182.4 cGy
X: -1.51 cm

Radiation induced lung injury

- **Onset**
  - usually develop approximately 4 to 12 weeks following irradiation
  - fibrotic radiation pneumonitis develop after 6 to 12 months

TABLE 1] Risk Factors for Radiation-Induced Lung Injury

Radiation risk factors
% Total lung volume receiving ≥ 20 Gy (V20), ≥ 30%
% Total lung volume receiving ≥ 5 Gy (V5), ≥ 65%
Mean lung dose, > 20 Gy
Absolute volume lung spared >5 Gy (AVS5), < 500 cc
Target location, lower lobe
Disease risk factors
Refractory or relapsed disease (lymphoma)
Supraclavicular field (breast cancer)
Bulky disease
Chemotherapy
Re-irradiation
Host risk factors
Age ≥ 50 y
Autoimmune disease
Interstitial lung disease
Former or current smoker
COPD



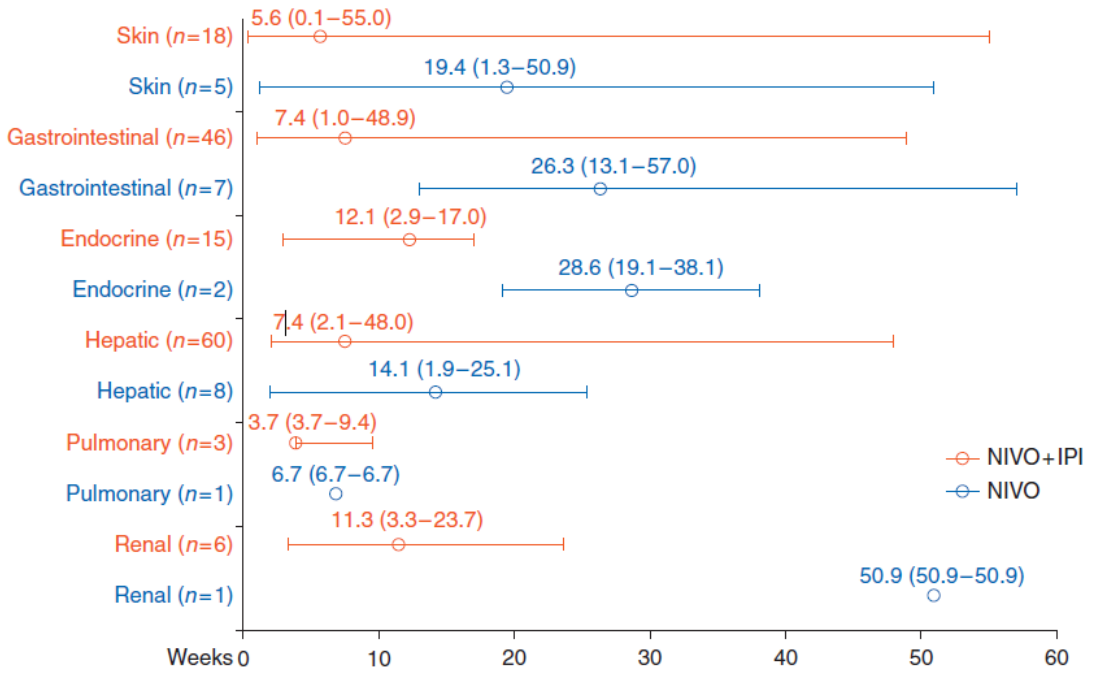
CHEST 2019; 156(1):150-162

Radiation induced lung injury

- **Onset**
  - usually develop approximately 4 to 12 weeks following irradiation
  - fibrotic radiation pneumonitis develop after 6 to 12 months

6. 관해공고요법(consolidation)

연번	항암요법	투여대상
1	durvalumab[주1] (제2020-81호: 2020.4.1)	PD-L1 발현 양성(발현 비율 ≧ 1%[주5])이면서 백금기반 동시적 항암화학방사선요법 2주기 이상 투여 후 질병진행이 없는 안정병변 이상의 절제 불가능한 국소 진행성(stage III)으로 CCRT 치료 종료 이후 42일 내에 투여하는 경우 ※ 급여 인정 기간은 12개월로 함 (주1항 최대 2년 적용 불가) ※ 이전 PD-1 inhibitor 등 면역관문억제제 치료를 받지 않은 경우에 한함



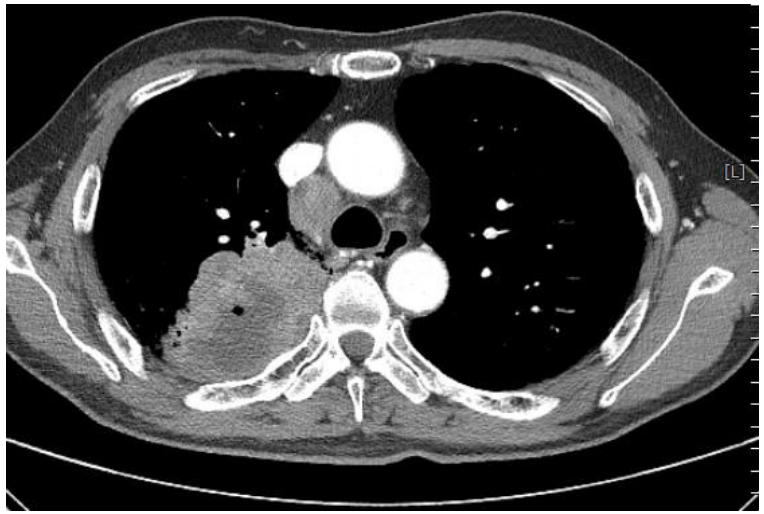
- **Consult with organ-specific specialists prior to resumption of immunotherapy**

