IO AND TARGETED THERAPY IN NSCLC: SEQUENCE, TOXICITY

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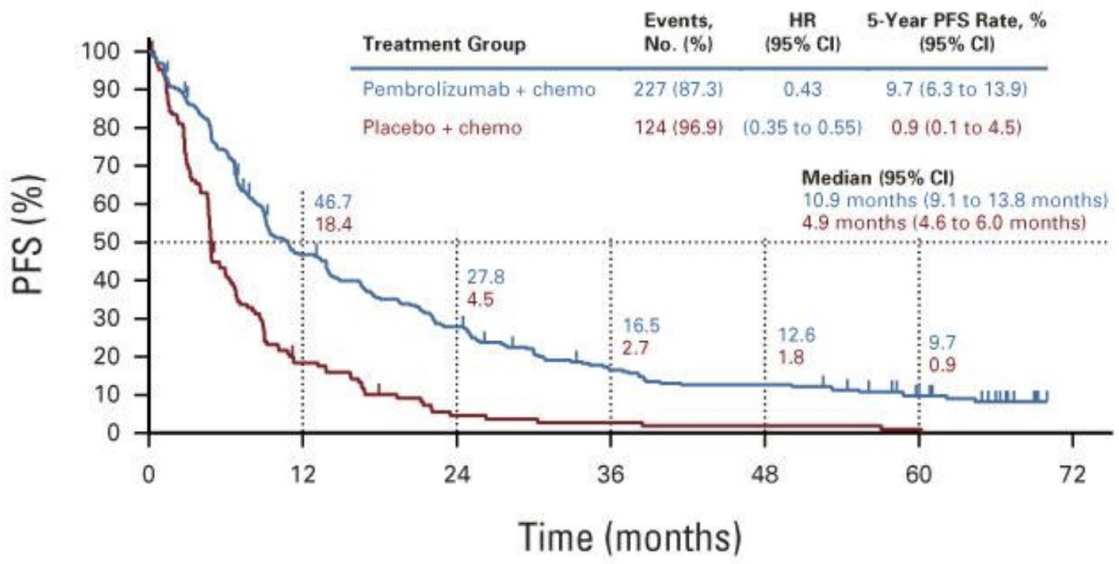
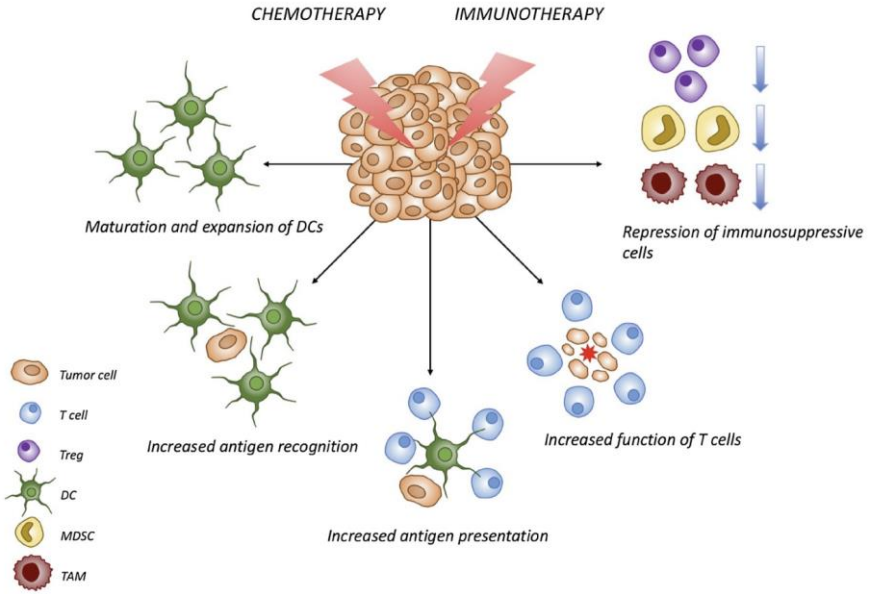
Chemo/ICI combinations have improved outcomes



Improved 5-year PFS rate with addition of pembrolizumab to first-line platinum doublet in KEYNOTE-189

Preclinical – impact of chemotherapy on immunogenicity of disease



Will similar combinations with targeted therapies be possible for patients with actionable oncogene driven cancers?

Can we safely transition form ICIs to targeted therapies?

Garassino et al. J Clin Oncol. 2023; Leonetti et al. Drug Resist Update, 2019

There are FDA-approved Targeted Therapy + ICI Combinations in RCC, melanoma

Atezolizumab + Vemurafenib/Cobimetinib in BRAFm melanoma

- **Safety profile tolerable,** 50% vs 35% rates of pyrexia

Pembrolizumab + Lenvatinib (multikinase VEGFR, PDGFR, FGFR, RET, KIT) in RCC

- Safety profile tolerable
- **Toxicities similar to expected for monotherapy safety profiles**

