

Rare immune-related adverse events associated with immunotherapy in lung cancer

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Enhancement of Antitumor Immunity by CTLA-4 Blockade

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One reason for the poor immunogenicity of many tumors may be that they cannot provide signals for CD28-mediated costimulation necessary to fully activate T cells. It has recently become apparent that CTLA-4, a second counterreceptor for the B7 family of costimulatory molecules, is a negative regulator of T cell activation. Here, in vivo administration of antibodies to CTLA-4 resulted in the rejection of tumors, including preestablished tumors. Furthermore, this rejection resulted in immunity to a secondary exposure to tumor cells. These results suggest that blockade of the inhibitory effects of CTLA-4 can allow for, and potentiate, effective immune responses against tumor cells.

Science. 1996 Mar 22;271(5256):1734-6.

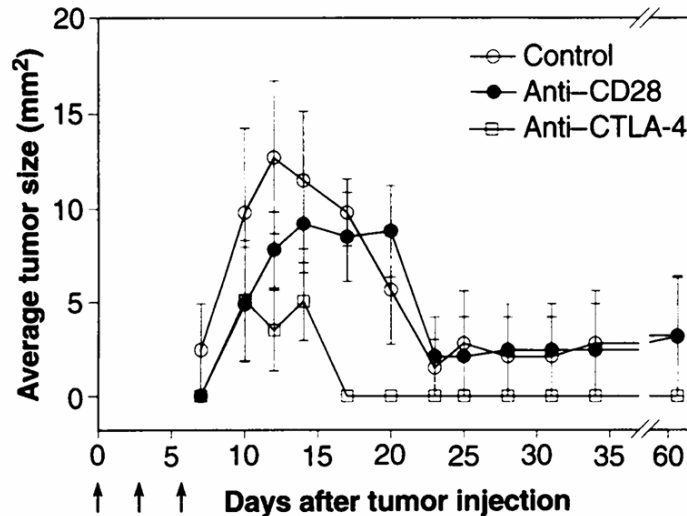


Fig. 1. Treatment with anti-CTLA-4 accelerates rejection of a B7-1-positive colon carcinoma (23). A volume of 100 μ l of cell suspension (4×10^6 cells) was injected subcutaneously into the left flanks of groups of five female BALB/c mice. Two of the groups received three intraperitoneal injections of either anti-CTLA-4 or anti-CD28 (18). Injections of 100, 50, and 50 μ g of antibody were given on days 0, 3, and 6, respectively, as indicated by the arrows. Control animals received no injections. Data points represent the average of the products of bisecting tumor diameters. Error bars represent standard error of the mean.

Signaling pathway of T-cell activation and CTLA-4 surface expression

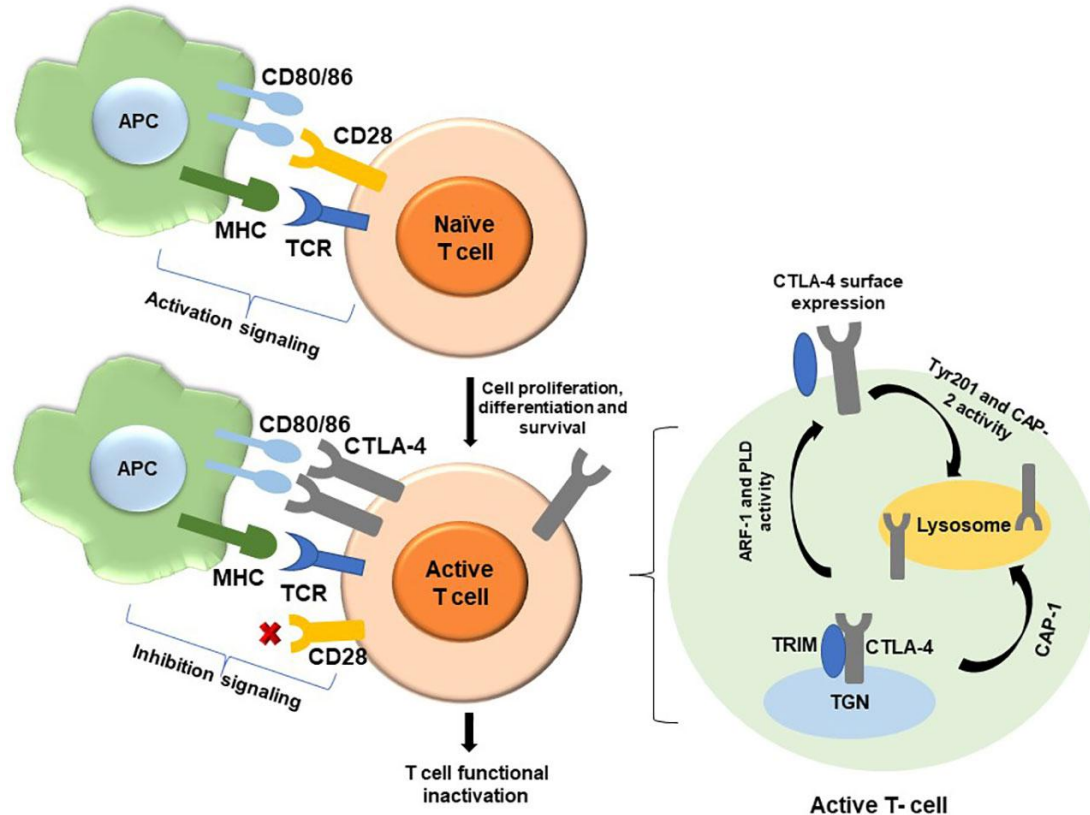
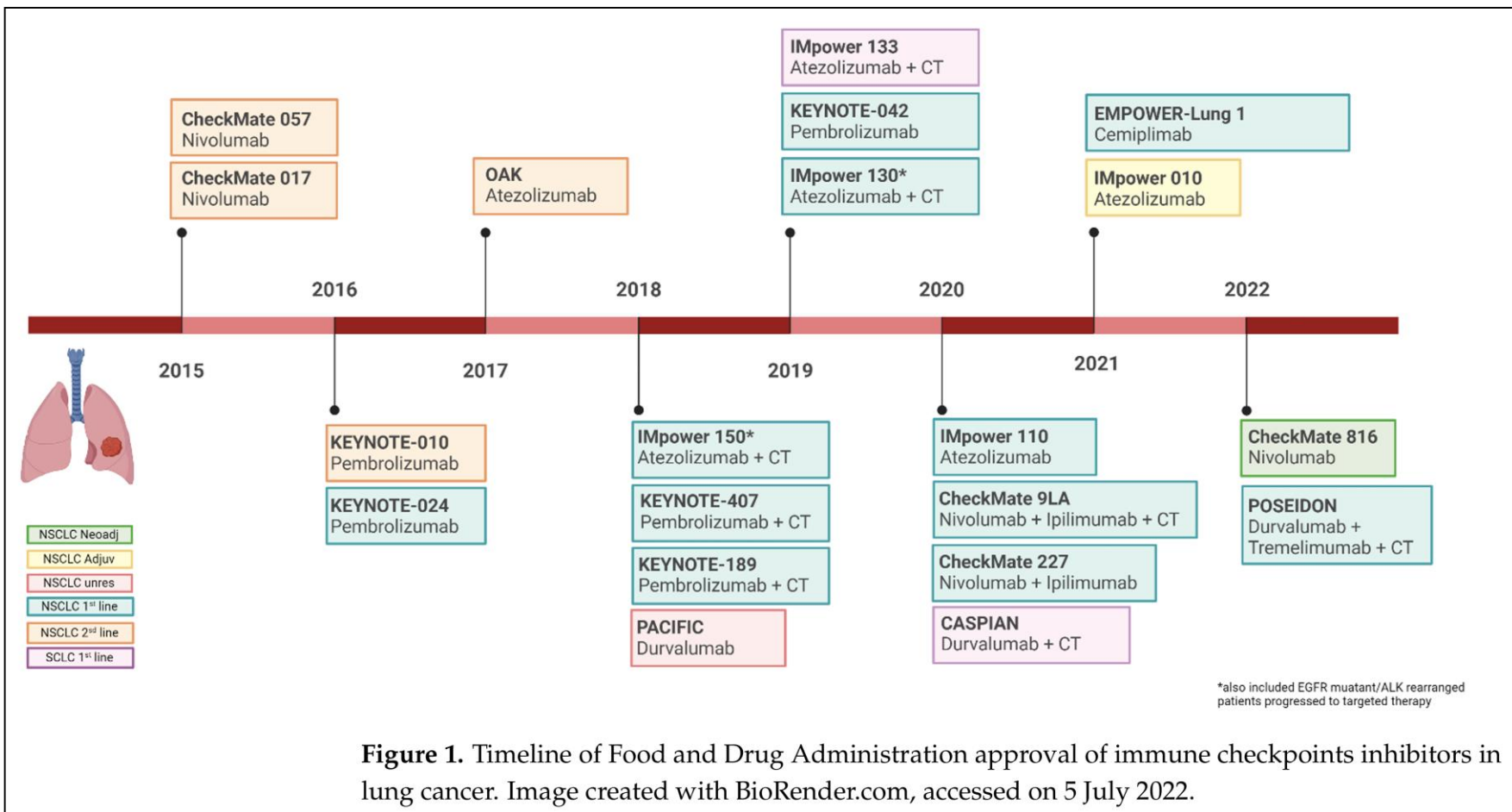


Table 1. FDA-approved immune checkpoint inhibitors with approved indications (as of February 2023).

Drug	Target	Approval	Indications
Ipilimumab (Yervoy®)	CTLA-4	2011	Melanoma, renal cell carcinoma, colorectal cancer, hepatocellular carcinoma, non-small cell lung cancer, malignant pleural mesothelioma, esophageal cancer
Nivolumab (Opdivo®)	PD-1	2014	Melanoma, non-small cell lung cancer, malignant pleural mesothelioma, renal cell carcinoma, classical Hodgkin lymphoma, squamous cell carcinoma of the head and neck, urothelial carcinoma, colorectal cancer, hepatocellular carcinoma, esophageal cancer, gastric cancer, gastroesophageal junction cancer, esophageal adenocarcinoma
Pembrolizumab (Keytruda®)	PD-1	2014	Melanoma, non-small cell lung cancer, head and neck squamous cell carcinoma, classical Hodgkin lymphoma, primary mediastinal large B-cell lymphoma, urothelial carcinoma, non-muscle invasive bladder cancer, colorectal cancer, gastric cancer, esophageal cancer, cervical cancer, hepatocellular carcinoma, Merkel cell carcinoma, renal cell carcinoma, endometrial carcinoma, cutaneous squamous cell carcinoma, triple-negative breast cancer
Atezolizumab (Tecentriq®)	PD-L1	2016	Non-small cell lung cancer, small cell lung cancer, hepatocellular carcinoma, melanoma, alveolar soft part sarcoma
Durvalumab (Imfinzi®)	PD-L1	2017	Non-small cell lung cancer, small cell lung cancer, biliary tract cancer, hepatocellular carcinoma
Avelumab (Bavencio®)	PD-L1	2017	Merkel cell carcinoma, urothelial carcinoma, renal cell carcinoma
Cemiplimab (Libtayo®)	PD-1	2019	Cutaneous squamous cell carcinoma, basal cell carcinoma, non-small cell lung cancer
Dostarlimab (Jemperli®)	PD-1	2021	Endometrial cancer
Relatlimab (Opdualag® , combination with Nivolumab)	LAG-3	2022	Melanoma

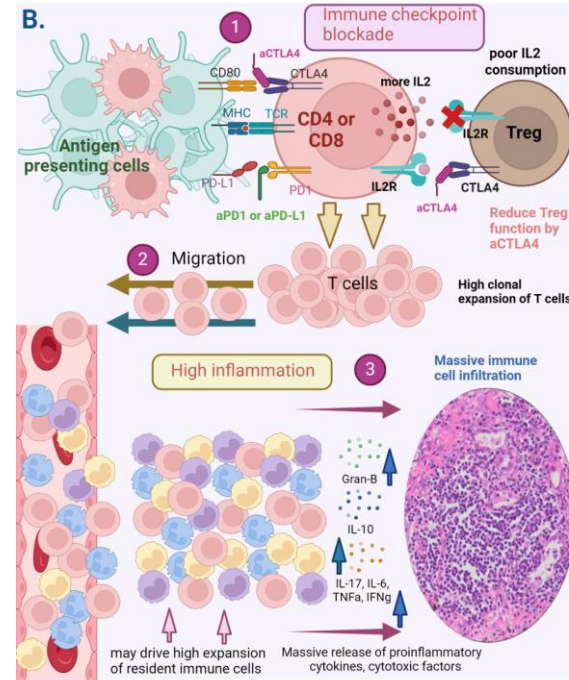
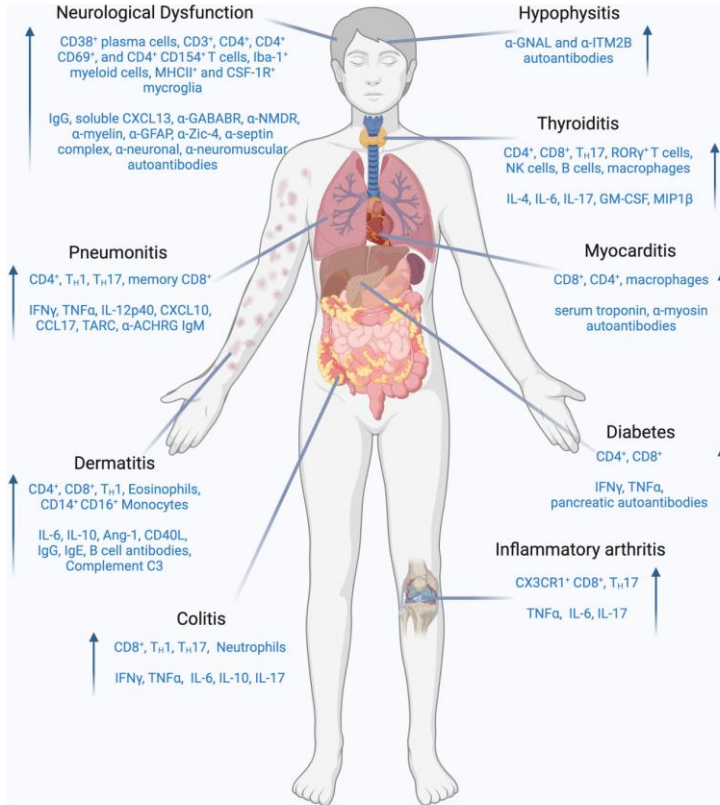


Immune-Related Adverse Events (irAEs)

- Side effects caused by the overactivation of the immune system due to immune checkpoint inhibitors (ICIs) or other immunotherapies.
- These events occur when the immune system mistakenly attacks normal tissues and organs, leading to autoimmune-like reactions.