Annals of Oncology 28 (Supplement 4): i119–i142, 2017

CASE #3

- **M/63; current smoker 30PY**
- **NSCLC (sqcc, T4N2M0, IIIC), SP263 100%**
- **CCRT**
  - Paclitaxel, Carboplatin weekly 6th cycle
  - Radiation: 2020/2/24~4/3, 6600cGy
- **Durvalumab**
  - 2020/4/14~
  - after 3rd cycle: dyspnea, cough

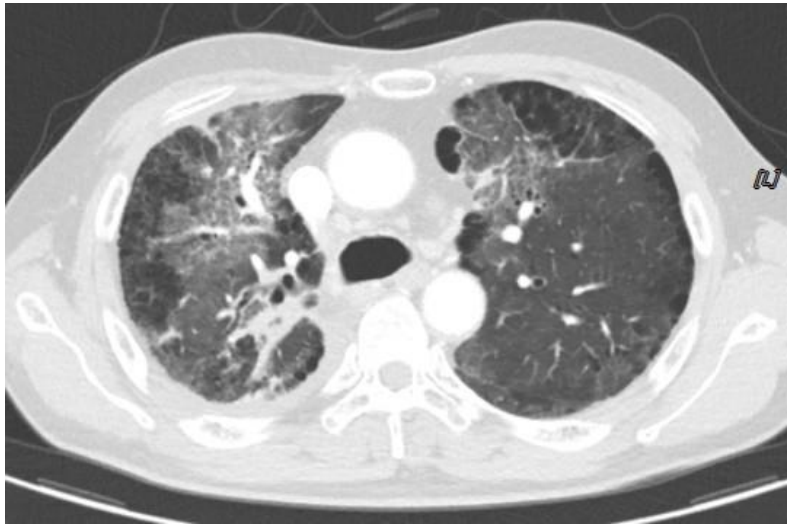
baseline of CCRT

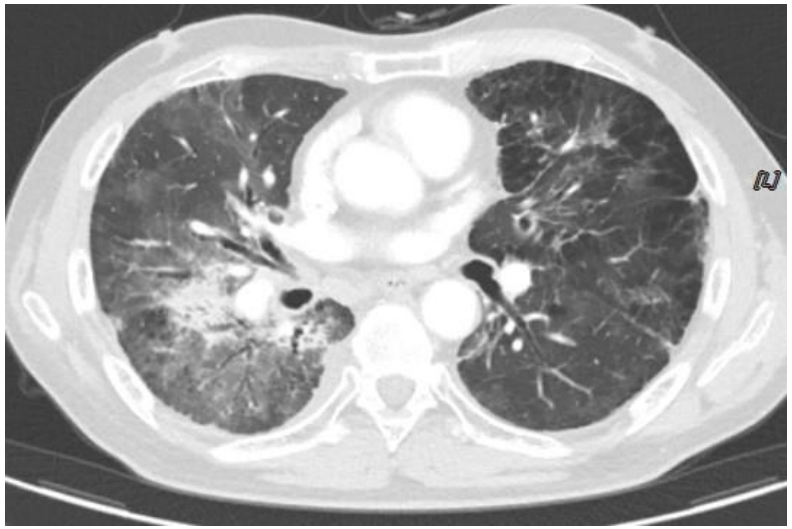


After CCRT

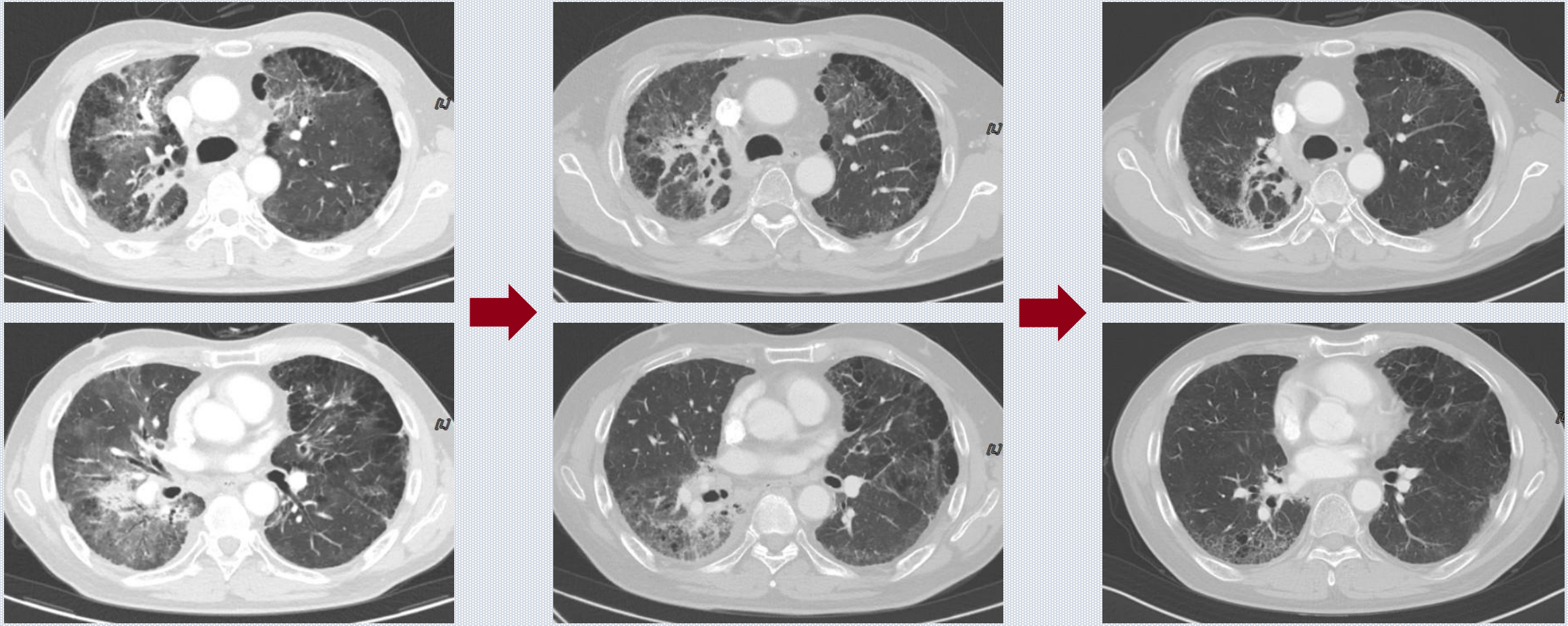
CASE #3

- **Pneumonitis**
  - Hospitalization
  - Antibiotics
  - BAL: WBC 1050/μL (lymphocyte), gram & virus negative
  - KL-6: 1037
  - holding durvalumab
  - Steroid
    - methylprednisolone 1mg/kg for 4week
    - 30mg → 20mg → 10mg → 5mg
- **Rechallenge**
  - 2020/6/22 ~ 2021/4/6