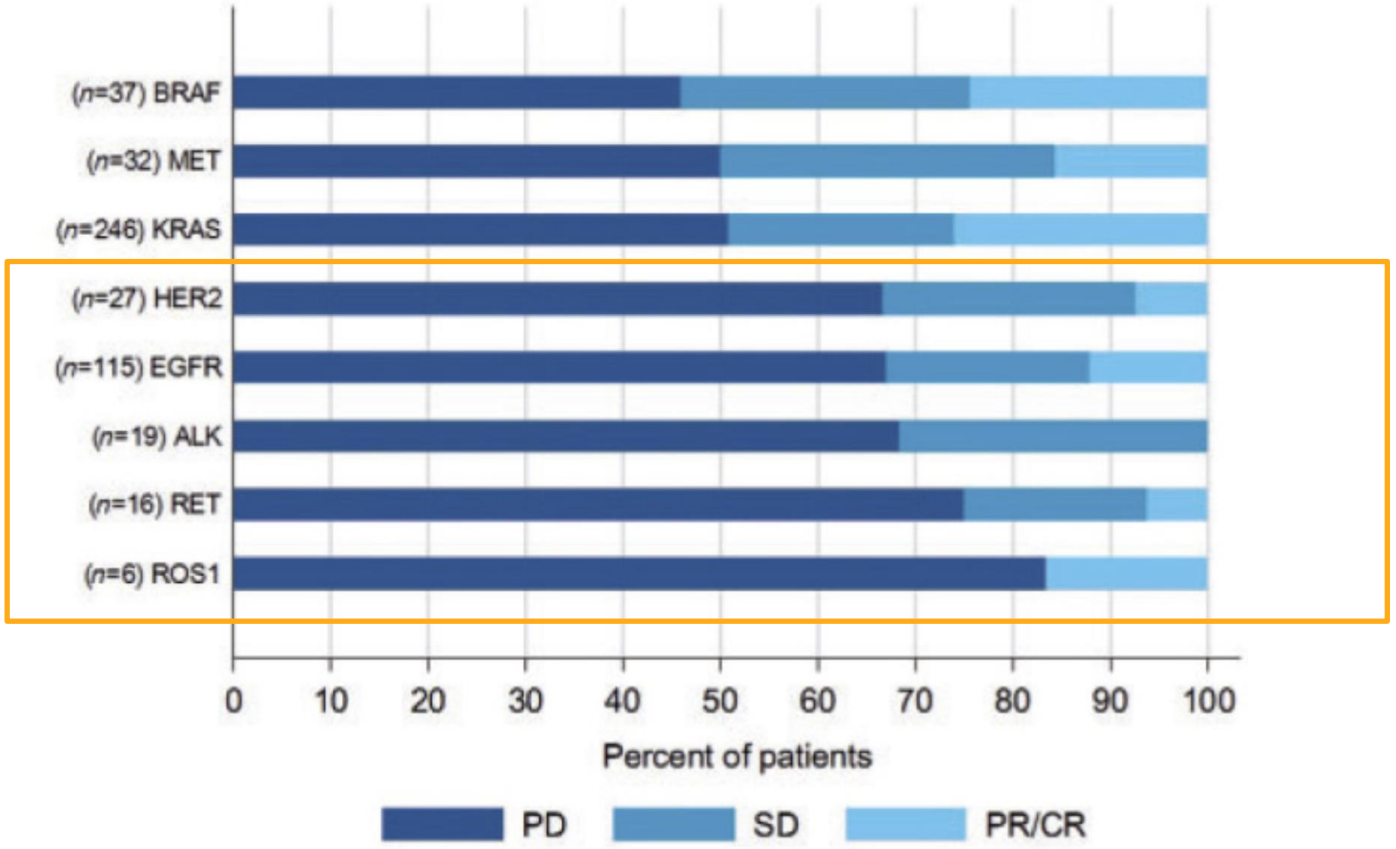
Pembrolizumab + Cabozantinib (MET, multikinase) in RCC

- Safety profile tolerable
- **Toxicities felt similar to expected monotherapy safety profiles**

Ascierto et al, Lancet Oncol. 2023; Choueiri et al NEJM 2021;384:829-841; Motzer et al NEJM 2021;384:1289-1300

In NSCLC ICI monotherapy activity is limited for the non-smoking associated driver mutations

Data from the IMMUNOTARGET Registry



Mazieres et al Ann Oncol. 2019

Early efforts to combine ICIs and TKIs in NSCLC
Osimertinib + Durvalumab: Lessons learned from the TATTON study