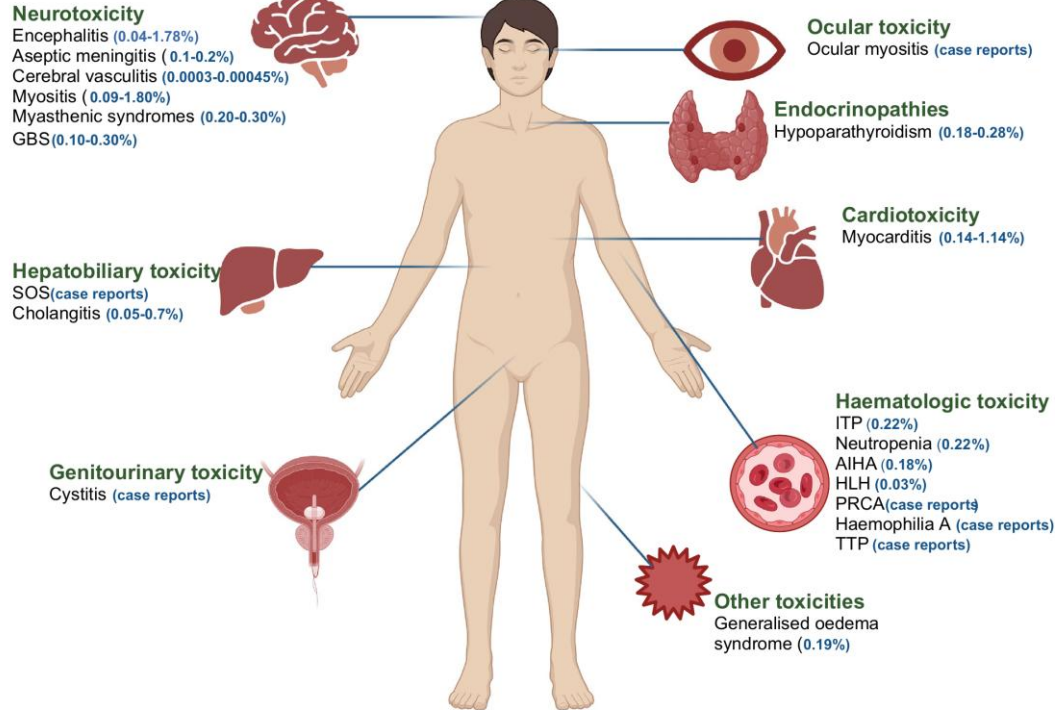
구분	일반적인 부작용(AEs)	면역 관련 부작용(irAEs)
발생 원인	약물 자체의 독성 (예: 세포독성 항암제)	면역체계의 과활성화 (자가면역 반응)
주요 증상	오심, 구토, 혈액 독성(골수 억제), 간독성 등	피부염, 장염, 간염, 내분비 질환(갑상선염, 당뇨병 등), 폐렴 등
발생 시점	약물 투여 직후 또는 일정 기간 후	투여 후 수주~수개월 이후에도 발생 가능
치료 방법	용량 조절, 약물 중단 등	스테로이드 및 면역억제제 사용이 필요할 수 있음

Cellular and molecular players involved in ICI-induced irAEs



Immune check point blockade(ICB) may break the peripheral tolerance.

Rare immune-related adverse events (irAEs)



KEYNOTE-024 Study Design(NCT02142738)

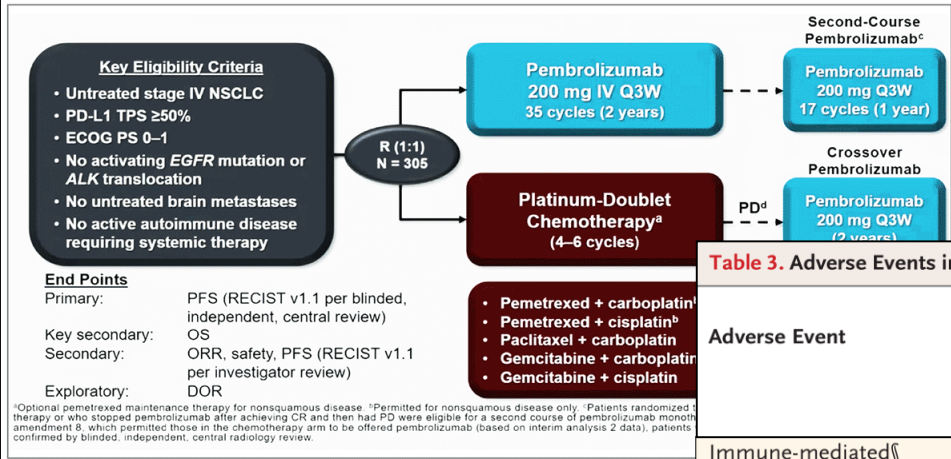
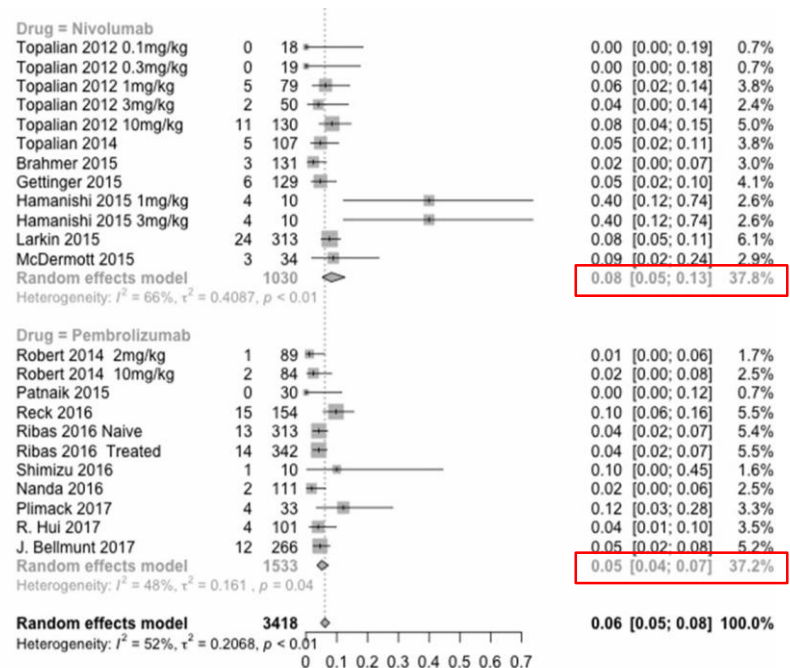
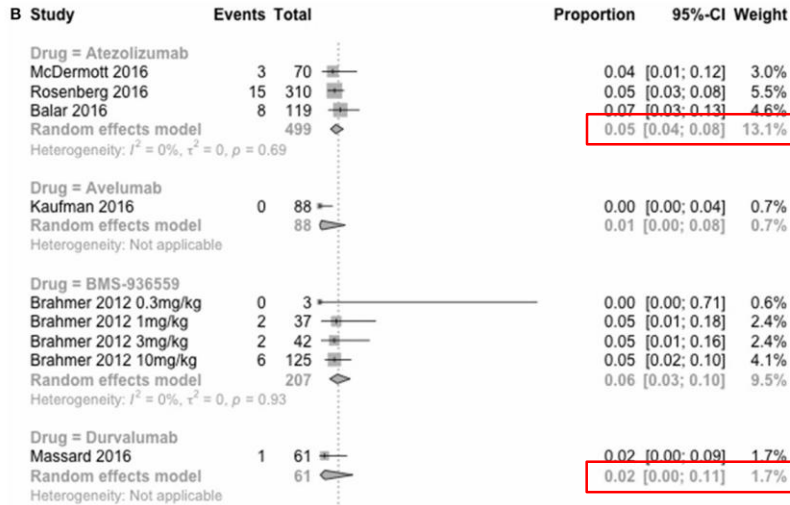


Table 3. Adverse Events in the As-Treated Population.*

Adverse Event	Pembrolizumab Group (N=154)		Chemotherapy Group (N=150)	
	Any Grade	Grade 3, 4, or 5	Any Grade	Grade 3, 4, or 5
	<i>number of patients (percent)</i>			
Immune-mediated [§]				
Any	45 (29.2)	15 (9.7)	7 (4.7)	1 (0.7)
Hypothyroidism	14 (9.1)	0	2 (1.3)	0
Hyperthyroidism	12 (7.8)	0	2 (1.3)	0
Pneumonitis	9 (5.8)	4 (2.6)	1 (0.7)	1 (0.7)
Infusion reaction	7 (4.5)	0	2 (1.3)	0
Severe skin reaction	6 (3.9)	6 (3.9)	0	0
Thyroiditis	4 (2.6)	0	0	0
Colitis	3 (1.9)	2 (1.3)	0	0
Myositis	3 (1.9)	0	0	0
Hypophysitis	1 (0.6)	1 (0.6)	0	0
Nephritis	1 (0.6)	1 (0.6)	0	0
Pancreatitis	1 (0.6)	1 (0.6)	0	0
Type 1 diabetes mellitus	1 (0.6)	1 (0.6)	0	0

*Optional pemetrexed maintenance therapy for nonsquamous disease. ^aPermitted for nonsquamous disease only. ^bPatients randomized to therapy or who stopped pembrolizumab after achieving CR and then had PD were eligible for a second course of pembrolizumab monotherapy amendment 8, which permitted those in the chemotherapy arm to be offered pembrolizumab (based on interim analysis 2 data), patients confirmed by blinded, independent, central radiology review.

Incidence of immune-related adverse events – Severe grade



PD-1/PD-L1 Immune Checkpoint Inhibitor Adverse Events

- Analysis of the FDA Adverse Events Database

Adverse Event	Pembrolizumab		Nivolumab		Cemiplimab		Dostarlimab		Toripalimab		Tislelizumab	
	Events	ROR	Events	ROR	Events	ROR	Events	ROR	Events	ROR	Events	ROR
Diarrhoea	1726	1.961	1867	1.832	16	0.767	10	1.841	6	3.646	9	1.776
Fatigue	1596	1.430	1351	1.035	36	1.403	11	1.613	9	4.554	-	-
Pyrexia	1284	2.822	1539	2.937	26	2.466	5	1.756	6	7.126	4	1.504
Thrombocytopenia	1172	3.898	452	2.572	-	-	13	7.080	-	-	15	8.838
Hypertension	1114	3.750	-	-	-	-	-	-	-	-	4	2.348
Rash	1100	1.784	1313	1.848	36	2.574	4	1.041	3	2.532	11	4.564
Decreased Appetite	1024	3.417	1048	3.018	15	2.142	-	-	7	12.901	7	4.081
Nausea	1023	0.850	989	0.708	20	0.721	6	0.811	5	2.240	-	-
Hypothyroidism	977	25.930	919	20.911	10	10.615	-	-	6	81.360	12	53.695
Interstitial Lung Disease	872	14.053	877	12.200	14	9.401	-	-	-	-	-	-
Asthenia	755	1.438	644	1.055	21	1.749	-	-	6	6.298	5	1.670
Malaise	753	1.078	740	0.914	11	0.681	-	-	-	-	-	-
Neutropenia	700	3.619	-	-	-	-	4	3.338	5	13.954	27	23.585
Renal Dysfunction	663	5.262	-	-	11	3.737	-	-	-	-	5	33.065
Anaemia	659	2.606	563	1.916	-	-	5	3.220	4	8.442	11	7.860
Acute Kidney Injury	657	2.94	625	2.413	10	1.927	-	-	-	-	-	-
Pneumonitis	655	20.024	897	24.363	19	24.113	7	33.482	3	45.859	-	-
Dyspnoea	651	0.794	811	0.858	20	1.071	8	1.621	3	1.935	-	-
Colitis	650	14.416	1541	29.467	10	9.242	-	-	-	-	-	-
Pneumonia	643	1.517	834	1.710	32	3.358	5	1.929	-	-	4	1.652
Vomiting	601	0.87	616	0.77	13	0.819	6	1.431	4	3.111	-	-
Arthralgia	562	0.984	563	0.852	13	0.992	3	0.854	-	-	-	-
Weight Decreased	489	1.267	641	1.443	-	-	4	1.695	-	-	-	-
Hepatic Dysfunction	483	9.536	1406	10.559	21	6.895	-	-	8	27.732	-	-
Peripheral Neuropathy	467	3.569	-	-	-	-	-	-	-	-	-	-
Pruritus	-	-	650	1.157	20	1.805	-	-	5	5.606	-	-
Adrenal Insufficiency	-	-	644	45.012	-	-	-	-	-	-	-	-
Myocarditis	-	-	460	29.085	17	49.943	4	43.709	4	143.905	-	-
Headache	-	-	425	0.377	13	0.584	-	-	-	-	-	-
Sepsis	-	-	-	-	15	4.358	-	-	-	-	-	-
Hemorrhage	-	-	-	-	11	2.795	-	-	-	-	-	-
Stroke	-	-	-	-	10	1.364	-	-	-	-	-	-

Adverse Event	Atezolizumab		Avelumab		Durvalumab	
	Events	ROR	Events	ROR	Events	ROR
Pyrexia	630	3.475	47	2.422	136	2.500
Diarrhoea	530	1.481	72	1.932	76	0.704
Fatigue	461	1.016	62	1.31	72	0.528
Anaemia	455	4.549	-	-	65	2.153
Interstitial Lung Disease	433	17.187	43	15.905	151	20.135
Hypothyroidism	367	23.193	51	30.184	68	14.087
Nausea	352	0.727	49	0.969	48	0.331
Pneumonia	343	2.031	24	1.337	86	1.714
Rash	339	1.359	41	1.566	74	0.997
Neutropenia	939	7.213	-	-	339	5.916
Decreased appetite	329	2.709	28	2.175	51	1.402
Dyspnoea	310	0.948	30	0.869	117	1.217
Thrombocytopenia	516	4.269	26	4.052	113	3.972
Pneumonitis	294	21.799	22	15.05	215	55.300
Hypertension	293	2.418	47	3.719	-	-
Asthenia	263	1.245	24	1.076	43	0.682
Hepatic Dysfunction	255	12.471	48	12.128	56	9.120
Proteinuria	241	23.134	-	-	-	-
Ascites	240	15.186	-	-	-	-
Vomiting	238	0.859	30	1.032	-	-
Adrenal insufficiency	231	42.411	35	58.993	-	-
Acute kidney injury	224	2.484	29	3.061	-	-
Colitis	220	11.824	38	19.384	72	12.996
Sepsis	200	3.321	-	-	61	3.420
Constipation	195	1.687	-	-	-	-
Chills	-	-	35	5.151	-	-
Malaise	-	-	35	1.19	-	-
Peripheral Neuropathy	-	-	35	6.359	-	-
Myocarditis	-	-	27	43.085	58	33.018
Pruritus	-	-	25	1.217	-	-
Renal Dysfunction	-	-	24	4.446	-	-

Contents

- Rare immune-related adverse events Cases
- Biomarkers for irAE prediction
- Impact of irAE on clinical outcomes in lung cancer
- Management of immune-related adverse events
- Effect of steroids on the clinical outcome of lung cancer
- Re-challenge of IO, after irAE

RARE IMMUNE-RELATED ADVERSE EVENTS – CASE (1)