CASE #3

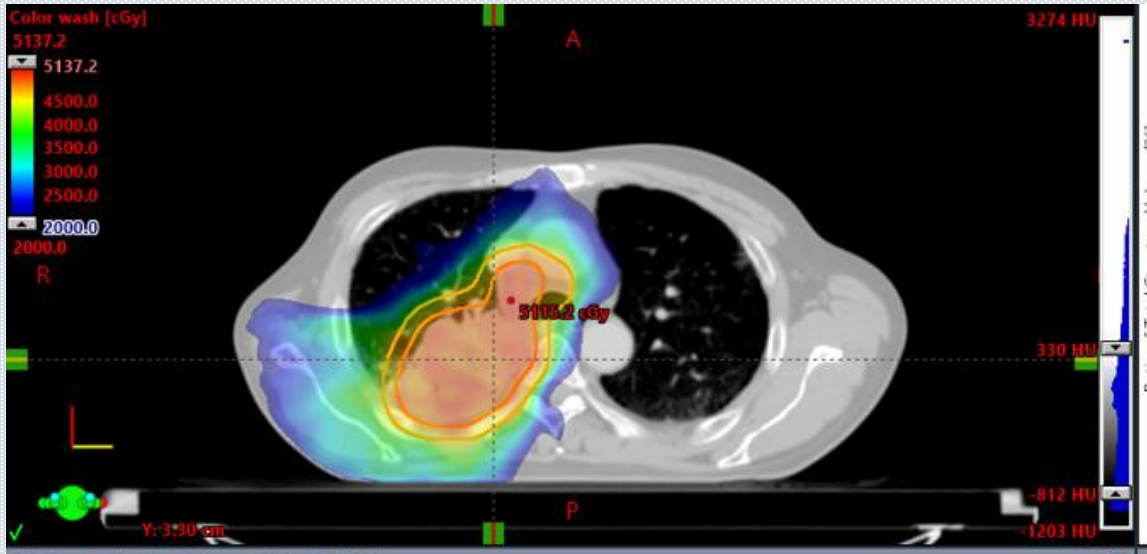


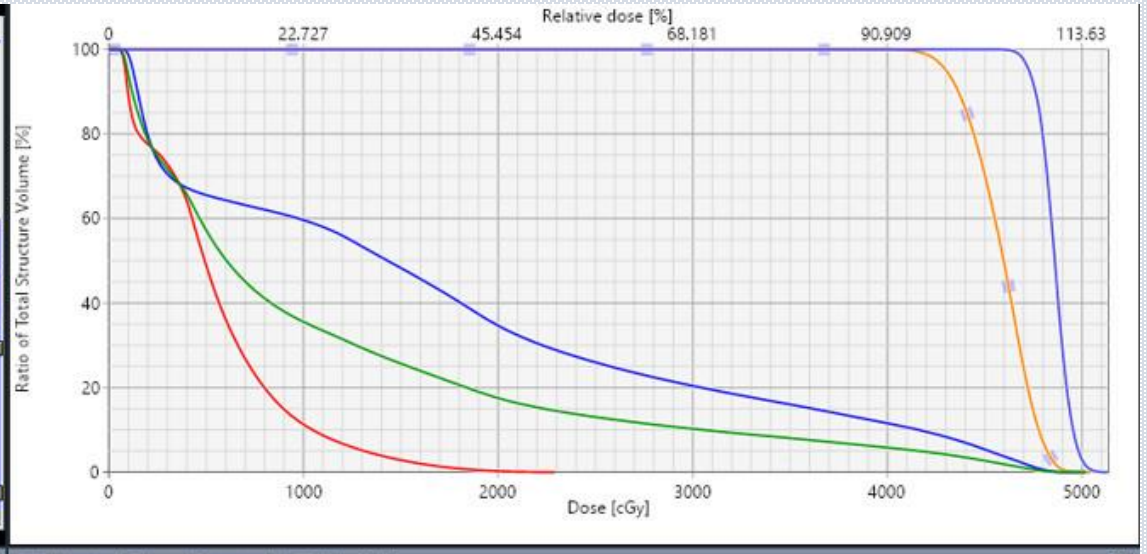
2020/05/23

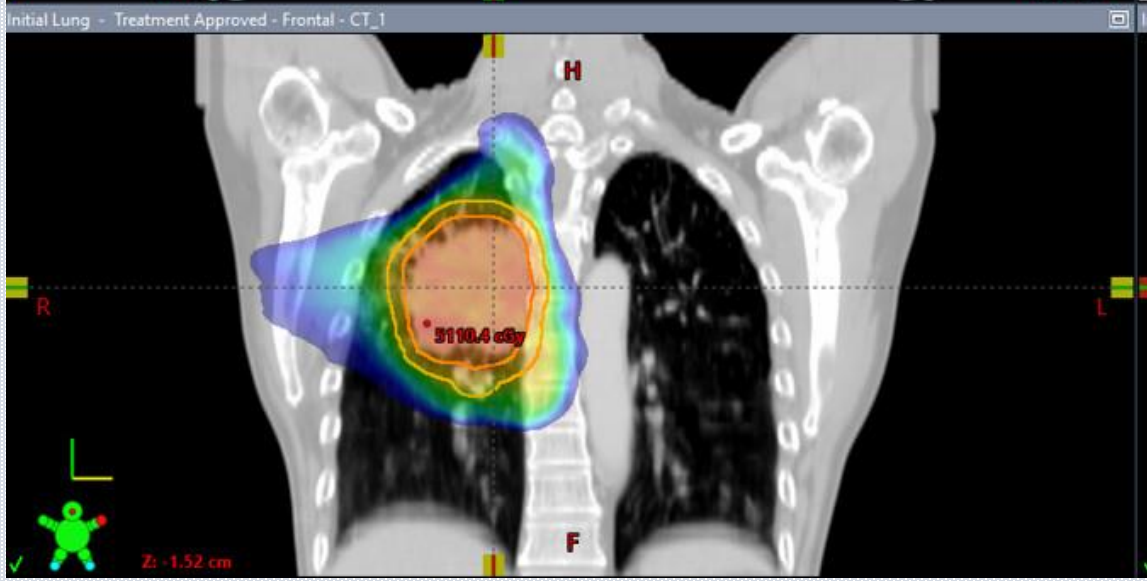
rechallge

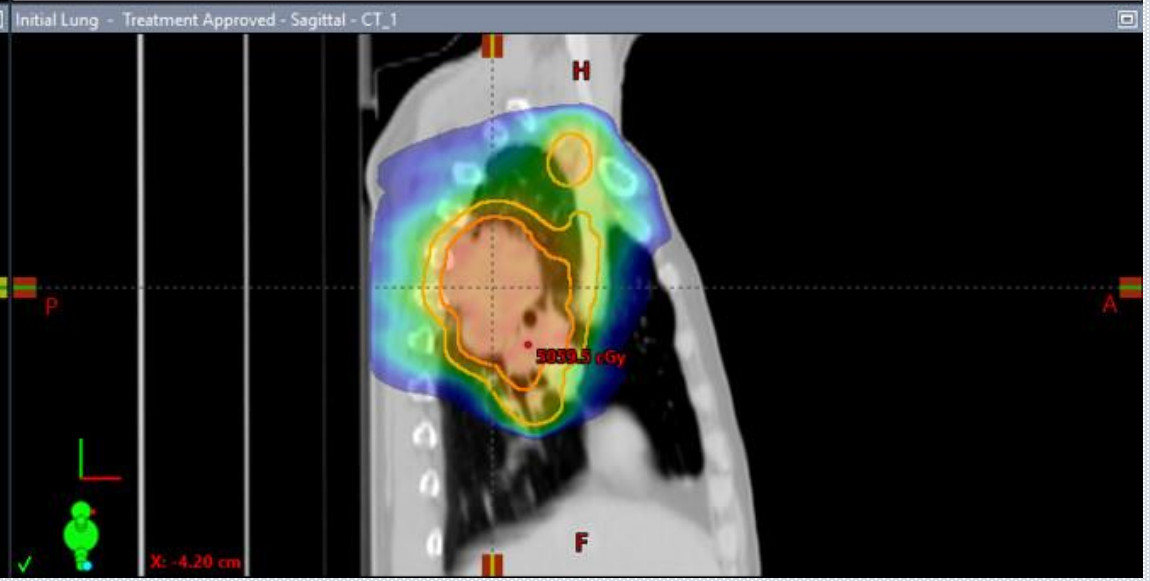
after durvalumab consolidation

CASE #3


Color wash [cGy]
5137.2
5137.2
4500.0
4000.0
3500.0
3000.0
2500.0
2000.0
2000.0
A
R
P
3274 HU
330 HU
-812 HU
-1203 HU
5118.2 cGy
Y: 3.30 cm