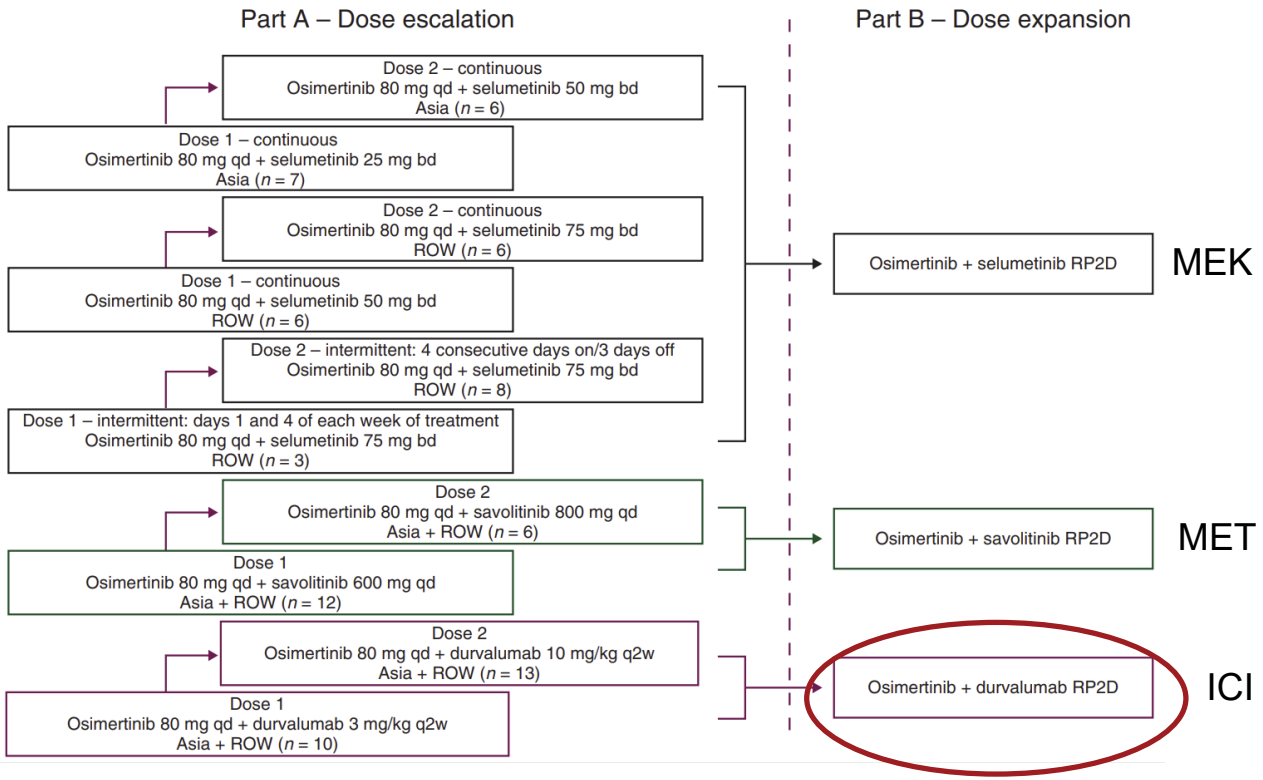


Table 4. Most common all-causality adverse events, reported in ≥20% of patients in the osimertinib plus durvalumab arm

	Durvalumab			
	3 mg/kg q2w (*n* = 10)		10 mg/kg q2w (*n* = 13)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Patients with any AE	10 (100.0)	6 (60.0)	13 (100.0)	5 (38.5)
Rash[a]	5 (50.0)	1 (10.0)	6 (46.2)	0
Vomiting	7 (70.0)	1 (10.0)	3 (23.1)	0
Diarrhea	3 (30.0)	0	6 (46.2)	0
Nausea	4 (40.0)	0	4 (30.8)	0
Decreased appetite	3 (30.0)	1 (10.0)	4 (30.8)	0
Dry skin[a]	3 (30.0)	0	4 (30.8)	0
Anemia	4 (40.0)	0	2 (15.4)	1 (7.7)
Constipation	3 (30.0)	0	3 (23.1)	0
Fatigue	3 (30.0)	0	3 (23.1)	0
ILD[a]	2 (20.0)	1 (10.0)	3 (23.1)	1 (7.7)
Pyrexia	2 (20.0)	0	3 (23.1)	1 (7.7)

Excess risk of ILD when osimertinib given concurrently with durvalumab (22% on study vs ~3% historical rate), development of this combination was discontinued

Ahn et al. J Thorac Oncol. 2022

First- or Second-Generation EGFR TKIs + ICIs?

Afatinib + pembrolizumab for squamous NSCLC (LUX-Lung-IO), n = 24

- **4 patients (17%) had TRAEs of pneumonia or pneumonitis,** 1 patient had immune-mediated hepatitis

Erlotinib or gefitinib + pembrolizumab 1L for EGFRm NSCLC (KEYNOTE-021, cohorts E and F)

- **Gefitinib: G3/G4 hepatotoxicity in 5 out of 7 patients (71.4%),** onset at 29-65 days treatment
- **Erlotinib: G3 hepatotoxicity in 1 out of 12 patients**