I: 474.0
Im: 127

DFOV 50.0 cm

5.99

0.00

50 % PET

3.3/

3.3mm /3.3sp

m=0.00 M=5.99 g/ml

P 250

I: 411.9
Im: 108

DFOV 50.0 cm

5.99

0.00

50 % PET

3.3/

3.3mm /3.3sp

m=0.00 M=5.99 g/ml

P 250

I: 382.5
Im: 99

DFOV 50.0 cm

5.99

0.00

50 % PET

3.3/

3.3mm /3.3sp

m=0.00 M=5.99 g/ml

P 250

I: 349.8
Im: 89

DFOV 50.0 cm

5.99

0.00

50 % PET

3.3/

3.3mm /3.3sp

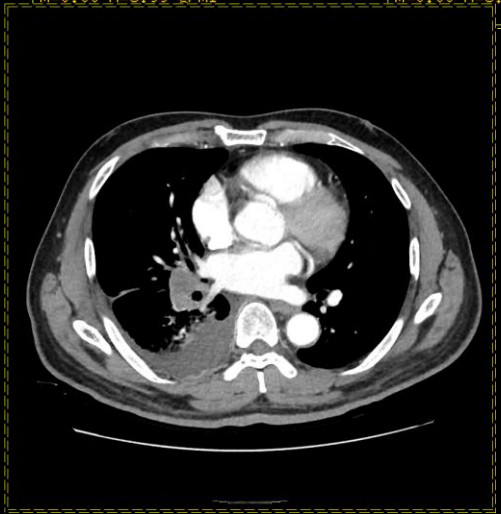
m=0.00 M=5.99 g/ml

P 250

Ex: Jun 02 2021

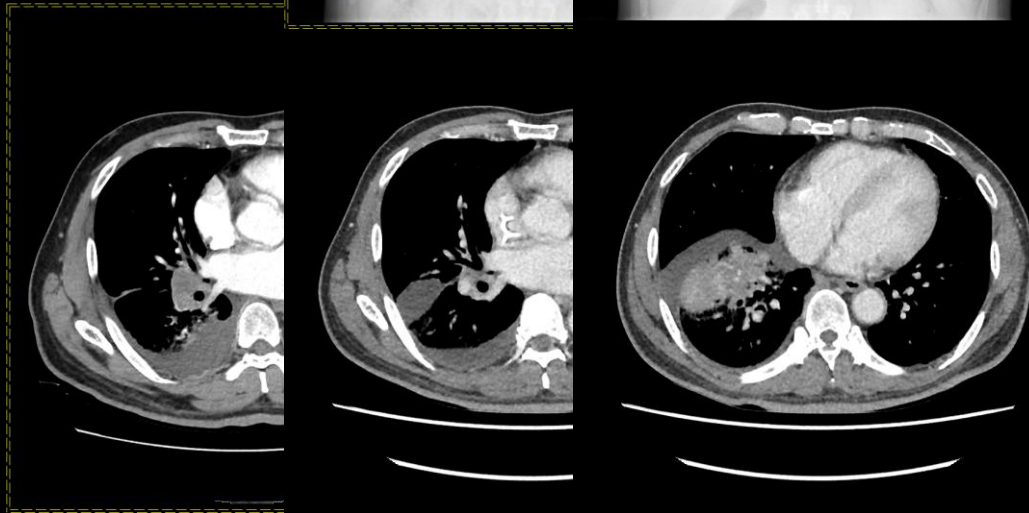
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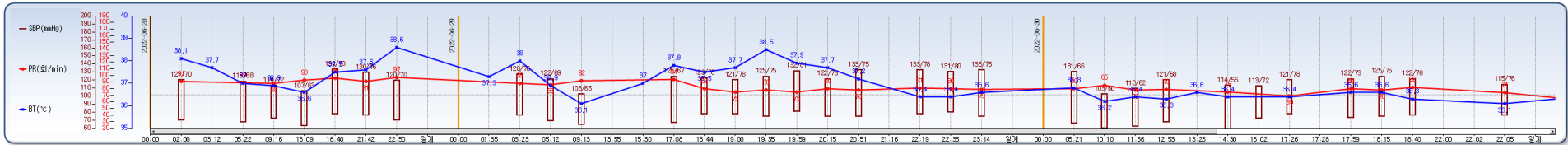
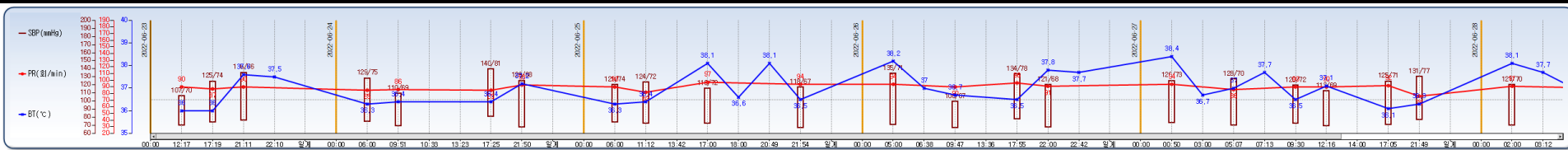
SCLC-ES. mets/Rt pleura, ant. diaphragmatic area LN, Liver, Lt adrenal gland
1L Palliative atezolizumab, etoposide, and carboplatin #1(2021.6.18)~



M/52

SCLC-ES. mets/Rt pleura, ant. diaphragmatic area LN, Liver, Lt adrenal gland
1L Palliative atezolizumab, etoposide, and carboplatin #1(2021.6.18)~ (2022.6)

Shortness of breath for 2 weeks



Sample Name	Whole Blood	Whole Blood	Whole Blood
Dr. Comment(의사)			CT 시행일에 검사
Remark(검사실)	+ Clot 확인 후 재검	+ Clot 확인 후 재검	+ Clot 확인 후 재검
WBC: $\times 10^3 / \mu\text{L}$ [4.0 ~ 10.0]	2.97 ▼	4.52	4.28
RBC: $\times 10^6 / \mu\text{L}$ [4.2 ~ 6.30]	3.84 ▼	4.12 ▼	4.08 ▼
Hemoglobin:g/dl [13.0 ~ 17.0]	11.0 ▼	12.0 ▼	12.1 ▼
Hematocrit:% [39 ~ 52]	32	36	36
Platelet: $\times 10^3 / \mu\text{L}$ [130 ~ 400]	60 ▼	115	30
MCV:f [81 ~ 96]	84	87	89
MCH:pg [27 ~ 33]	29	29	30
MCHC:g/dl [32 ~ 36]	34	34	34
RDW:% [11.5 ~ 14.5]	12.4	12.2	12.0
PDW:f [9.8 ~ 18.1]	13.2	10.4	11.7
Seg. neutrophil:% [50.0 ~ 75.0]	44.9 ▼	45.2 ▼	37.4 ▼
Lymphocyte:% [20.0 ~ 44.0]	48.8 ▲	48.9 ▲	57.5 ▲
Monocyte:% [2.0 ~ 9.0]	5.7	5.3	4.2
Eosinophil:% [1.0 ~ 5.0]	0.3 ▼	0.2 ▼	0.2 ▼
Basophil:% [0.0 ~ 2.0]	0.3	0.4	0.7
Absolute neutrophil count: $\times 10^3 / \mu\text{L}$	1.33 ▼	2.04	1.60
ESR:mm/hr [0 ~ 9]	2	2	

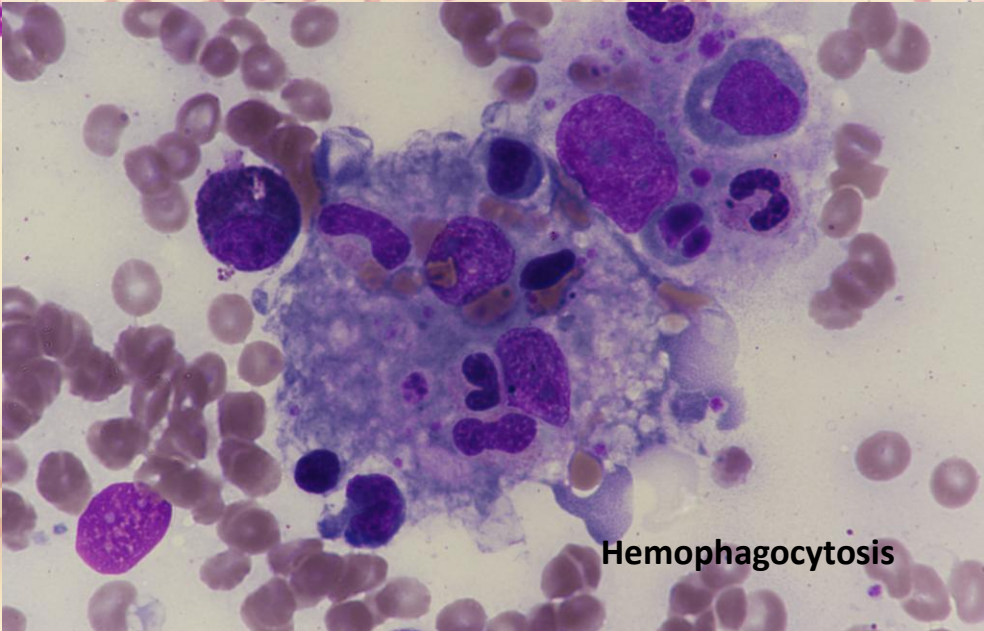
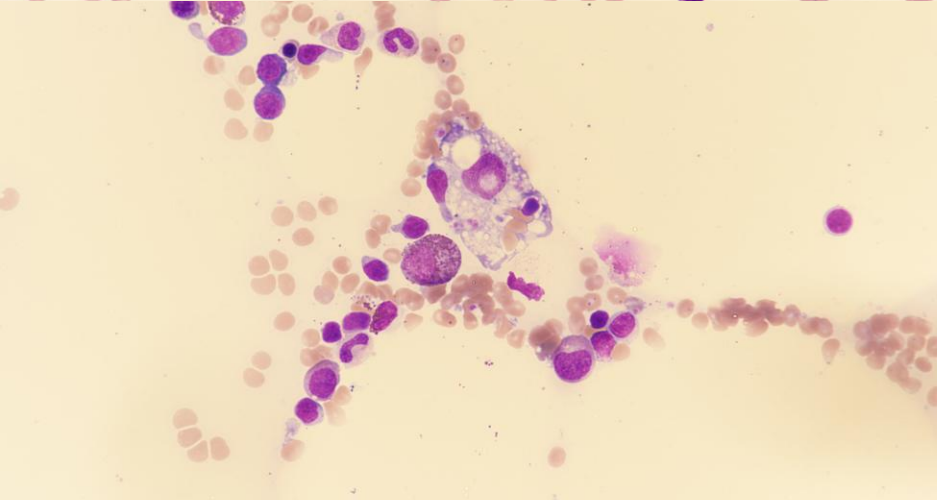
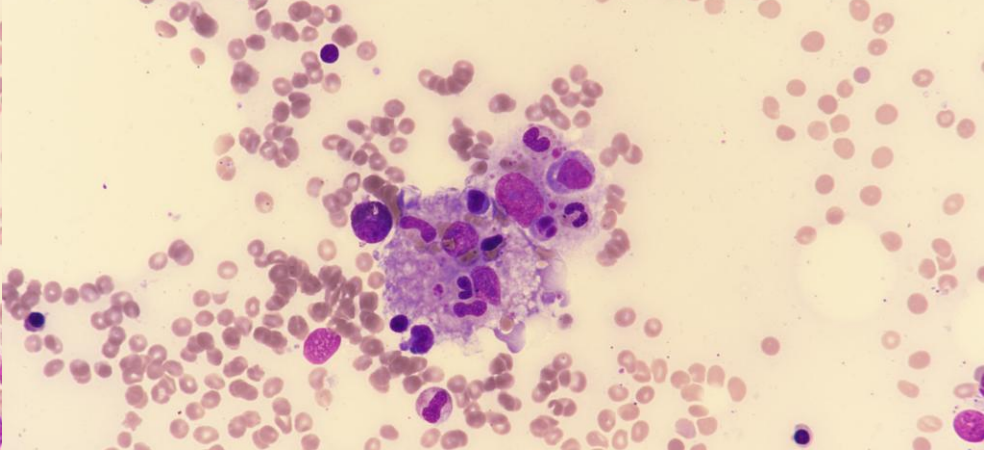
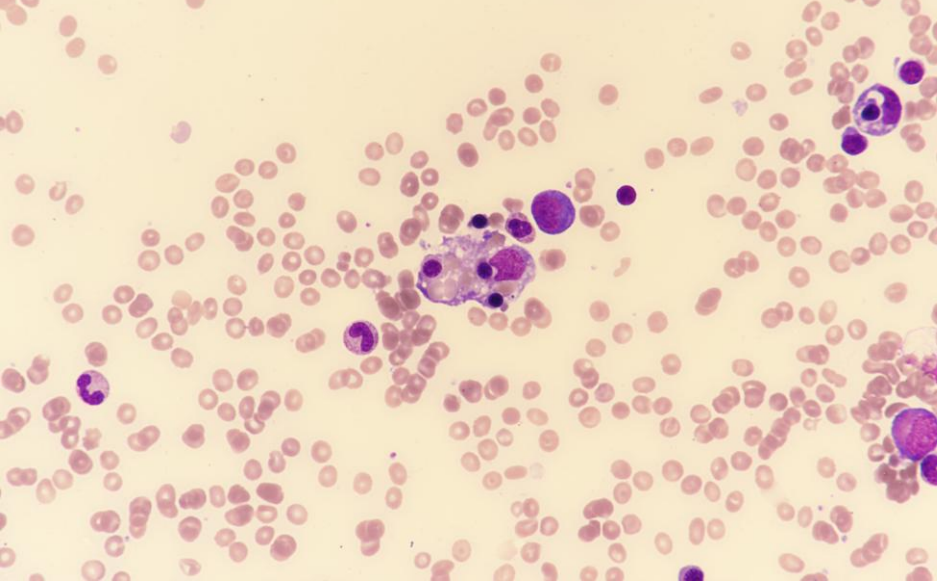
Ca(calcium):mg/dL [8.8 ~ 10.6]	8.2 ▼	8.2 ▼
P(IP):mg/dL [2.5 ~ 4.5]	2.0 ▼	2.9
Glucose:mg/dL [74 ~ 106]	207 ▲	130 ▲
BUN:mg/dL [8.0 ~ 20.0]	14.1	19.7
Uric acid:mg/dL [3.5 ~ 7.2]	2.0 ▼	4.0
Cholesterol:mg/dL [120 ~ 200]	97 ▼	113 ▼
Protein,total:g/dl [6.5 ~ 8.3]	5.2 ▼	5.8 ▼
Albumin:g/dl [3.5 ~ 5.2]	2.9 ▼	3.5
T.Bilirubin:mg/dL [0.3 ~ 1.20]	0.95	0.87
ALP:U/L [30 ~ 120]	196 ▲	109
AST(GOT):U/L [1 ~ 37]	297 ▲	162
ALT(GPT):U/L [0 ~ 41]	133 ▲	84
Creatinine:mg/dL [0.67 ~ 1.17]	1.19 ▲	0.99
GGT(γ-GT):U/L [9 ~ 64]	150 ▲	65
CK:U/L [0 ~ 171]		
LDH:U/L [140 ~ 271]	2,437 ▲	1,501 ▲
Na:mmol/L [136.0 ~ 146.0]	136.8	141.9
K:mmol/L [3.5 ~ 5.1]	3.5	3.8
Cl:mmol/L [101.0 ~ 109.0]	109.6 ▲	112.3 ▲
CO2:mmol/L [21 ~ 31]		
TG-Triglyceride:mg/dL [0 ~ 150]		
HDL-cholesterol:mg/dL [40 ~ 60]		
LDL-cholesterol:mg/dL [0 ~ 130]		
CRP 정량:mg/L [0.0 ~ 5.0]	60.6 ▲	18.4 ▲
Mg:mg/dL [1.8 ~ 2.6]	1.9	2.0
IgG:mg/dL [700.0 ~ 1600.0]		
IgA:mg/dL [70.0 ~ 400.0]		
IgM:mg/dL [40.0 ~ 230.0]		
eGFR (MDRD):mL/min/1.73m ²	>60(64)	>60(79)
eGFR (CKD-EPI):mL/min/1.73m ²	>60(70)	>60(87)

Sample Name	Whole Blood
Dr. Comment(의사)	
Remark(검사실)	
PROTROMBIN TIME(sec) [11.9 ~ 14.0]	16.2 ▲
PROTROMBIN TIME(%):X [86 ~ 127]	60
PROTROMBIN TIME(INR):INR [0.8 ~ 1.20]	1.40 ▲
Activated PTT(aPTT):sec [29.1 ~ 43.5]	52.0 ▲
Fibrinogen:mg/dL [200 ~ 450]	108 ▼
FDP:ug/mL [0.0 ~ 5.0]	> 120 ▲
D-dimer:ug/mL FEU [0.0 ~ 0.50]	> 20.00 ▲