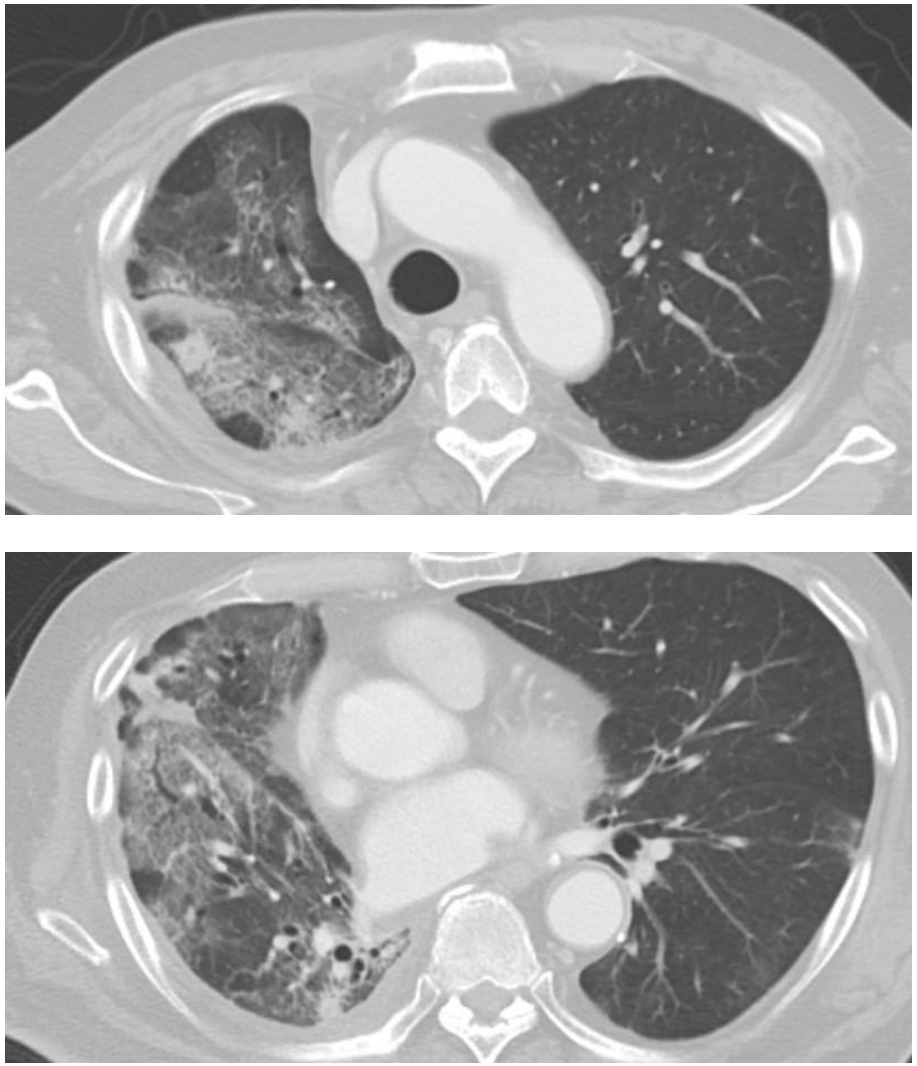

Relative dose [%]
0
22.727
45.454
68.181
90.909
113.63
100
80
60
40
20
0
Ratio of Total Structure Volume [%]
0
1000
2000
3000
4000
5000
Dose [cGy]


Initial Lung - Treatment Approved - Frontal - CT_1
H
R
L
F
5110.4 cGy
Z: -1.52 cm


Initial Lung - Treatment Approved - Sagittal - CT_1
H
P
A
F
5039.5 cGy
X: -4.20 cm

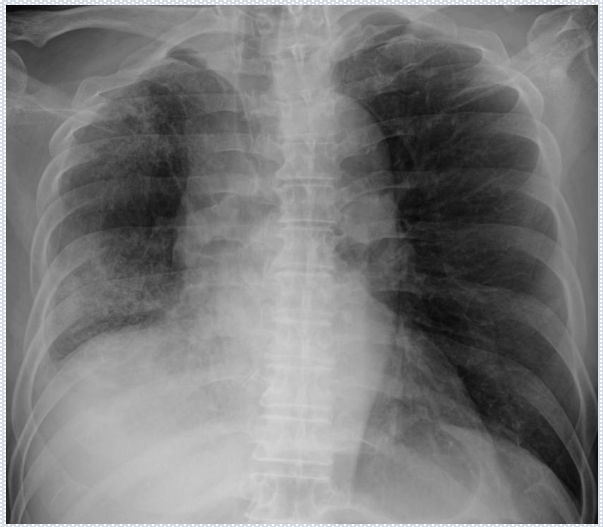
CASE #4

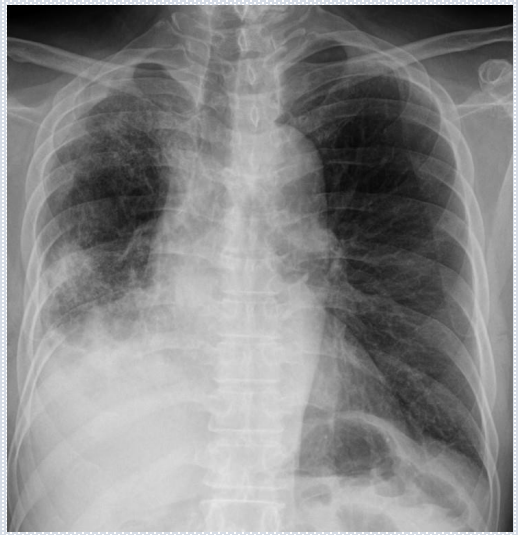
- **M/65, current smoker, 40PY**
- **NSCLC (adenocarcinoma), SP263 5%**
- **RUL lobectomy → 8th rib posterior arc recurrence**
- **Radiation (8th rib posterior arc)**
- **Pemetrexed, Cisplatin, Pembrolizumab**
  - JAN/2022: 4th cycle
- **COVID-19 infection: MAR/2022**
- **Pemetrexed, Pembrolizumab**
  - after additional 2 cycle
  - dyspnea
  - CT reading: Patch GGO and consolidation; R/O radiation pneumonitis