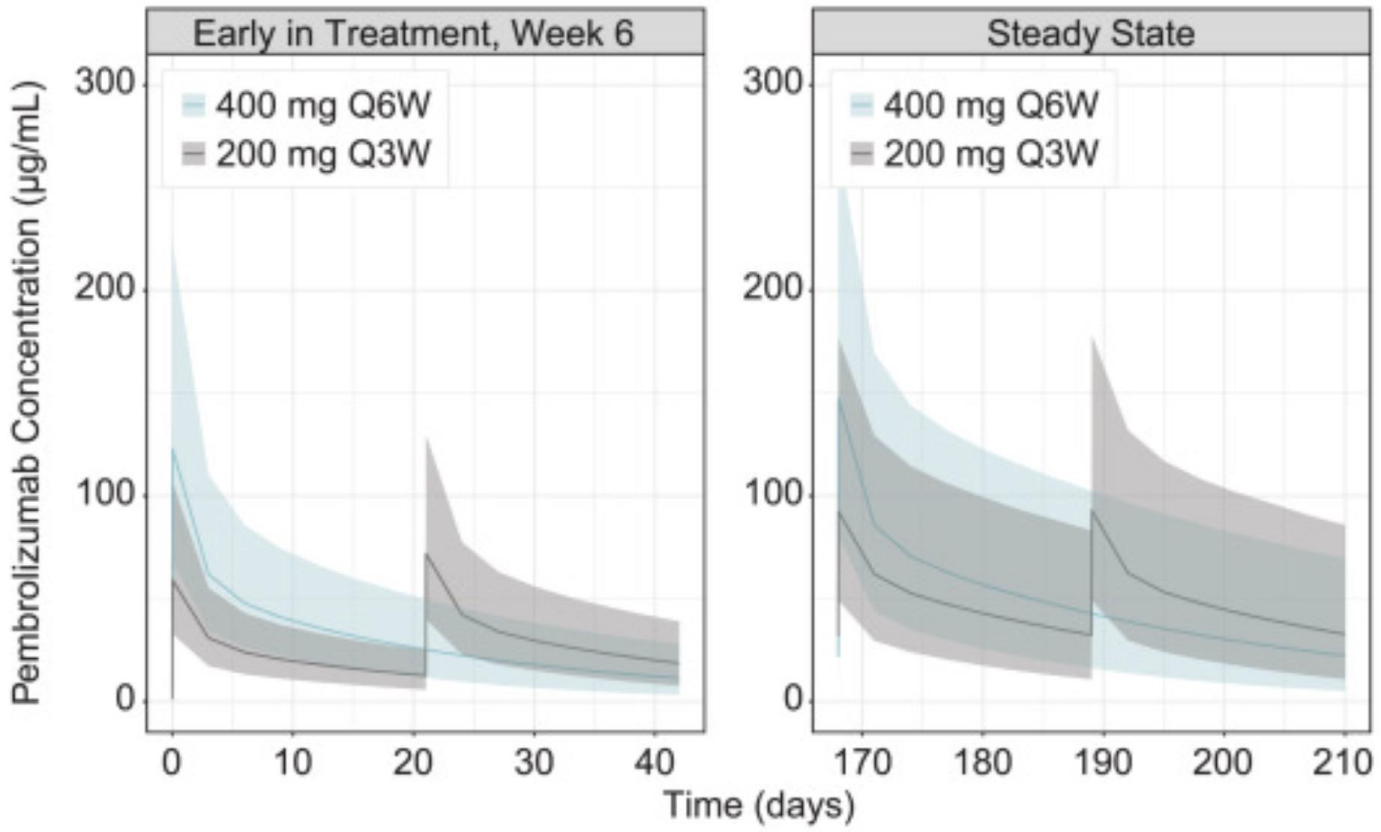
Erlotinib + atezolizumab (EGFR wt and EGFRm NSCLC),n = 28

- **One patient (4%) with G1 pneumonitis**
- **One patient (4%) with G3 elevated ALT**

Clinical benefits have not been demonstrated and these combinations are not used in clinical practice

Levy et al. Lung Cancer. 2022;166:107-113; Yang et al. J Thorac Oncol. 2019;14(3):553-559; Rudin et al. ESMO Open. 2023;8(2):101160.

Current checkpoint inhibitor immunotherapies remain in circulation for many months, creating potential de facto combination therapy with next-line therapy