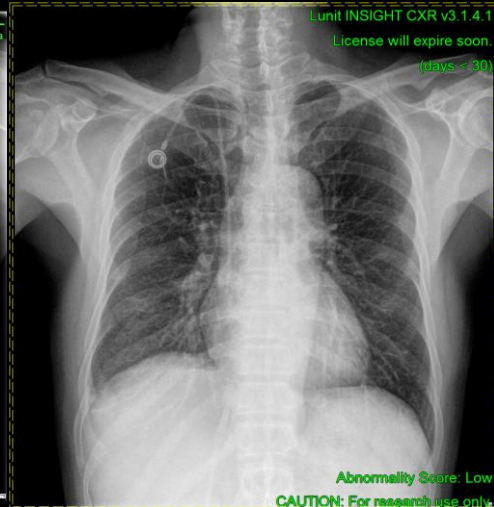
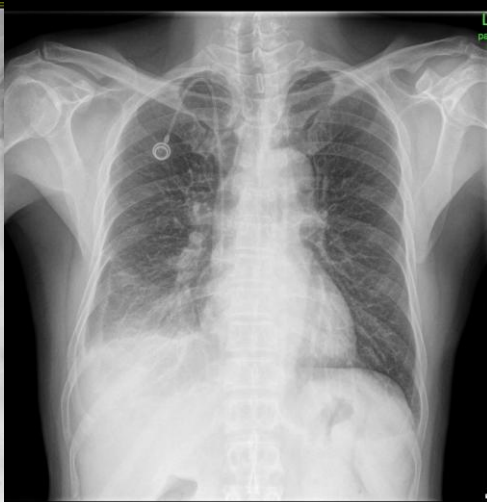
Ferritin 16,500ng/mL

Bronchial washing sample

- Pneumonia FilmArray(-)
- Gram stain(-)
- AFB stain/Culture(-/-)



Hemophagocytosis



M/52

SCLC-ES. mets/Rt pleura, ant. diaphragmatic area LN, Liver, Lt adrenal gland
1L Palliative atezolizumab, etoposide, and carboplatin #1(2021.6.18)~ (2022.6)

Shortness of breath for 2 weeks
→ Hemophagocytic lymphohistiocytosis(HLH)
– methyl-PD 1g for 5 days



NCCN Guidelines Version 1.2025 Management of Immune Checkpoint Inhibitor-Related Toxicities

HEMATOLOGIC ADVERSE EVENT(S)	ASSESSMENT	GRADING	MANAGEMENT
<p>HLH-like syndrome^{e,f,o} Differential/suspect in settings of pancytopenia • May overlap with hyperinflammatory syndromes such as cytokine release syndrome (CRS)^p</p>	<p>• See Assessment on ICI_HEM-1 • Additional laboratory tests: ferritin, fibrinogen, soluble IL-2 receptor (based on CD25), triglycerides • HScore^q • Evaluate for and rule out other non-ICI-related etiologies of HLH (eg, infection, lymphoma)</p>	<p>No agreed upon grading scale; individual abnormalities may be graded (anemia, thrombocytopenia, fever, liver enzymes)</p>	<ul style="list-style-type: none">• Hold immunotherapy^h• Inpatient care^r with hematology consult (due to high mortality rate if left untreated)<ul style="list-style-type: none">▶ Consider consult with expert in the management of HLH-like syndromes• Prednisone/IV methylprednisolone 0.5–1 mg/kg once daily^s (or dexamethasone at equivalent dose)^{s,t}• If no response to steroids after 5 days, consider adding tocilizumab,^{u,v} anakinra, ruxolitinib, cyclosporine, or emapalumab-lzsg

- Fever, organomegaly, pancytopenia
- Significantly elevated ferritin and low fibrinogen
- Hemophagocytosis - bone marrow aspiration

Diagnosis of HLH

Table 2. HLH-2004 diagnostic criteria

The diagnosis of HLH can be established if Criterion 1 or 2 is fulfilled.
1. A molecular diagnosis consistent with HLH
2. Diagnostic criteria for HLH fulfilled (5 of the 8 criteria below) Fever Splénomegaly Cytopenias (affecting ≥ 2 of 3 lineages in the peripheral blood) Hemoglobin < 90 g/L (hemoglobin < 100 g/L in infants < 4 wk) Platelets $< 100 \times 10^9/L$ Neutrophils $< 1.0 \times 10^9/L$ Hypertriglyceridemia and/or hypofibrinogenemia Fasting triglycerides ≥ 3.0 mmol/L (ie, ≥ 265 mg/dL) Fibrinogen ≤ 1.5 g/L Hemophagocytosis in bone marrow or spleen or lymph nodes. No evidence of malignancy. Low or no NK cell activity (according to local laboratory reference) Ferritin ≥ 500 $\mu\text{g/L}$ sCD25 (ie, soluble IL-2 receptor) ≥ 2400 U/mL

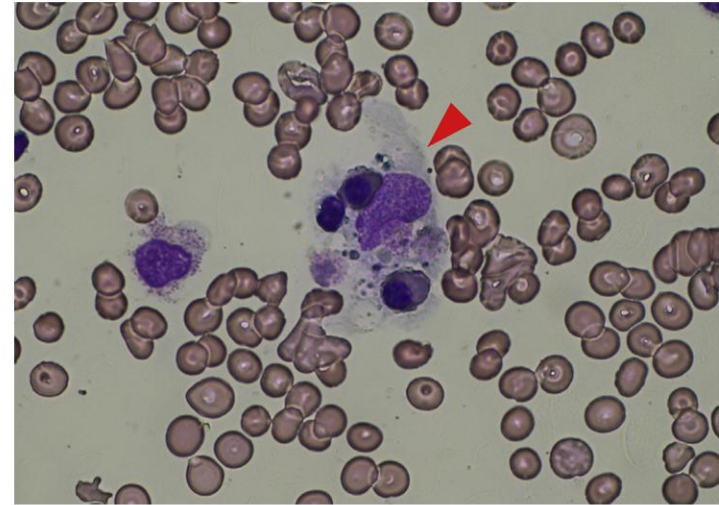


Figure 2. Bone marrow smear using May-Giemsa stain. A hemophagocytic macrophage is indicated by the arrowhead. Original magnification $\times 1000$.

Diagnosis of HLH

Table 4. The HScore

Parameter	No. of points (criteria for scoring)
Known underlying immunosuppression*	0 (no) or 18 (yes)
Temperature (°C)	0 (<38.4), 33 (38.4–39.4), or 49 (>39.4)
Organomegaly	0 (no), 23 (hepatomegaly or splenomegaly), or 38 (hepatomegaly and splenomegaly)
No. of cytopenias†	0 (1 lineage), 24 (2 lineages), or 34 (3 lineages)
Ferritin (ng/ml)	0 (<2,000), 35 (2,000–6,000), or 50 (>6,000)
Triglyceride (mmoles/liter)	0 (<1.5), 44 (1.5–4), or 64 (>4)
Fibrinogen (gm/liter)	0 (>2.5) or 30 (≤2.5)
Serum glutamic oxaloacetic transaminase (IU/liter)	0 (<30) or 19 (≥30)
Hemophagocytosis features on bone marrow aspirate	0 (no) or 35 (yes)

* Human immunodeficiency virus positive or receiving long-term immunosuppressive therapy (i.e., glucocorticoids, cyclosporine, azathioprine).

† Defined as a hemoglobin level of ≤9.2 gm/dl and/or a leukocyte count of ≤5,000/mm³ and/or a platelet count of ≤110,000/mm³.

Table 5. Probability of hemophagocytic syndrome according to the HScore*

HScore	Probability of hemophagocytic syndrome, %
90	<1
100	1
110	3
120	5
130	9
140	16
150	25
160	40
170	54
180	70
190	80
200	88
210	93
220	96
230	98
240	99
250	>99

* The best cutoff value for HScore was 169, corresponding to a sensitivity of 93%, a specificity of 86%, and accurate classification of 90% of the patients.

Immune checkpoint inhibitor-associated HLH

- Disorder involving inappropriate macrophage activation
 - T cell and macrophage hyper-activation, subsequent uncontrolled release of pro-inflammatory cytokines resulting in tissue injury and multi-organ dysfunction
- Rare and potentially fatal toxicity
- More commonly associated with PD-1 than CTLA-4 inhibitors
 - But, not universal *Oncologist* 2019;24:584–8.
- Affect men more than women
- Timing of onset from ICI initiation - ranging from 6 to 18 weeks
 - Median of 26 days *Oncologist* 2019;24:584–8.

The diagnosis of HLH is often delayed due to lack of clinician awareness of the condition as well as overlapping differential diagnoses with similar symptoms and laboratory abnormalities.

NCCN Recommendations

The NCCN panel recommends the following criteria for when there is clinical concern for HLH/MAS: 1) Rapidly rising and high ferritin (>5000 ng/mL) with cytopenias in the context of fever, especially if accompanied by any of the following: Grade ≥ 3 increase in serum bilirubin, aspartate aminotransferase (AST), alanine transaminase (ALT); Grade ≥ 3 oliguria or increase in serum creatinine; or grade ≥ 3 pulmonary edema; 2) presence of hemophagocytosis in bone marrow or organs based on histopathologic assessment of cell morphology and/or CD68 immunohistochemistry (IHC).

Management of ICI-associated HLH

- Early recognition and aggressive management of ICI-associated HLH is critical, due to associated mortality of up to one-fourth of patients.
- Complex and not 'one size fits all'
- High-dose corticosteroids
- Cytokine modulation - IL-6 antagonist tocilizumab
- Cytotoxic chemotherapies - Etoposide (if no response)

Immune Checkpoint Inhibitor-Related [NCCN Guidelines Index](#)
[Table of Contents](#)
[Discussion](#)

MANAGEMENT

- Hold immunotherapy^h
- Inpatient care^f with hematology consult (due to high mortality rate if left untreated)
 - ▶ Consider consult with expert in the management of HLH-like syndromes
- Prednisone/IV methylprednisolone 0.5–1 mg/kg once daily^s (or dexamethasone at equivalent dose)^{s,t}
- If no response to steroids after 5 days, consider adding tocilizumab,^{u,v} anakinra, ruxolitinib, cyclosporine, or emapalumab-lzsg

RARE IMMUNE-RELATED ADVERSE EVENTS – CASE (2)



2024.6.19

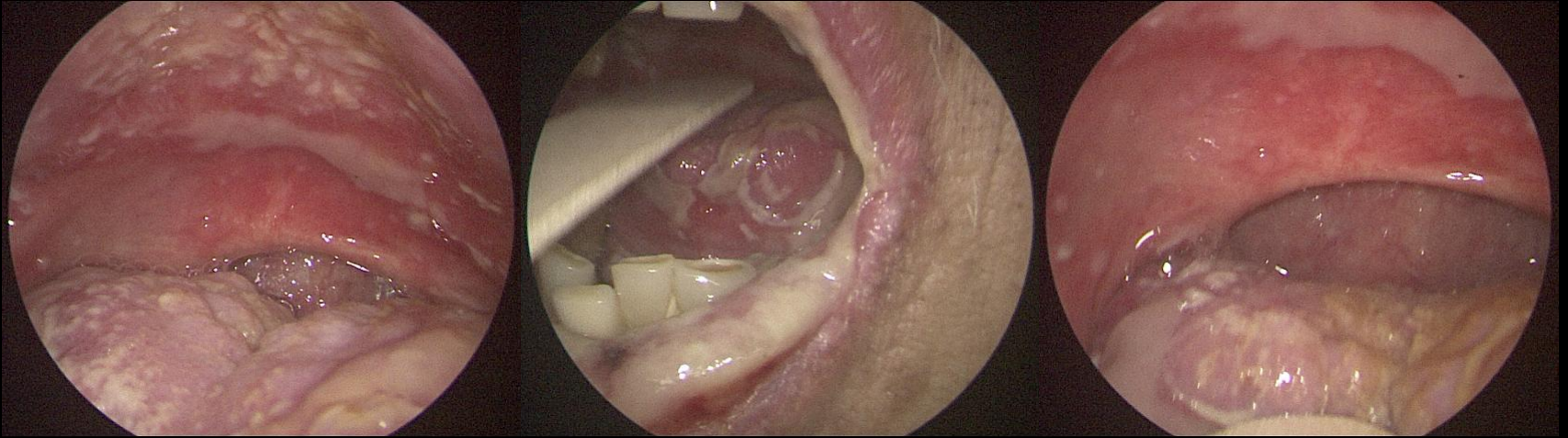
M/68

NSCLC in RLL, SqCC, IVA
1L Palliative Pembrolizumab, paclitaxel,
and carboplatin #1(2024.7.3)

Skin problems (2024.7.23)



M/68
NSCLC in RLL, SqCC, IVA
1L Palliative Pembrolizumab, paclitaxel,
and carboplatin #1(2024.7.3)
Skin problems (2024.7.23)



M/68

NSCLC in RLL, SqCC, IVA

1L Palliative Pembrolizumab, paclitaxel, and carboplatin #1(2024.7.3)

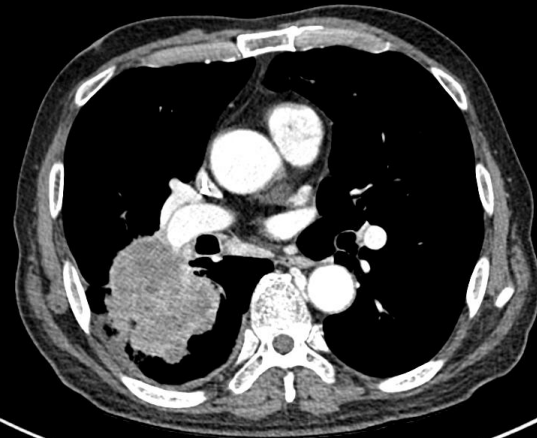
Skin/mucosal problems → Stevens-Johnson syndrome (SJS) or early Toxic epidermal necrolysis (TEN)
- Consultation(dermatology, Ophthalmology, and ENT), methyl-PD 0.5mg/kg



2024.6.19



2024.9.25



2024.12.18

M/68

NSCLC in RLL, SqCC, IVA

1L Palliative Pembrolizumab, paclitaxel, and carboplatin #1(2024.7.3)

SJS or early TEN (2024.7)

ICI-associated dermatologic toxicity

- Most common complication observed in up to 30-50% of ICI-patients
 - Incidence of severe skin reactions 2.0% (PD-1 and PD-L1 inhibitors in NSCLC)

Transl Lung Cancer Res. 2017 Dec;6(Suppl 1):S8-S20.

- Generally mild and typically do not require discontinuation of ICI
- Inflammatory dermatoses, blistering dermatoses, and severe adverse skin reactions
- Average time to onset: approximately 4 weeks after the 1st treatment (it can vary from 2 to 150 weeks)
- Anti-CTLA-4 therapy (60%), anti-PD-1 or anti-PD-L1 (20%), but combination therapy (59-72%)

Stevens-Johnson syndrome/ Toxic epidermal necrolysis

- Rare and can be life-threatening
- Reported in patients treated with anti-PD-1 and anti-CTLA-4 inhibitors
- Accompanied by mucosal involvement (ocular, oral, or anogenital)
- Rapid and acute, or may appear progressively from a less severe skin toxicity

SJS, TEN, and SJS/TEN overlap

Skin and subcutaneous tissue disorders					
CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Stevens-Johnson syndrome	-	-	Skin sloughing covering <10% BSA with associated signs (e.g., erythema, purpura, epidermal detachment, and mucous membrane detachment)	Skin sloughing covering 10 - 30% BSA with associated signs (e.g., erythema, purpura, epidermal detachment and mucous membrane detachment)	Death
<p>Definition: A disorder characterized by less than 10% total body skin area separation of dermis. The syndrome is thought to be a hypersensitivity complex affecting the skin and the mucous membranes.</p> <p>Navigational Note: -</p>					
Toxic epidermal necrolysis	-	-	-	Skin sloughing covering \geq 30% BSA with associated symptoms (e.g., erythema, purpura, or epidermal detachment)	Death
<p>Definition: A disorder characterized by greater than 30% total body skin area separation of dermis. The syndrome is thought to be a hypersensitivity complex affecting the skin and the mucous membranes.</p> <p>Navigational Note: -</p>					

Severe
Cutaneous
Adverse
Reaction

SJS, TEN,
AGEP, DRESS

1.3. SCAR

G3: Skin sloughing covering < 10% BSA with mucosal involvement–associated signs (eg, erythema, purpura, epidermal detachment, and mucous membrane detachment).