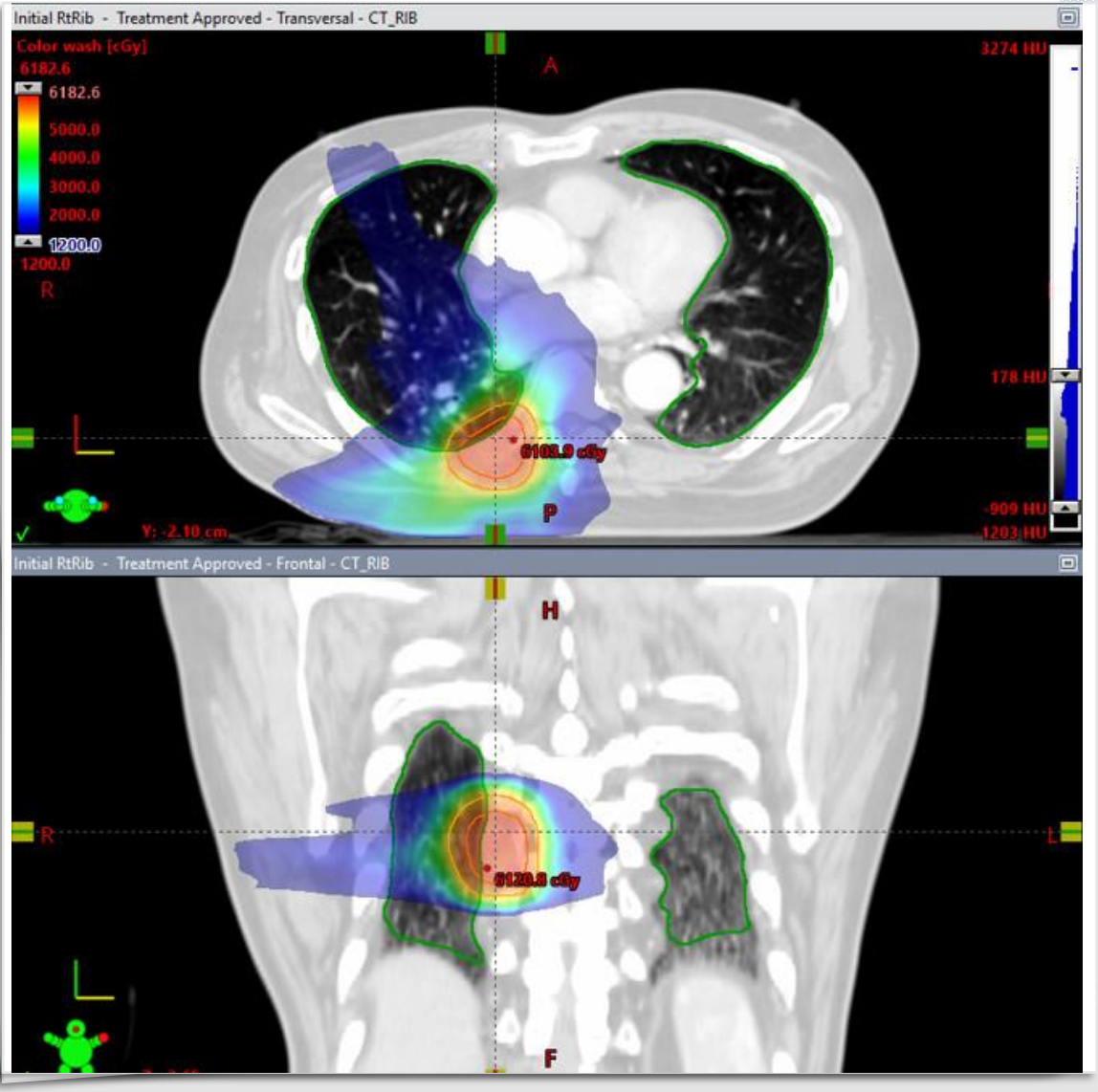


CASE #4

- **Pneumonitis**
  - radiation pneumonitis vs. IO related pneumonitis vs. post covid ILD vs. pneumonia
  - Hospitalization
  - Antibiotics
  - Oxygen therapy
  - BAL (X)
  - Methylprednisolone 1mg/kg