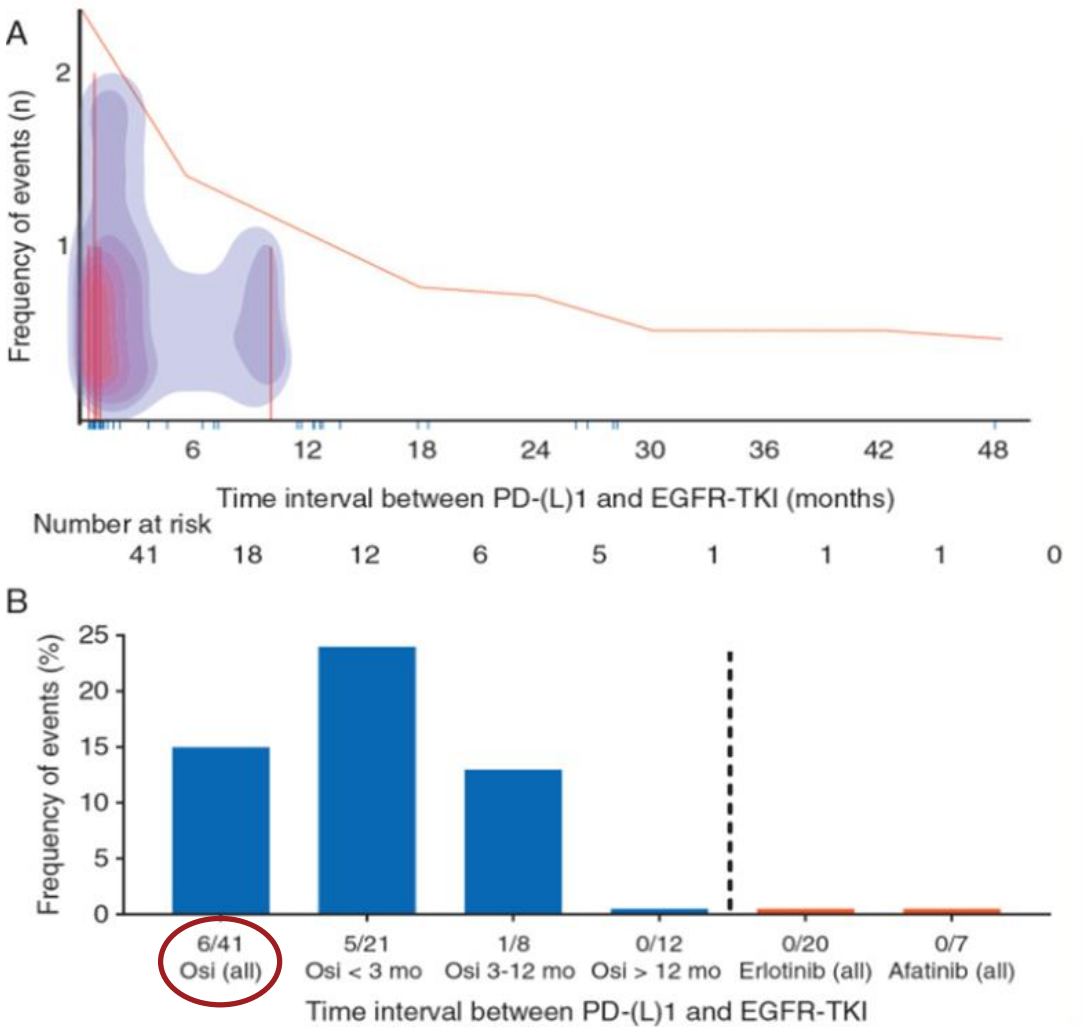


Pembrolizumab $t_{1/2}$ is 22 days → five half lives requires >3.5 months

Creates opportunity for long dosing intervals, Q3W vs Q6W modeling shown here

Pembrolizumab package insert; Lala et al Eur J Cancer. 2020;131:68-75.

EGFR TKIs given sequentially after ICI therapy



Schoenfeld et al. Annals of Oncology. 2019;30:839-44

Six of 41 patients treated with osimertinib post-ICI had a severe irAE, all but one in the first three months treatment

- Pneumonitis (n=3, 7%), colitis (n=1), hepatitis (n=4)
- Four additional patients had dyspnea treated with steroids empirically, indeterminate for an irAE, not included in the figure → ?17% rate
- Median 20 days to onset

Rechallenge with TKI post irAE?

- 4 of 5 patients successfully rechallenged, all successful rechallenges either with >2 month delay or with earlier generation TKI

No patients treated with erlotinib or afatinib had irAEs

Safety of ALK inhibitors in combination with ICIs

Crizotinib

- Crizotinib + nivolumab (CheckMate 370, n = 13): **38% G3+ hepatotoxicity**
- Crizotinib + pembrolizumab: Excess hepatotoxicity/DLTs, **early closure**
- Crizotinib + avelumab (JAVELIN 101, n = 12), **42% DLT rate**

Ceritinib

- Ceritinib + nivolumab, n = 36, 14-32% G3+ increased transaminates,64% rash, 14% G3+ lipase. **Discontinued for intolerability.**

Alectinib

- Alectinib + atezolizumab, n = 21. **10% G3 elevated ALT or bilirubin, 19% G3 rash**
- Grade 3 AE rate 67% (vs 30% expected for monotherapy)

Lorlatinib

- Lorlatinib + Avelumab (JAVELIN 101), n = 15; 11% rash, 11% G3 GGT increase. Combination felt comparable to expected monotherapy toxicities

Spigel et al. J Thorac Oncol (2018) 13(5):682–8; Felip et al. J Thorac Oncol (2020) 15(3):392–403; Kim et al. JTO Clin Res Rep. 2022;3(8):100367; Shaw et al J Clin Oncol (2018) 36:9008; Patel at al Oncologist 2020 25(7):561-e1012.

Sequential ALK inhibitors? Crizotinib after ICI Exposure

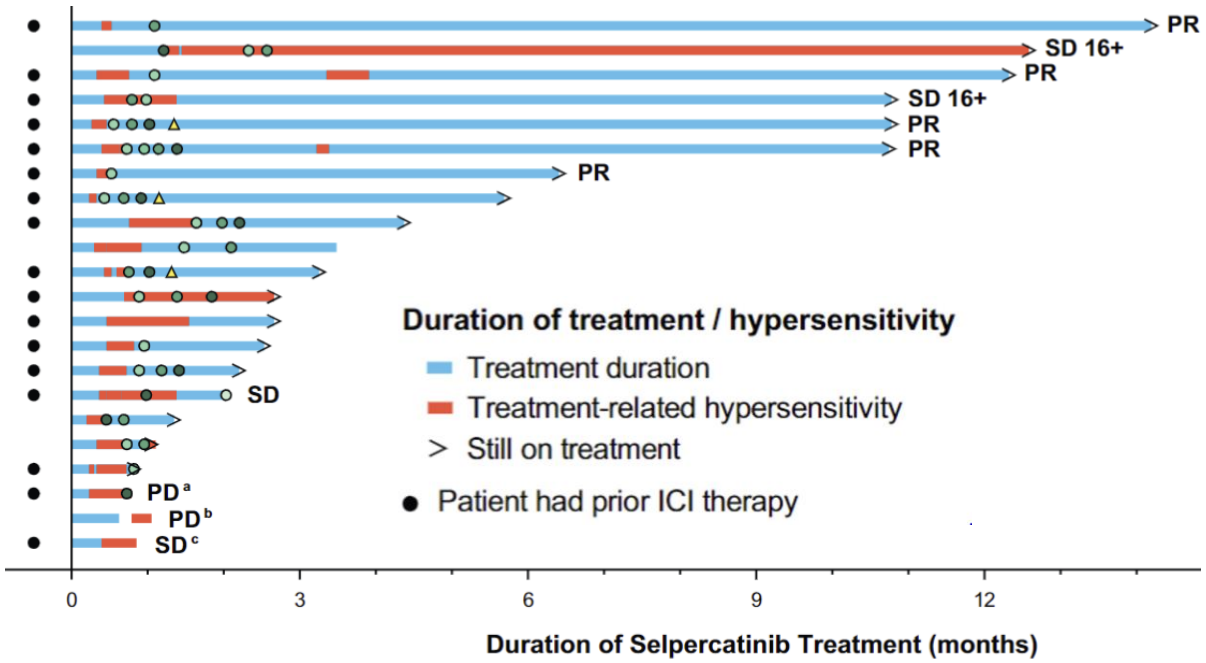
Table 2. Increase in ALT/AST Level with Crizotinib after an ICI versus with Crizotinib Alone