Hold ICPI therapy and consult with dermatology.

Admit to burn unit and/or consult wound services with attention to supportive care including fluid and electrolyte balance, minimizing insensible water losses, and preventing infection.

Treat skin with topical emollients and other petrolatum emollients, oral antihistamines, and high-strength topical corticosteroids. Dimethicone may also be offered as an alternative to petrolatum.

Administer IV methylprednisolone (or equivalent) 0.5-1 mg/kg and convert to oral corticosteroids on response, wean over at least 4 weeks.

Given the immune mechanism of action of these medicines, use of immune suppression (Table A2) is warranted and should be offered. The usual prohibition of corticosteroids for SJS is not relevant here, as the underlying mechanism is a T-cell immune-directed toxicity. Adequate suppression is necessary with corticosteroids or other agents and may be prolonged in cases of DRESS or drug hypersensitivity syndrome.

For mucous membrane involvement of SJS or TEN, appropriate consulting services should be offered to guide management in preventing sequelae from scarring (eg, ophthalmology, otolaryngology, urology, or gynecology as appropriate).

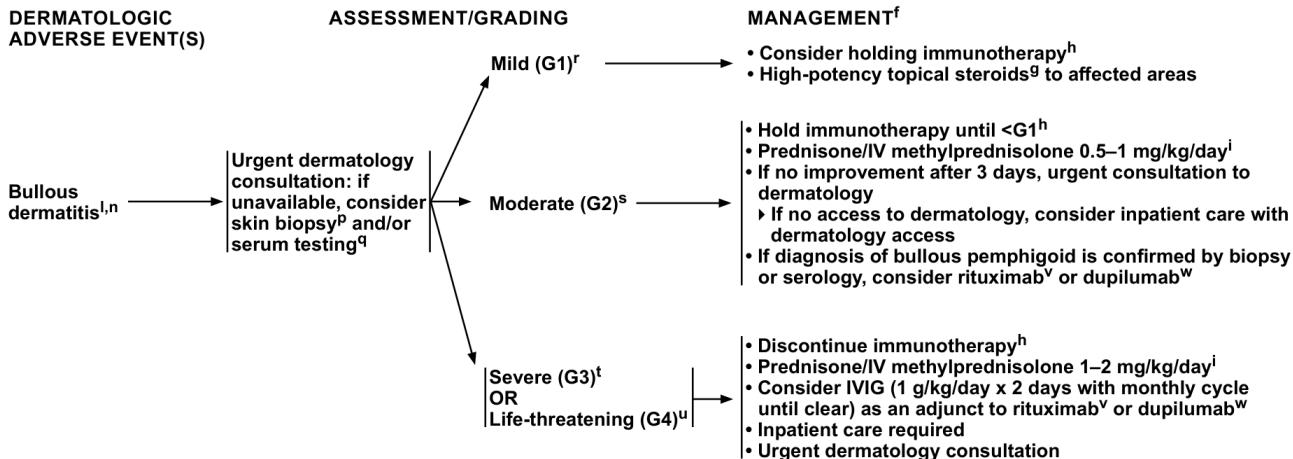
G4: Skin erythema and blistering or sloughing covering ≥ 10% BSA with associated signs (eg, erythema, purpura, epidermal detachment, and mucous membrane detachment) and/or systemic symptoms and concerning associated blood work abnormalities (eg, liver function test elevations in the setting of DRESS or DIHS).

Permanently discontinue ICPI.

Admit patient immediately to a burn unit or ICU with consulted dermatology and wound care services. Consider further consultations based on management of mucosal surfaces (eg, ophthalmology, urology, gynecology, or otolaryngology).

Initiate IV methylprednisolone (or equivalent) 1-2 mg/kg, tapering when toxicity resolves to normal.

IVIg or cyclosporine may also be considered in severe or steroid-unresponsive cases. Consider pain or palliative consultation and/or admission in patients presenting with DRESS manifestations.



Note: All recommendations are category 2A unless otherwise indicated.

[Footnotes on ICI_DERM-3A](#)

BIOMARKERS FOR IMMUNE-RELATED ADVERSE EVENTS PREDICTION

Biomarkers for irAE prediction and diagnosis

Cellular	Absolute lymphocyte count, Neutrophil/lymphocyte ratio, Platelet to lymphocyte ratio, Absolute eosinophil count, CD4+cells, Regulatory T cells, T-cell repertoire, CD8+ cells
Endocrine	TSH
Antibody	Anti-thyroglobulin antibody, Anti-BP180 IgG, Anti-GAD65, IA-2, ZnT8, islet cell antibodies, ANA
Cytokines/ chemokines	IFN- γ , CXCL9, CXCL10, CXCL11, CXCL19, CCL5, G-CSF, GM-CSF, fractalkine, FGF-2, IFN- α 2, IL-12p70, IL-1a, IL-1b, IL-RA, IL-2, IL-13, IL-6, IL-8, soluble CD25, IL-17, Leptin, Soluble CD163, TNF- α , CRP
Tissue	Tumor gene mutations
Microbiome	<i>Firmicutes/Faecalibacterium</i> , <i>Bacteroidetes</i> , Metabolic products
Genetics	HLA-DR4, Gene expression panel, CD177 and CEACAM1
Imaging	CT chest radiomics

IMPACT OF IMMUNE-RELATED ADVERSE EVENTS ON CLINICAL OUTCOMES

Early irAEs and Clinical outcome in Advanced NSCLC

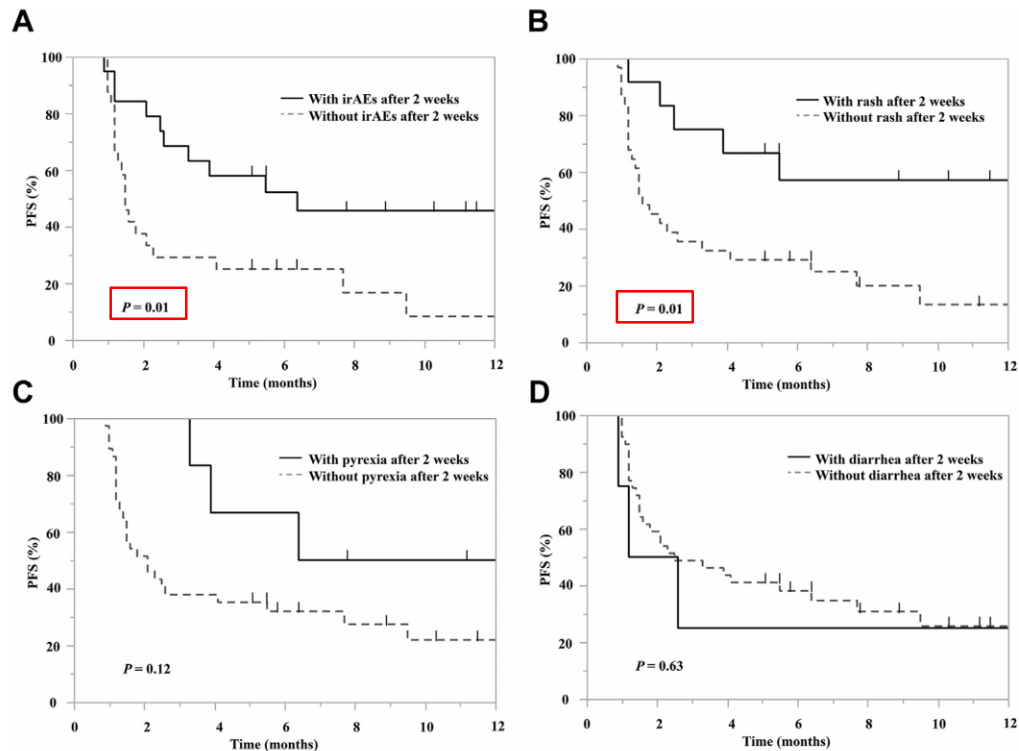
Nivolumab(2nd~ line) - Prospective Cohort Study

Table 2. Association between the Presence of Immune-Related Adverse Events and Treatment Response

Parameter	Patients		p Value
	With irAEs	Without irAEs	
Patient evaluation of irAEs after 2 wk, n (%)			
ORR	7 of 19 (37)	4 of 24 (17)	0.17
DCR	14 of 19 (74)	7 of 24 (29)	< 0.01 ^a
Patient evaluation of irAEs after 6 wk, n (%)			
ORR	9 of 27 (33)	2 of 16 (13)	0.17
DCR	16 of 27 (59)	5 of 16 (31)	0.12

^a $P < 0.05$.

irAE, immune-related adverse event; ORR, objective response rate; DCR, disease control rate.



Early irAEs and Clinical outcome in Advanced NSCLC

Nivolumab(2nd line)

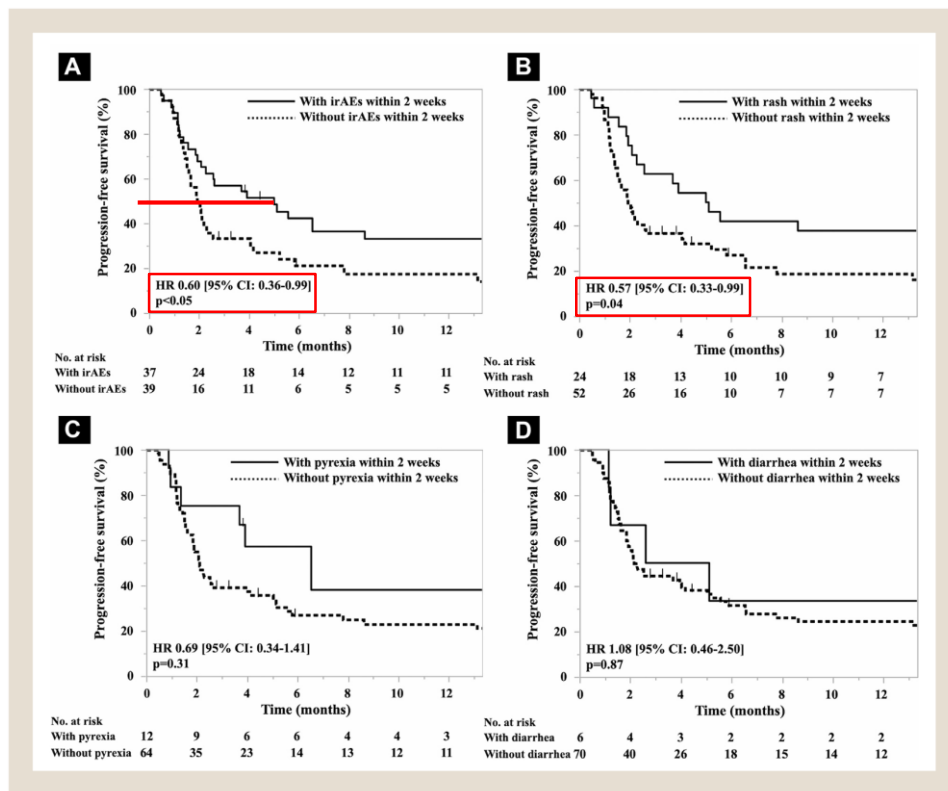
- Prospective Cohort Study

A Median PFS ($p = 0.046$)

- With irAEs within 2 wks: 5.0 months
[2.1-8.6 months]
- Without irAEs within 2 wks: 2.0 months
[1.9-2.5 months]

Supplemental Table 3 Association Between irAEs Within 2 Weeks of Beginning Nivolumab and Tumor Response (Prospective Single-center Cohort)

Variable	irAE	No irAE	P Value
Any irAE	n = 36	n = 38	
ORR	14 (39)	5 (13)	.01 ^a
DCR	21 (58)	13 (34)	.04 ^a



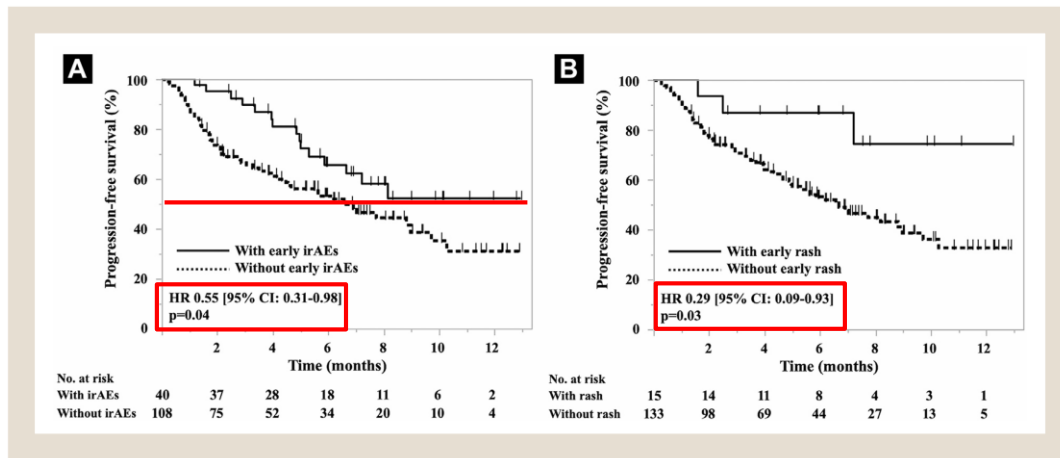
Early irAEs and Clinical outcome in Advanced NSCLC

Pembrolizumab(1st line, PD-L1 TPS ≥50%)
- retrospective multicenter cohort

- A** Median PFS ($p = 0.04$)
- With early irAEs: not reached
 - Without early irAEs: 6.9 months
[4.2-9.7 months]

Supplemental Table 5 Association Between Specific Early irAEs and Tumor Response (Retrospective Multicenter Cohort)

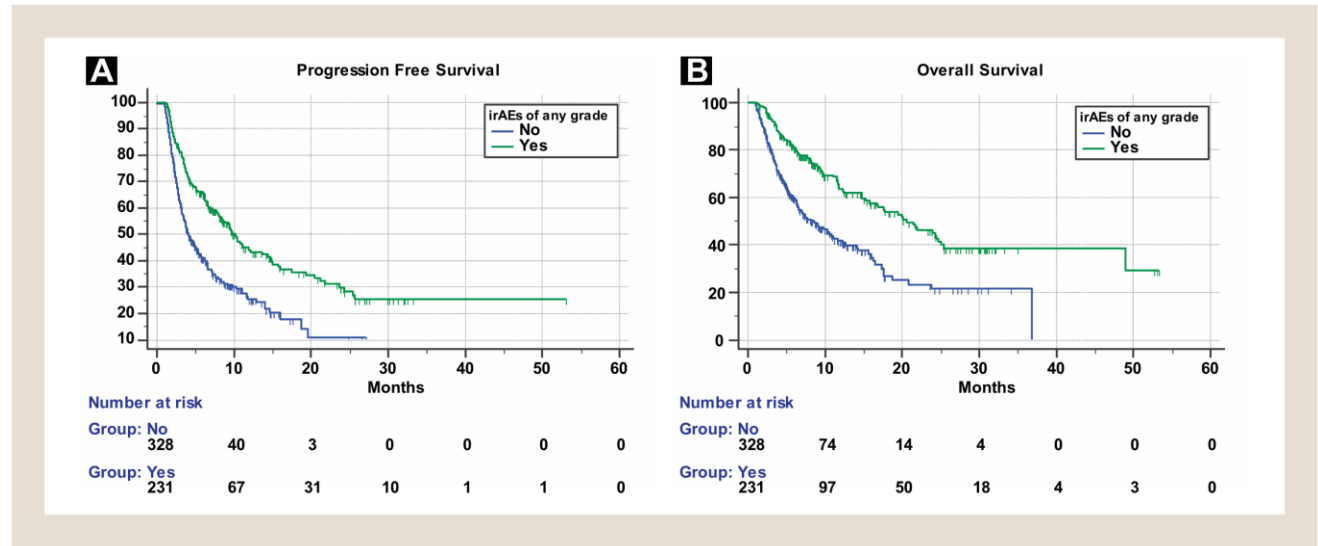
Variable	Early irAEs (n = 39)	No Early irAEs (n = 106)	P Value
Any irAE			
ORR	30 (77)	47 (44)	<.01 ^a
DCR	36 (92)	73 (69)	<.01 ^a