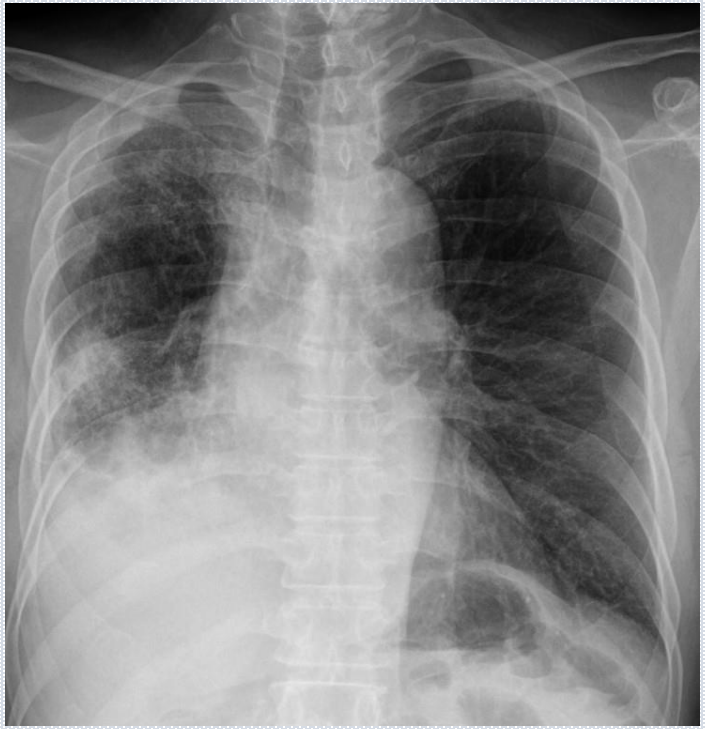




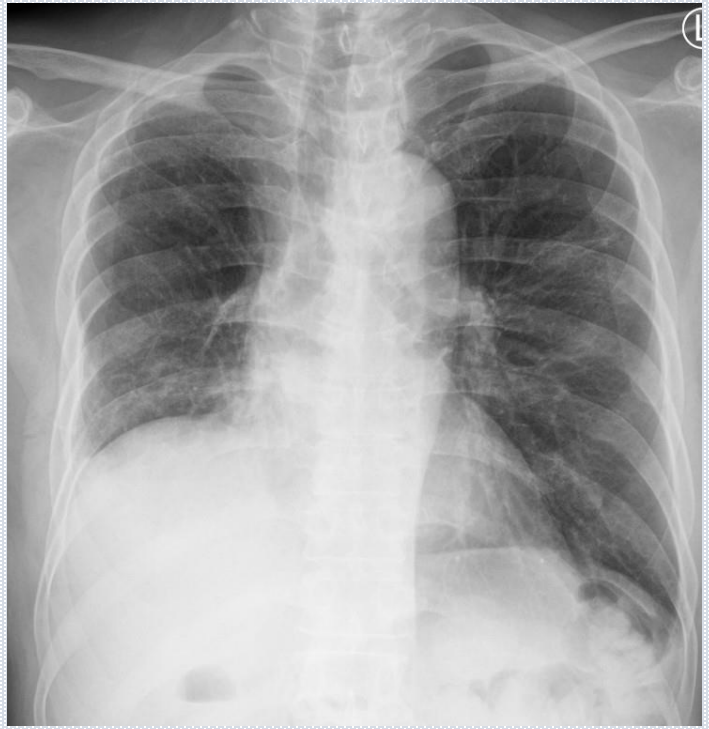


CASE #4

- sputum PCP PCR +



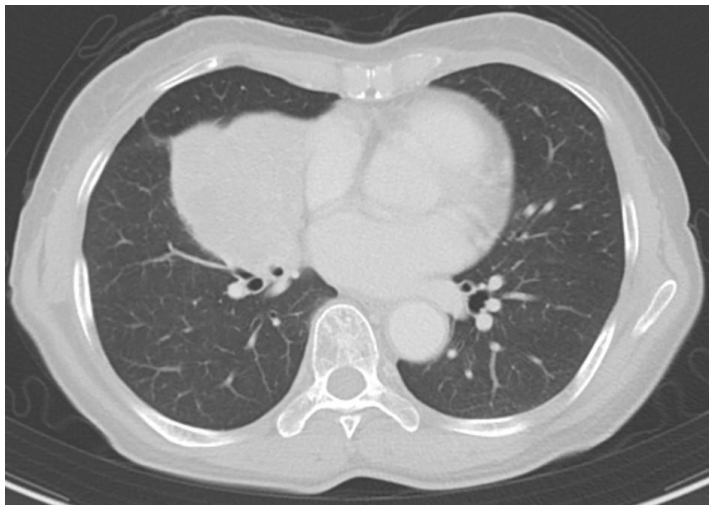
1 week

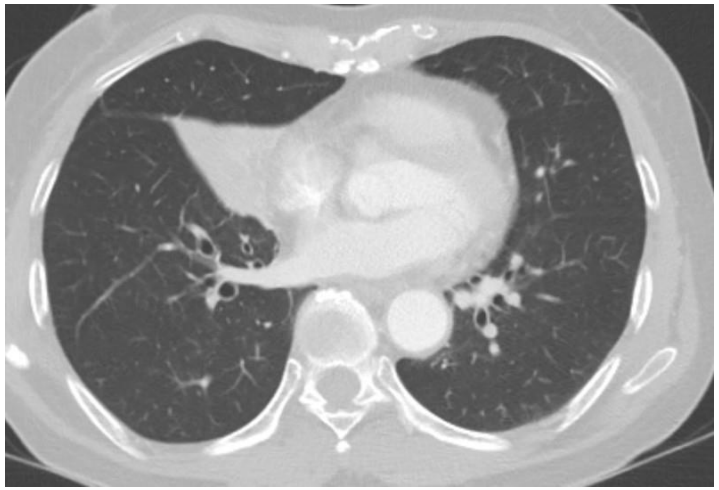


2 weeks

CASE #5

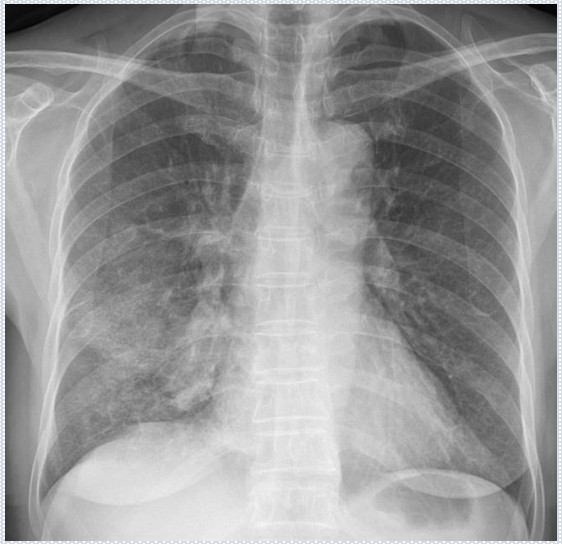
- **F/67, current smoker 25PY**
- **NSCLC (Sqcc, IIIB), SP 263 40%**
- **CCRT**
  - Paclitaxel, Carboplatin weekly 6th cycle
  - Radiation: 2022/4/21~6/3, 6600cGy
- **Durvalumab**
  - 2022/6/17~
  - after 2nd cycle: dyspnea

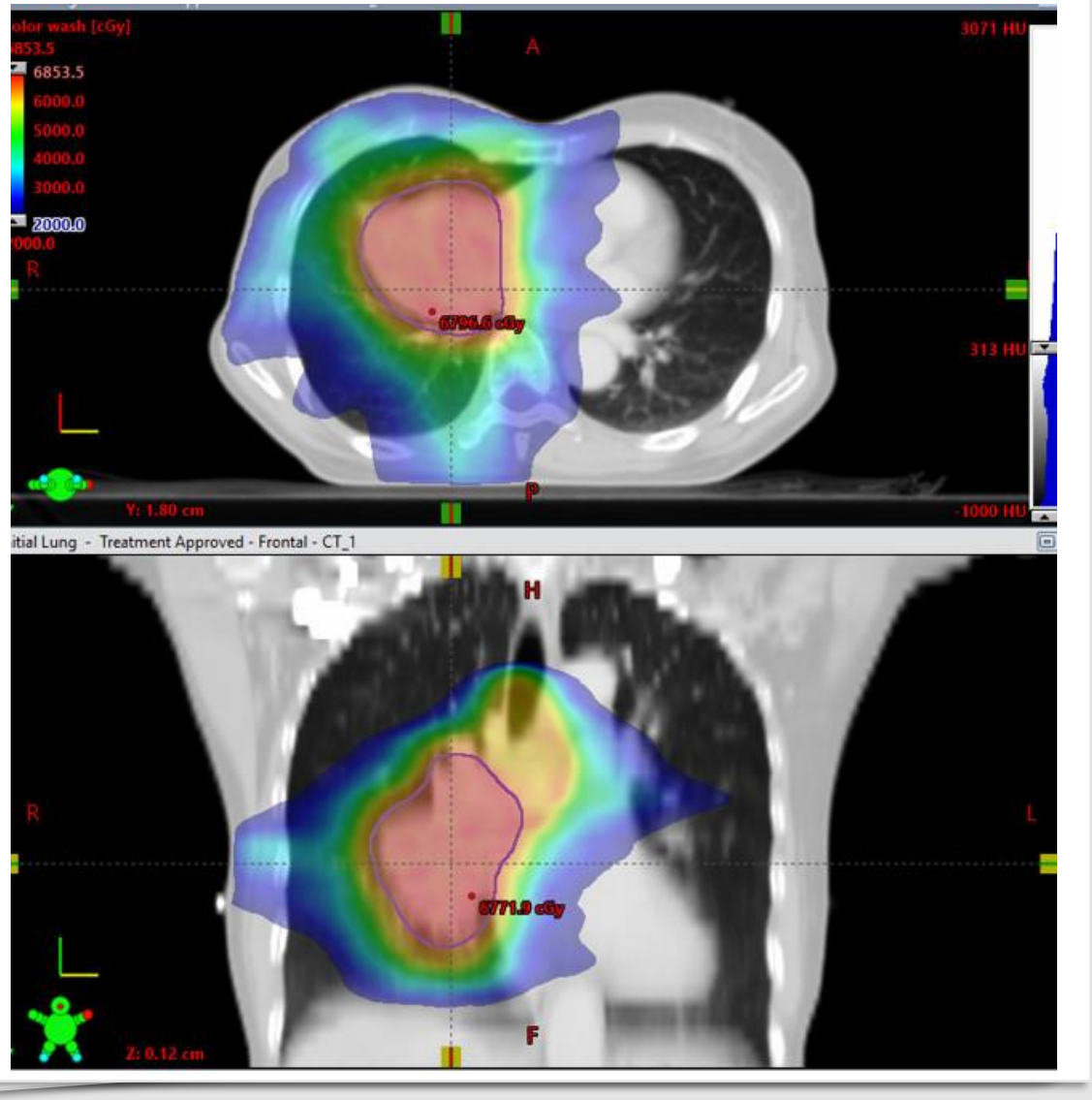




CASE #5

- Antibiotics
- BAL: WBC 650 (lymphocyte: 70%)
  - PCP PCR +
- Bactrim + methylprednisolone
- Rechallenge of durvalumab





Summary

- Organ-specific considerations following guidelines
- Discontinuation in case of irAE of cardiovascular and nervous system
- Possible continuation in case of irAE of endocrine system
- Important but difficult to differental diagnosis of radiation pneumonitis, ICI induced pneumonitis and pnumonia
- Radiation dose plots may be helpful
- Testing to idenfy bacteria (BAL) is still important

Thank you for your attention!