	Patients, n		Cumulative Incidence of Liver Toxicity		
Increase in ALT/AST Level	Total	Liver Toxicity	Point Estimate, %	(95% CI)	*p* Value
Grade 3/4 increase in ALT level					<0.0001
ICI → TKI	11	5	45.5	(14.9-72.2)	
TKI	442	34	8.1	(5.7-11.0)	
Grade 4 increase in ALT level					<0.0001
ICI → TKI	11	3	27.3	(5.8-55.4)	
TKI	442	4	0.9	(0.3-2.2)	
Grade 3/4 increase in AST level					<0.0001
ICI → TKI	11	4	36.4	(10.0-64.2)	
TKI	442	14	3.4	(1.9-5.5)	
Grade 4 increase in AST level					<0.0001
ICI → TKI	11	3	27.3	(5.8-55.4)	
TKI	442	1	0.2	(0.02-1.3)	

Note: Grading is per the Common Terminology Criteria for Adverse Events, version 4.0.
Point estimate is reported at the time of last observed event.
ALT, alanine transaminase; AST, aspartate transaminase; TKI, tyrosine kinase inhibitor; ICI, immune checkpoint inhibitor; CI, confidence interval.

Lin et al. J Thorac Oncol. 2019;14(1):135-140.

RET Inhibitors
Data from LIBRETTO-001, Selpercatinib for RET+ Solid Tumors



	Prior ICI	No Prior ICI
Hypersensitivity (n=22)	11.2%	2.8%
Serious TEAE Hypersensitivity (n = 9)	5.3%	2.3%

There was a modest increase hypersensitivity reactions to selpercatinib when given following checkpoint inhibitors
These were generally manageable and did not prevent subsequent ongoing therapy

McCoach et al. J Thorac Oncol. 2022;17(6):768-778

BRAF/ICI Combinations Tolerable in Melanoma

KEYNOTE-022: Dabrafenib/Trametinib + Pembrolizumab

G3+ AST Elevation (8.3% vs 5.0%), AST 6.7% vs 5%, Fever 11.7 vs 5%, pneumonitis 6.7 vs 1.7%

COMBI-i: Dabrafenib/trametinib + Spartalizumab: G3+ TRAES 17% pyrexia, 11% lipase, 8% GGT inc, 8% CPK increase, 11% neutropenia

DREAMseq:

DREAMseq (Doublet, Randomized Evaluation in Advanced Melanoma Sequencing): A phase III trial—ECOG-ACRIN EA6134

@pawel_sobczuk

#ASCOPlenarySeries

AIM: to compare the efficacy and toxicity of the sequence of nivolumab/ipilimumab followed by dabrafenib/trametinib to the converse sequence

PATINETS: treatment-naive BRAFV600-mutant advanced melanoma, ECOG 0-1

1:1

265 pts

Nivolumab + Ipilimumab N=133 → PD → Dabrafenib + Trametinib N=24

ORR 46%

G3+ toxicity: 60%

ORR 48%

Dabrafenib + Trametinib N=132 → PD → Nivolumab + Ipilimumab N=46

ORR 43%

G3+ toxicity: 52%

ORR 30%

Median follow-up: 27.7 months

2-year OS

72%

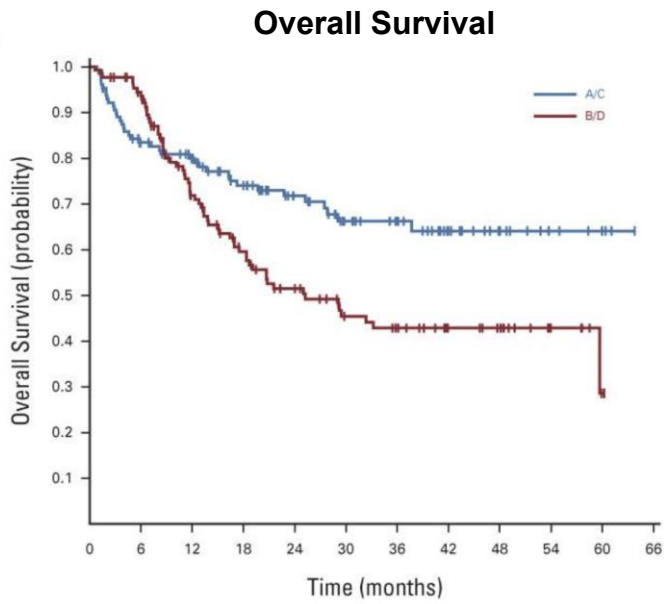
vs

52%

p=0.0095

CONCLUSION:

- **the treatment sequence beginning with Nivolumab+Ipilimumab resulted in superior OS**
- **The difference became evident at 10 months**