Correlations between irAEs and Efficacy

- “Real-life” multicenter retrospective observational study
- Advanced NSCLC
- 559 patients

Type of anti-PD-1	
Pembrolizumab	123 (22)
Nivolumab	436 (78)
Line of immunotherapy	
First	116 (20.8)
Non-first	443 (79.2)



	Multivariate Analysis					
	ORR		PFS		OS	
	OR ^a (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
irAEs of any grade (Yes vs. No)	0.43 (0.29-0.65)	<.0001	0.59 (0.47-0.76)	<.0001	0.55 (0.41-0.72)	<.0001

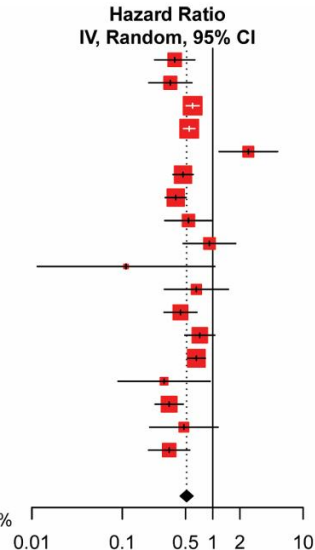
irAE associated with outcomes in NSCLC

Overall survival

A

Study	TE	SE	Weight	Hazard Ratio IV, Random, 95% CI
Ahn, 2019	-0.97	0.2611	5.2%	0.38 [0.23, 0.63]
Aso, 2020	-1.08	0.2803	4.8%	0.34 [0.20, 0.59]
Baldini, 2020	-0.51	0.0844	9.9%	0.60 [0.51, 0.71]
Barlesi, 2020	-0.60	0.0734	10.1%	0.55 [0.48, 0.64]
Barron, 2020	0.91	0.3798	3.3%	2.48 [1.18, 5.22]
Cortellini, 2019	-0.76	0.1303	8.6%	0.47 [0.36, 0.61]
Cortellini, 2020	-0.94	0.1354	8.5%	0.39 [0.30, 0.51]
Haratani, 2018	-0.62	0.3080	4.3%	0.54 [0.30, 0.99]
Hosoya, 2020	-0.08	0.3411	3.8%	0.92 [0.47, 1.80]
Kim, 2018	-2.21	1.1535	0.5%	0.11 [0.01, 1.06]
Ksienski, 2019	-0.42	0.4158	2.9%	0.66 [0.29, 1.49]
Lim, 2020	-0.82	0.2136	6.3%	0.44 [0.29, 0.67]
Lisberg, 2018	-0.33	0.1944	6.8%	0.72 [0.49, 1.05]
Naqash, 2020	-0.42	0.1162	9.0%	0.66 [0.53, 0.83]
Osorio, 2017	-1.24	0.5985	1.6%	0.29 [0.09, 0.94]
Ricciuti, 2019	-1.11	0.1823	7.1%	0.33 [0.23, 0.47]
Suh, 2018	-0.73	0.4440	2.6%	0.48 [0.20, 1.15]
Zhou, 2021	-1.11	0.2672	5.1%	0.33 [0.20, 0.56]

Total (95% CI) 100.0% **0.51 [0.44, 0.60]**
 Heterogeneity: Tau² = 0.06; Chi² = 51.55, df = 17 (P < 0.01); I² = 67%
 Test for overall effect: Z = -8.14 (P < 0.01)

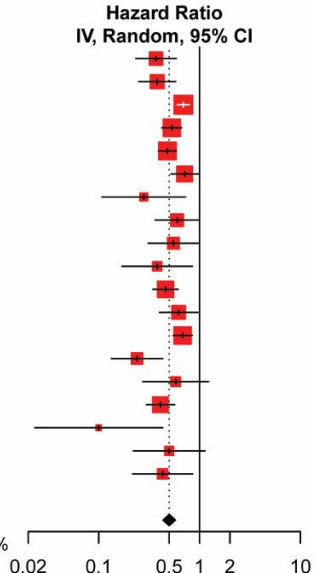


Progression-free survival

B

Study	TE	SE	Weight	Hazard Ratio IV, Random, 95% CI
Ahn, 2019	-0.99	0.2360	5.1%	0.37 [0.23, 0.59]
Aso, 2020	-0.97	0.2147	5.6%	0.38 [0.25, 0.58]
Baldini, 2020	-0.37	0.0702	10.1%	0.69 [0.60, 0.79]
Cortellini, 2019	-0.63	0.1153	8.7%	0.53 [0.42, 0.66]
Cortellini, 2020	-0.73	0.1056	9.0%	0.48 [0.39, 0.59]
Fujimoto, 2018	-0.34	0.1590	7.2%	0.71 [0.52, 0.97]
Haratani, 2018	-1.27	0.4852	1.8%	0.28 [0.11, 0.72]
Hosoya, 2020	-0.51	0.2581	4.6%	0.60 [0.36, 0.99]
Hosoya, 2020	-0.60	0.2936	3.9%	0.55 [0.31, 0.98]
Kim, 2018	-0.97	0.4106	2.4%	0.38 [0.17, 0.85]
Lim, 2020	-0.78	0.1459	7.7%	0.46 [0.35, 0.61]
Lisberg, 2018	-0.48	0.2233	5.4%	0.62 [0.40, 0.96]
Naqash, 2020	-0.39	0.1111	8.8%	0.68 [0.55, 0.85]
Noguchi, 2020	-1.43	0.2992	3.8%	0.24 [0.13, 0.43]
Osorio, 2017	-0.54	0.3826	2.7%	0.58 [0.27, 1.23]
Ricciuti, 2019	-0.89	0.1637	7.1%	0.41 [0.30, 0.57]
Sato, 2018	-2.30	0.7443	0.9%	0.10 [0.02, 0.43]
Suh, 2018	-0.69	0.4174	2.3%	0.50 [0.22, 1.13]
Toi, 2018	-0.84	0.3506	3.0%	0.43 [0.22, 0.85]

Total (95% CI) 100.0% **0.50 [0.43, 0.58]**
 Heterogeneity: Tau² = 0.05; Chi² = 45.49, df = 18 (P < 0.01); I² = 60%
 Test for overall effect: Z = -9.70 (P < 0.01)

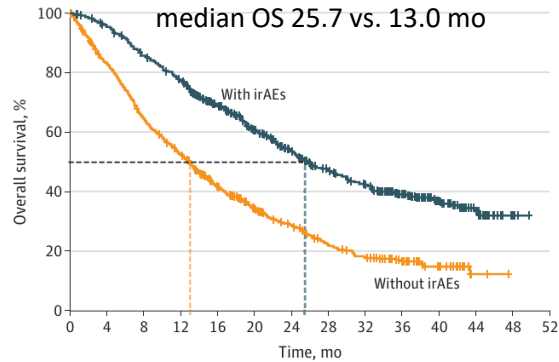


Meta-Analysis - 26 cohorts, including 8,452 patients with NSCLC receiving anti-PD-1 antibodies

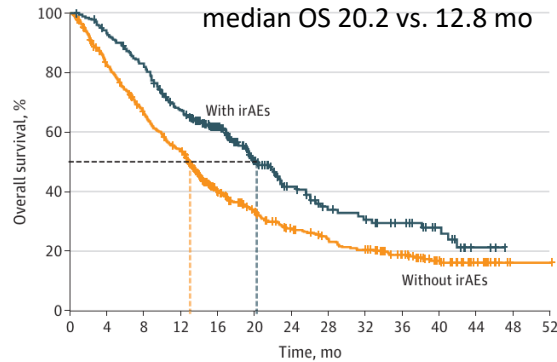
Association of irAE with efficacy of Atezolizumab

Figure 1. Overall Survival by Immune-Related Adverse Event (irAE) Status in the Atezolizumab-Containing and Control Arms

A Atezolizumab-containing arm



B Control arm



No. at risk

With irAEs	753	714	637	570	431	318	253	202	174	115	74	29	4
Without irAEs	804	658	509	404	249	164	121	84	66	41	20	2	

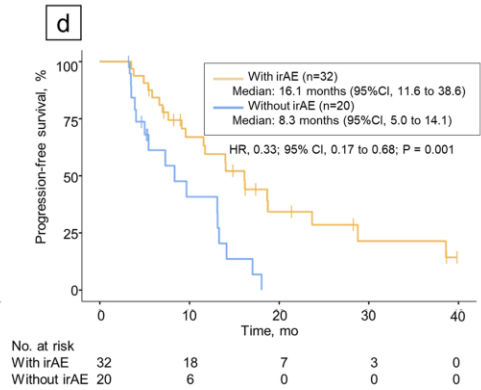
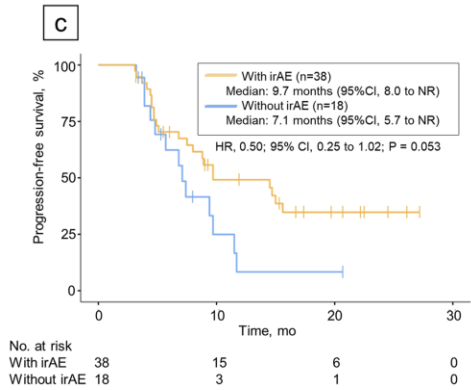
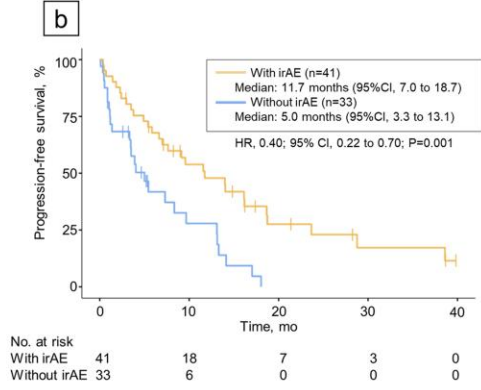
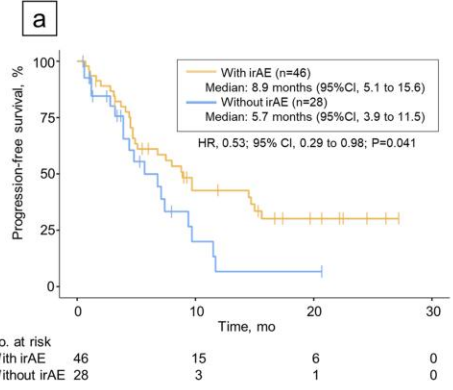
	289	267	234	188	131	75	47	32	28	22	14	3	
	611	494	390	316	175	130	97	79	68	46	27	13	1

Kaplan-Meier curves are not adjusted for the timing of irAE onset.

- Pooled Analyses of the Phase 3 IMpower130, IMpower132, and IMpower150 – Randomized Clinical Trials
- Stage IV non-squamous NSCLC - 2,503 patients
- Chemoimmunotherapy combinations involving atezolizumab

Association between the efficacy and irAEs

12-week landmark analysis



Pembrolizumab + platinum-based chemotherapy

Pembrolizumab monotherapy

Pembrolizumab + platinum-based chemotherapy

Pembrolizumab monotherapy

- Retrospective study
- Chemo-naïve advanced NSCLC
- 148 patients
- Pembrolizumab and platinum-based chemotherapy// Pembrolizumab monotherapy

Summary (1)

- Currently, no single marker has been established to predict immune-related adverse events (irAE).
- However, it is clear that immune-related adverse events are associated with improved outcomes, including overall response rate (ORR), progression-free survival (PFS), and overall survival (OS), in patients with non-small cell lung cancer (NSCLC).

MANAGEMENT OF IMMUNE-RELATED ADVERSE EVENTS

Steroid treatment

- **Grade 1:** Continue ICI therapy with clinical monitoring.
- **Grade 2:** Temporarily stop ICI therapy and administer prednisone (0.5 mg/kg/day), tapering off as symptoms improve.
- **Grade 3 and 4:** Permanently discontinue ICIs. High-dose systemic steroids (1-2 mg/kg/day) are used, often requiring hospitalization for intravenous methylprednisolone (over 4-6 weeks).

Management of immune-related adverse events

Why is steroid use rising among male bodybuilders?

10 April 2022

Share  Save 



Josh Bridgman has been using steroids for about three years

BBC



By copilot

Healthy patient

Principles of Steroid use

Principles of Steroid Use in the Management of irAEs

- We recommend **early intervention with steroids** for the general management of immune-related toxicity.
- If unable to taper steroids, steroid-sparing measures with secondary agents may be appropriate to minimize steroid exposure and expedite resumption of ICI therapy.
- In the absence of specific indications such as prior infusion reaction or concurrent chemotherapy, **routine premedication with steroids is not recommended** given the potential mitigation of immunotherapeutic effectiveness in the prophylactic setting.
- Steroid Dosing
 - See individual toxicity pages for specific recommendations on steroid dose by grade. Where immunotherapy rechallenge is indicated, see the [Principles of Immunotherapy Rechallenge \(IMMUNO-C\)](#) for guidance by organ site.
 - **Higher potency (eg, Class 2 or 3) topical steroids are preferred for short-term use for immune-related dermatitis**, compared to longer term use of lower potency steroids.
 - **Prednisone is the preferred oral steroid** due to ease of dosing and wide availability. **IV methylprednisolone is the preferred IV steroid.**
- Steroid Taper
 - **Longer steroid tapers (>4 weeks, sometimes 6–8 weeks or longer)** may be required to prevent recurrent irAE events, particularly pneumonitis, hepatitis, and neuromuscular toxicities.

Topical steroid



TABLE 2

Potency Ratings of Topical Corticosteroids

Class (potency)	Agent	Formulations	Maximum duration*
I (super high)	Betamethasone dipropionate augmented 0.05%	Ointment, lotion, gel	3 weeks
	Clobetasol propionate 0.05%	Ointment, cream, lotion, gel, foam, solution, shampoo, spray	
	Fluocinonide 0.1%	Cream	
	Flurandrenolide 4 mcg per cm ²	Tape	
	Halobetasol propionate 0.05%	Ointment, cream	
II (high)	Amcinonide 0.1%	Ointment, cream	12 weeks
	Betamethasone dipropionate 0.05%	Ointment	
	Betamethasone dipropionate augmented 0.05%	Cream	
	Desoximetasone 0.25%	Ointment, cream	
	Desoximetasone 0.05%	Gel	
	Diflorasone diacetate 0.05%	Ointment	
	Fluocinonide 0.05%	Ointment, cream, gel, solution	
	Halcinonide 0.1%	Ointment, cream, solution	
III, IV, V (medium)	Amcinonide 0.1%	Lotion	12 weeks
	Betamethasone dipropionate 0.05%	Cream, lotion	
	Betamethasone valerate 0.12%	Foam	
	Betamethasone valerate 0.1%	Ointment, cream, lotion	
	Diflorasone diacetate 0.05%	Cream	
	Fluocinolone acetonide 0.025%	Ointment, cream	
	Flurandrenolide 0.05%	Ointment, cream, lotion	
	Fluticasone propionate 0.05%	Cream, lotion	
	Fluticasone propionate 0.005%	Ointment	
	Hydrocortisone butyrate 0.1%	Ointment, cream, lotion, solution	
	Hydrocortisone valerate 0.2%	Ointment, cream	
	Mometasone furoate 0.1%	Ointment, cream, lotion, solution	
	Triamcinolone acetonide 0.5%	Ointment, cream	
	Triamcinolone acetonide 0.1%	Ointment, cream, lotion	
	Triamcinolone acetonide 0.147 mg per g	Spray	
VI, VII (low)	Alclometasone dipropionate 0.05%	Ointment, cream	No specified limit
	Desonide 0.05%	Ointment, cream, lotion, gel, foam	
	Fluocinolone acetonide 0.01%	Cream, solution, oil	
	Hydrocortisone 1%	Ointment, cream, lotion, spray	
	Hydrocortisone 2.5%	Ointment, cream, lotion, solution	
	Triamcinolone acetonide 0.025%	Ointment, cream, lotion	

*—According to expert guidelines, shorter durations should be used in children, for thin skin such as the face, or in occluded areas such as the groin and skinfolds.