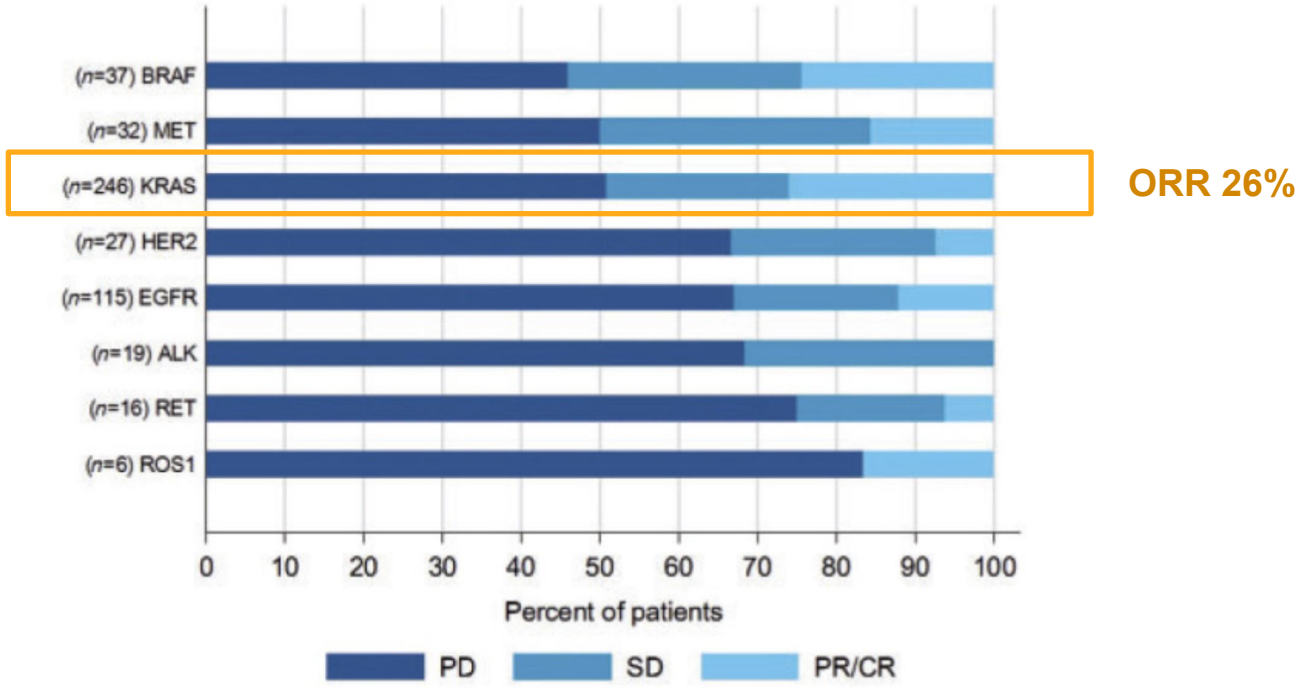


Ascierto et al Nat Med 25:941-946, 2019; Dummer er al. Nat Med 26:1557-1563, 2020; Atkins et al. J Clin Oncol. 2023;41(2):186-197; Atkins et al J Clin Oncol 2023..

What about KRAS inhibitor combinations, where ICI activity is expected?

Do sequential toxicity concerns apply for KRAS inhibitors in the second line setting?

Can RAS inhibitors replace chemotherapy in first-line ICI combinations?



ORR 26%

Mazieres et al Ann Oncol. 2019

CodeBreaK 100/101: Sotorasib + Pembrolizumab

TRAE, n (%)	Sotorasib 120 mg (N = 5)		Sotorasib 360 mg (N = 8)		Sotorasib 720 mg (N = 2)		Sotorasib 960 mg (N = 4)	
	Any	Grade ≥ 3	Any	Grade ≥ 3	Any	Grade ≥ 3	Any	Grade ≥ 3
All TRAEs	5 (100)	4 (80)	7 (88)	6 (75)	2 (100)	2 (100)	3 (75)	3 (75)
Hepatotoxicity	2 (40)	2 (40)	3 (38)	2 (25)	2 (100)	2 (100)	3 (75)	3 (75)
ALT increased	2 (40)	1 (20)	3 (38)	1 (13)	2 (100)	2 (100)	3 (75)	3 (75)
AST increased	2 (40)	2 (40)	3 (38)	0	2 (100)	2 (100)	3 (75)	1 (25)