Information from references 1 and 17-19.

Topical steroid

class 2에 해당되는 대표적인 topical corticosteroids를 몇가지만 소개해줘

Class 2로 분류되는 대표적인 중강도의 국소 스테로이드제는 다음과 같습니다:

- **Fluocinonide 0.05%** (Lidex)
- **Betamethasone dipropionate 0.05%** (고농도 크림 또는 연고, Diprolene AF 등)
- **Mometasone furoate 0.1%** (Elocon 크림 또는 로션)
- **Desoximetasone 0.25%** (Topicort)

이 약물들은 염증과 가려움증 완화에 효과적이며, 피부과 질환에 자주 처방됩니다. 하지만 사용 시에는 반드시 의사의 처방 및 지시를 따라야 하며, 장기 사용으로 인한 부작용 가능성에도 주의해야 합니다! 궁금한 점이나 관련된 추가 정보가 필요하시면 알려주세요. 😊

By copilot

class 2에 해당되는 대표적인 topical corticosteroids를 몇가지만 소개해줘

Class 2에 해당되는 대표적인 topical corticosteroids는 중등도 강도의 스테로이드입니다. 아래는 몇 가지 예시입니다:

1. **Betamethasone valerate 0.1%**

- 강력한 항염증 효과를 가지고 있으며, 피부염, 아토피 피부염 등 다양한 피부 질환에 사용됩니다.

2. **Fluticasone propionate 0.05%**

- 알레르기성 피부염 및 아토피 피부염 치료에 사용되며, 부작용이 적고 효과적인 약물입니다.

3. **Mometasone furoate 0.1%**

- 염증을 줄이고 가려움증을 완화하는데 효과적인 중간 강도의 스테로이드입니다.

이 약물들은 일반적으로 피부의 염증이나 가려움증을 완화하는 데 사용되며, 과도한 사용을 피하고 처방에 따라 사용하는 것이 중요합니다.

By ChatGTP

Adverse effects related to Steroid use

TABLE 12. Prevention and Management of Adverse Effects Related to Steroid Use

12.1. Pretreatment considerations

Baseline workup to include viral **hepatitis B and C serology** and consideration for **latent or active TB test**. In patients with **pre-existing HIV, testing HIV viral load** and CD4 count would be appropriate.

Patients with **pre-existing comorbid conditions**, such as **DM, hypertension, HF, cataract, glaucoma, infection, or osteoporosis**, should have their condition optimally managed before commencing steroids.

Ideal steroid dosing and duration is individualized and can vary by patient, oncologic agents, and type of irAE. Refer to each individual irAE section for more detail.

The lowest dose of steroids should be used for the shortest duration of time needed to achieve treatment goals and control deleterious effects of irAE, as the risk of toxicity with steroids is generally dose- and duration-dependent.

12.2. Prevention of opportunistic infection

Use of prophylaxis for an **opportunistic infection with PJP** may be considered once a patient has received a **prednisone equivalent of ≥ 20 mg/d for 4 or more weeks or > 30 mg for 3 weeks or more**. Physicians may proceed according to institutional guidelines.

The role of prophylactic fluconazole with prolonged steroid use (> 12 weeks) remains unclear and physicians should proceed according to institutional guidelines.²³⁴

Use of prophylaxis against herpes zoster reactivation may be offered to patients who have had zoster before and will be receiving corticosteroids.²³⁵

Management of Steroid Resistance

- Alternatives include **rituximab (anti-CD20)**, **infliximab (anti-TNF- α)**, **tocilizumab (anti-IL-6R)**, tailored to the affected organ systems.
- Organ-Specific Treatments:
 - Liver and Kidney toxicities: mycophenolate-based immunosuppressants
 - Pulmonary and Neurological toxicities: cyclophosphamide, IV Ig, plasma exchange
 - Severe Cardiotoxicity: abatacept (anti-CD80/86), alemtuzumab (anti-CD52)
- Additional Considerations:
 - Careful balancing is necessary to prevent organ damage while maintaining cancer treatment efficacy.
 - Steroid-sparing agents can lead to new adverse effects, requiring close monitoring.

IMPACT OF STEROID ON CLINICAL OUTCOMES

Impact of baseline steroids on efficacy

- Retrospective study
- 640 patients with advanced NSCLC
- Single-agent
 - Pembrolizumab
 - Nivolumab
 - Atezolizumab
 - Durvalumab

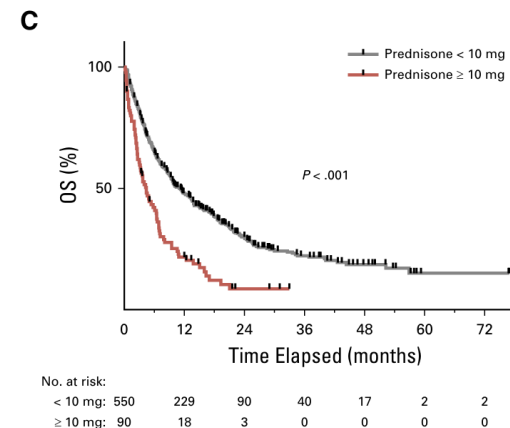
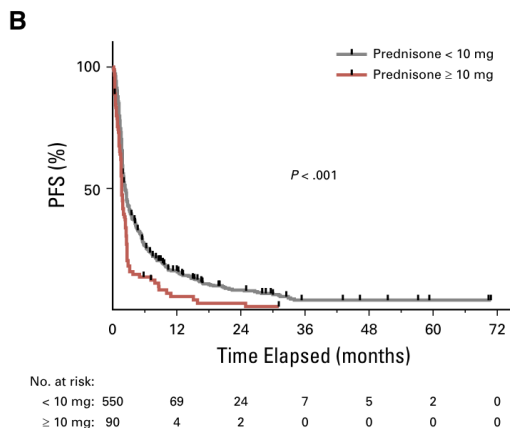


Table 2. Multivariable Analysis of Best Overall Response Rate, Progression-Free Survival, and Overall Survival in a Pooled Cohort of Patients: Memorial Sloan Kettering Cancer Center and Gustave Roussy Cancer Center Combined

Patient Characteristic	Best Overall Response		Progression-Free Survival		Overall Survival	
	Odds Ratio (95% CI)	<i>P</i>	Hazard Ratio (95% CI)	<i>P</i>	Hazard Ratio (95% CI)	<i>P</i>
Smoking status (never v ever)	0.33 (0.15 to 0.74)	.007	1.64 (1.30 to 2.04)	< .001	1.03 (0.81 to 1.33)	.78
ECOG performance status (≥ 2 v 0-1)	0.29 (0.11 to 0.75)	.11	1.97 (1.55 to 2.50)	< .001	2.29 (1.75 to 2.98)	< .001
History of brain metastases (yes v no)	0.88 (0.52 to 1.49)	.6	1.16 (0.96 to 1.41)	.1	1.37 (1.11 to 1.7)	.003
Corticosteroid use (≥ 10 mg v < 10 mg)	0.42 (0.17 to 1.01)	.053	1.31 (1.03 to 1.67)	.03	1.66 (1.28 to 2.16)	< .001

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Early use of systemic corticosteroid

- Retrospective study
- 210 patients with advanced NSCLC
- During the first 30 days of Nivolumab therapy
- Systemic corticosteroids (equivalent to >10 mg of prednisone/d)

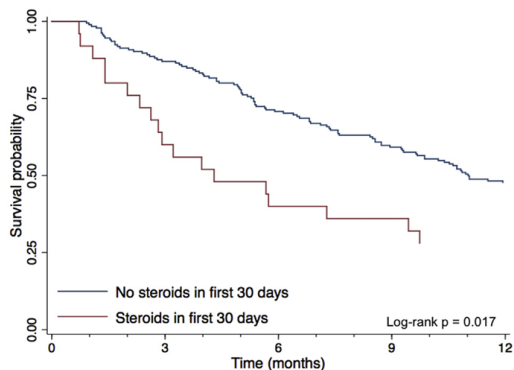


Figure 1. Kaplan-Meier estimate of overall survival from the start of nivolumab therapy according to exposure to systemic corticosteroids during the first 30 days of nivolumab therapy.

Table 3. Multivariate Cox Proportional Hazards Model for Patients Taking Nivolumab, Including Concurrently with Corticosteroids

Characteristic	Hazard Ratio	95% CI	p Value
Sex (ref = male)			
Female	1.03	0.66-1.62	0.88
Age (per year)	1.02	1.00-1.05	0.04
Race (ref = white)			
Other race	0.64	0.36-1.14	0.13
Smoking history (ref = never-smoker)			
Current or former smoker	0.77	0.41-1.43	0.40
Histologic subtype (ref = nonsquamous)			
Squamous	1.35	0.80-2.26	0.26
Time since diagnosis ^a (per month)	0.99	0.98-1.00	0.16
ECOG performance status (ref = 0)			
1	1.13	0.68-1.86	0.64
2	1.39	0.72-3.48	0.24
Prior brain metastasis ^b (ref = no)			
Yes	1.19	0.74-1.90	0.47
Steroids in first 30 days (ref = none)			
Steroids given	2.30	1.27-4.16	0.006

Boldface indicates statistical significance.

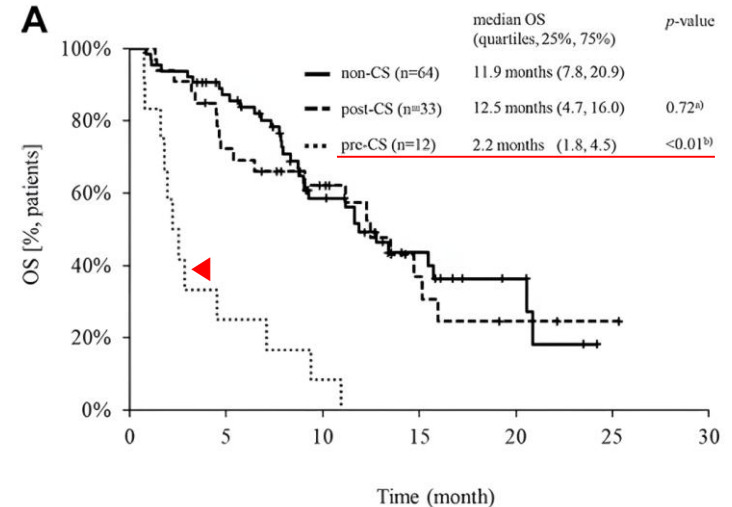
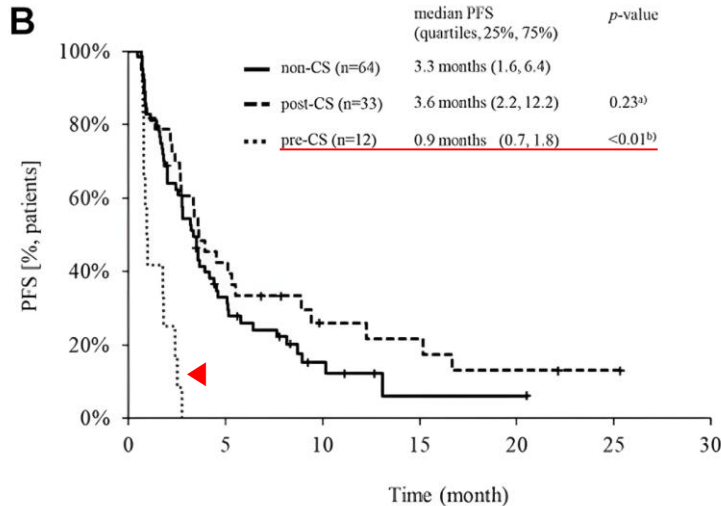
^aMonths from diagnosis NSCLC to start of nivolumab therapy.

^bBrain metastasis diagnosed before the start of nivolumab therapy.

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group.

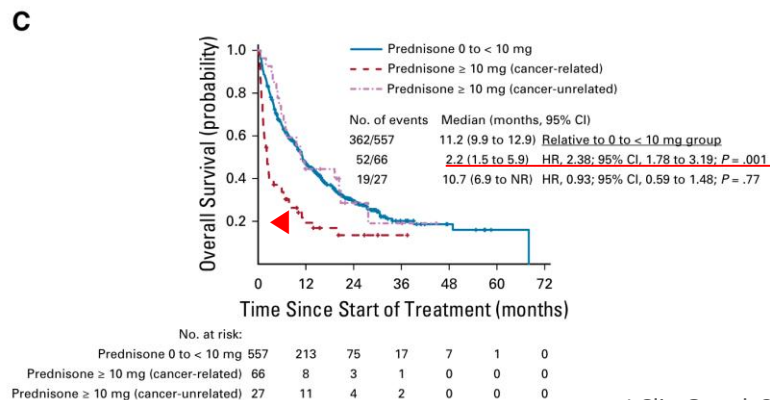
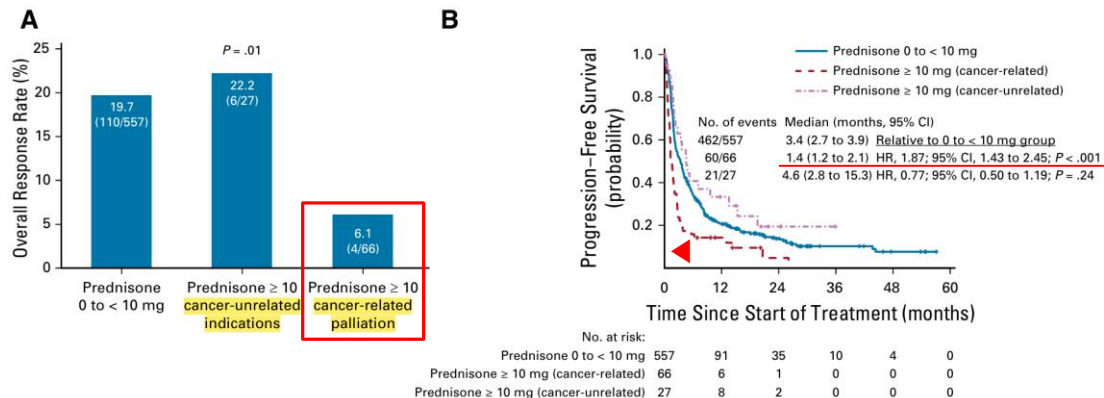
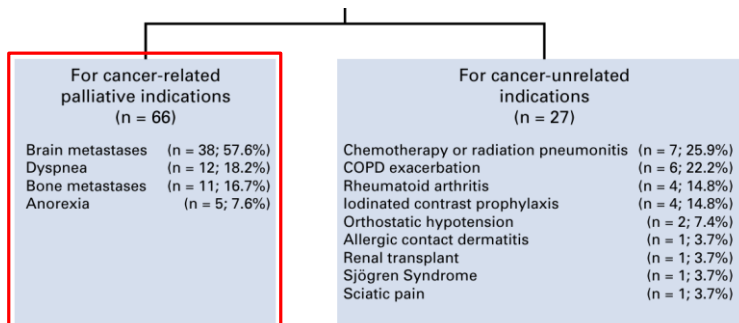
Effect of systemic corticosteroid before vs. after the 1st cycle

- Retrospective study
- 109 patients with advanced NSCLC (stage III and IV)
- Nivolumab
- Corticosteroids before the first cycle of nivolumab (pre-CS) vs. after the first cycle of nivolumab (post-CS)



Baseline Corticosteroids for cancer-related palliative vs. Non-palliative Indications

- Retrospective study
- 650 patients with advanced NSCLC
- PD-1 or PD-L1 inhibition as monotherapy or in combination with anti-CTLA-4 inhibition



Summary (2)

- Early steroid intervention is important for the general management of immune-related adverse effects.
- The use of steroids during the early stages of immunotherapy is associated with poor clinical outcomes.
- Steroids prescribed for palliative purposes in cancer patients tend to result in a worse prognosis, whereas their use for non-cancer-related reasons may have varying effects on the outcome.

IMMUNOTHERAPY RECHALLENGE

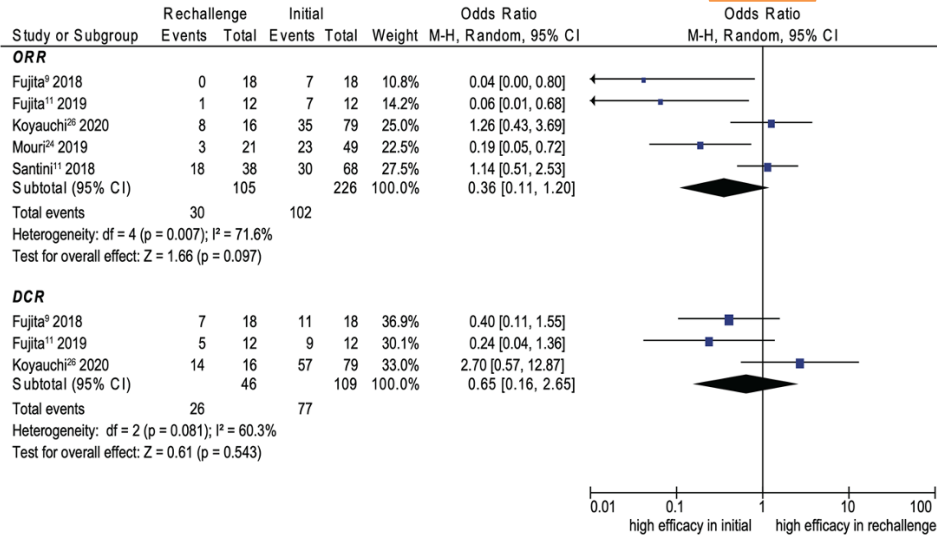
Principles of Immunotherapy Rechallenge

General Principles

- Discuss the **risks/benefits** of restarting immunotherapy with the patient.
- **About 1 in 3 patients may have recurrence of the same irAE after rechallenge.**^a Exercise caution when considering resumption of immunotherapy after significant irAEs. With some exceptions, **resumption of immunotherapy following grade 2–3 irAEs can be considered on resolution to \leq grade 1.** Monitor closely for recurrent symptoms.
 - › If re-challenged and toxicity returns, permanently discontinue class of immunotherapy.
 - › If an objective response (complete or partial) to ICI therapy was achieved, resumption of immunotherapy may not be necessary. The risk of toxicity on resumption may outweigh benefit.
- **irAEs that respond to immunosuppressive therapies may pose a lower risk for rechallenge.**
- **Permanent discontinuation of a given class of immunotherapy may be warranted for severe irAEs or for some moderate irAEs with high risk of morbidity/mortality.** For example, if a patient experiences grade 3 or 4 toxicity from an ipilimumab-containing regimen, consideration may be given to later therapy with a PD-1 or PD-L1 monotherapy after resolution of the earlier toxicity.
- Consult with organ-specific specialists prior to resumption of immunotherapy as appropriate following an immunotherapy hold due to irAEs.

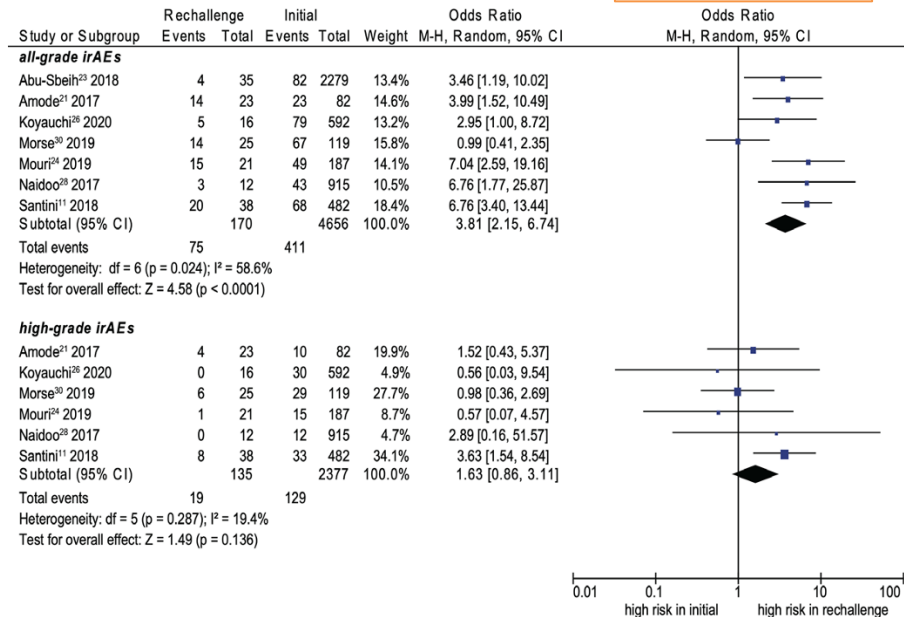
Safety and Efficacy of the rechallenge of ICIs after irAE

ORR



DCR

All grade irAE



High-grade irAE

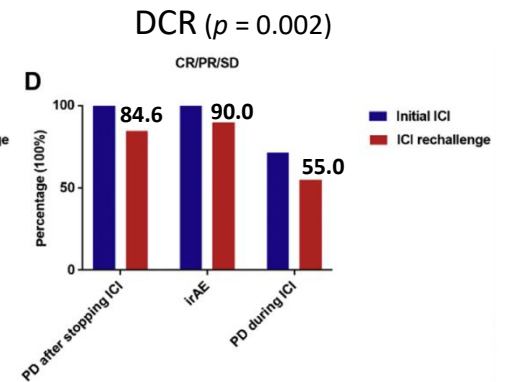
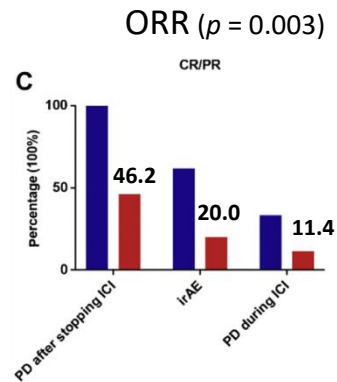
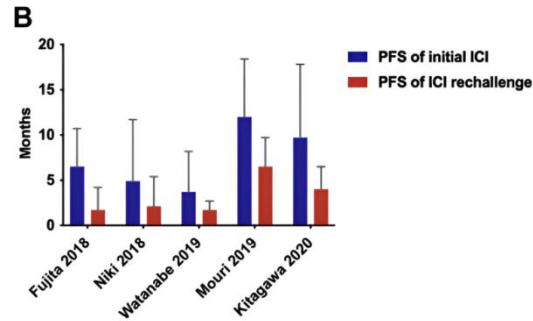
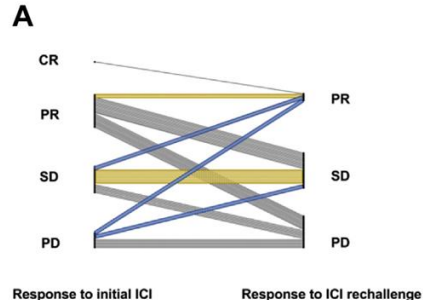
Total of 789 ICI rechallenge cases from 18 cohort, 5 case series, and 54 case reports
→ Meta-Analysis

Efficacy comparison based on different initial ICIs discontinuation reasons

15 studies including 442 patients (NSCLC) between 2018 and 2022 → meta-analysis

Different initial ICI discontinuation reasons

1. PD after stopping ICI
2. irAE
3. PD during ICI



- 34.7% of 69 patients with individual response to ICI and PFS experienced the same or better response to ICI rechallenge in comparison with initial ICI
- PFS in initial ICI was longer than that in ICI rechallenge (median: 8.90 vs. 3.67 months, HR 0.44)

Efficacy of ICIs retreatment and the reason for interruption of initial ICIs

- 1. Retreatment:** Re-administration of immune checkpoint inhibitors (ICIs) after initial treatment was stopped for any reason, following a period of break.
- 2. ICIs Rechallenge:** A specific type of retreatment for patients whose disease progressed either during the initial treatment or within 12 weeks after stopping immunotherapy.
- 3. ICIs Resumption:** A retreatment approach for patients who had stopped ICIs because of immune-related adverse events (irAEs) or after completing a fixed treatment course, provided there was no disease progression at the time.

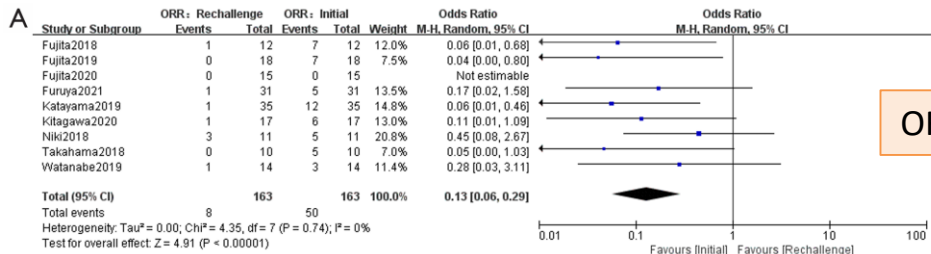
Table 2 The pooled ORR and DCR and the pooled incidence of irAEs

Reasons for discontinuation of prior ICIs	ORR	DCR	All-grade irAEs	High-grade irAEs
Retreatment (overall)	20%	54%	41%	13%
Rechallenge after PD	8%	39%	–	–
Resumption after irAEs and clinical decision	34%	71%	–	–

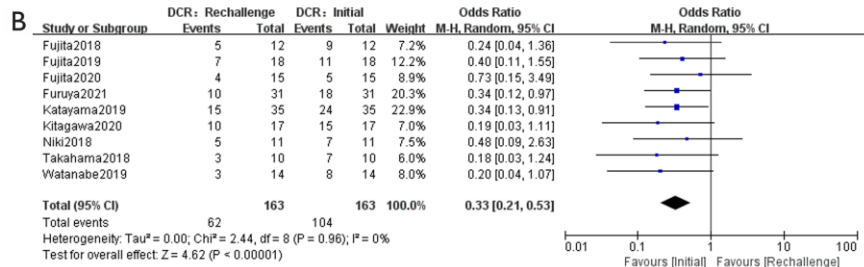
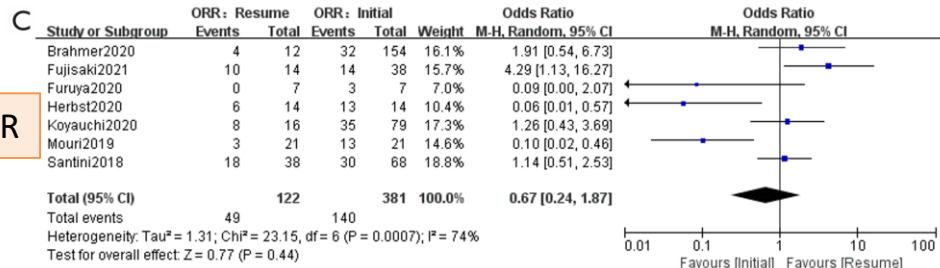
Grade ≥ 3 was defined as high-grade irAEs. ORR, objective response rate; DCR, disease control rate; PD, progression disease; irAEs, immune-related "adverse" events; ICI, immune checkpoint inhibitor.

18 studies (NSCLC) → meta-analysis

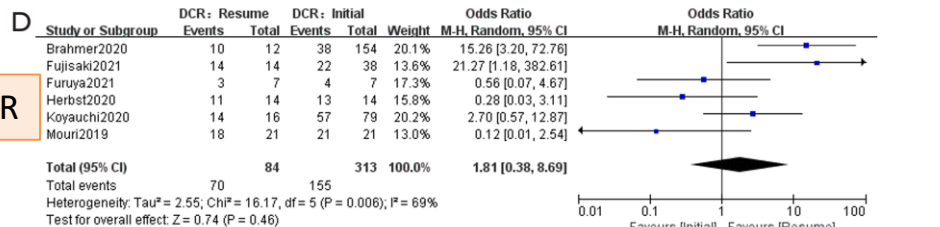
Efficacy of ICIs retreatment and the reason for interruption of initial ICIs



ORR



DCR

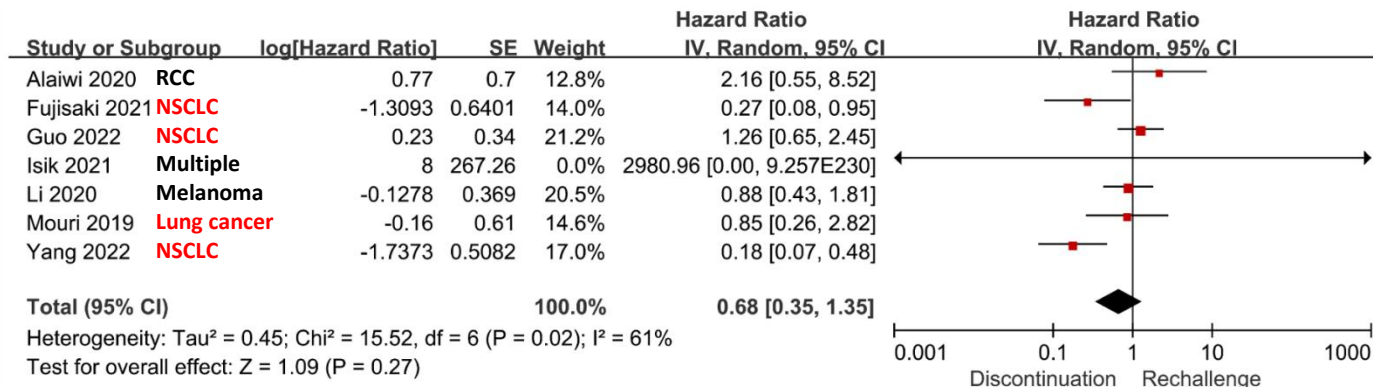


Rechallenge
after PD

Resumption after irAEs
and clinical decision

18 studies (NSCLC) → meta-analysis

Efficacy of Rechallenge With ICIs in Advanced Solid Tumor



Seven studies with 513 patients for survival analysis revealed a nonsignificant difference in OS between the ICIs rechallenge and discontinuation cohorts (hazard ratio [HR]: 0.68, 95% confidence interval (CI): 0.35 to 1.35, $p = 0.27$).

Summary (3)

- The decision to rechallenge therapy should involve a careful evaluation of the associated risks and benefits.
- If an immune checkpoint inhibitor that was previously stopped due to immune-related adverse events is reused, some level of therapeutic response may be anticipated. However, this does not ensure an improvement in overall survival (OS).

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