Excess hepatotoxicity with concurrent pembrolizumab

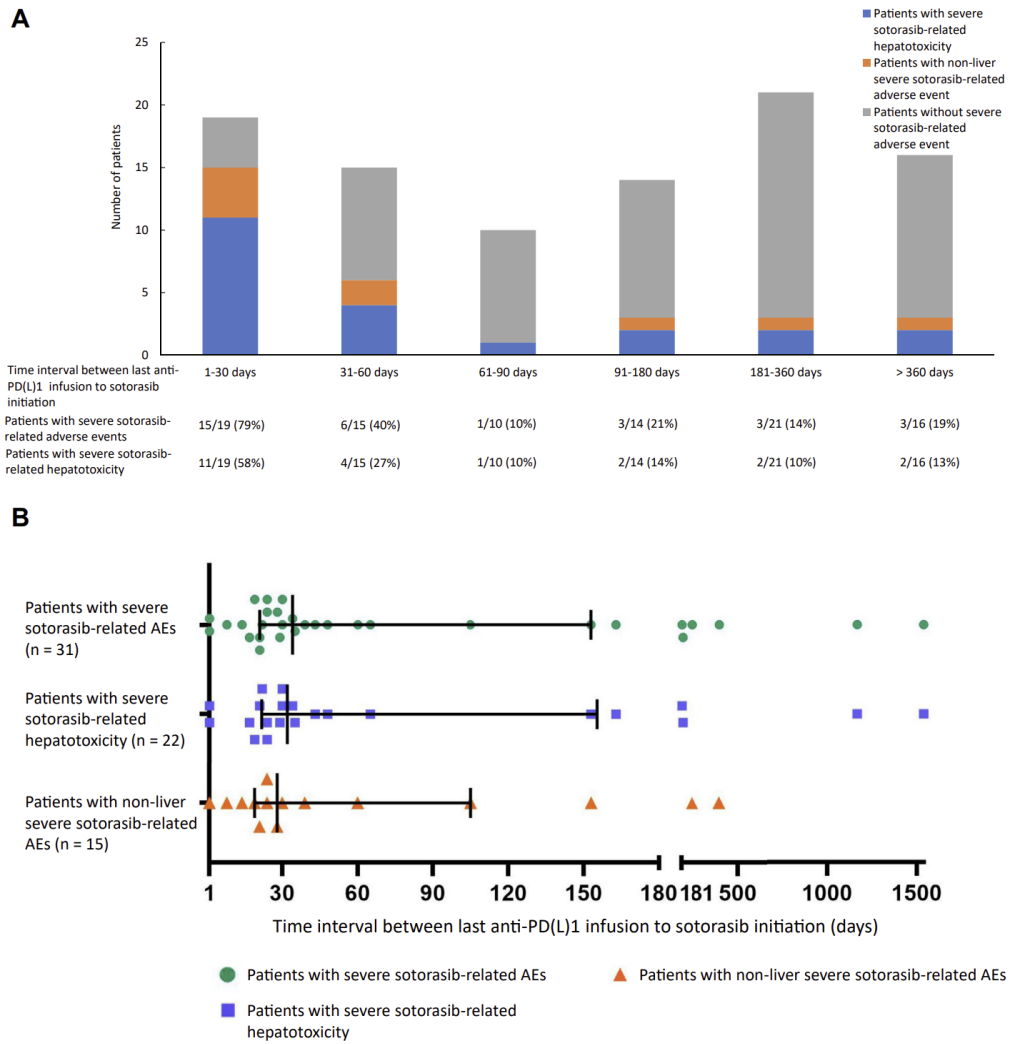
Safety for Sotorasib Lead-in + Pembrolizumab

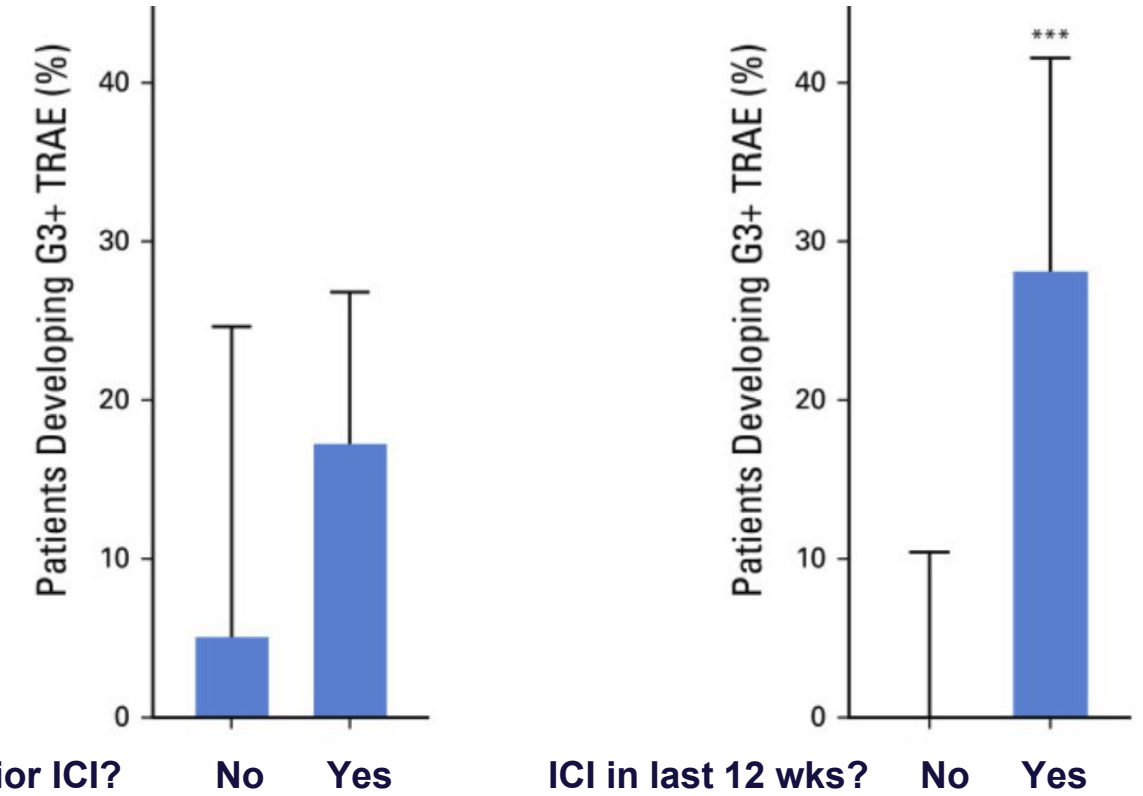
TRAE*, n (%)	Sotorasib 120 mg (N = 3)		Sotorasib 240 mg (N = 5)		Sotorasib 360 mg (N = 11)	
	Any	Grade ≥ 3	Any	Grade ≥ 3	Any	Grade ≥ 3
All TRAEs	3 (100)	3 (100)	3 (60)	1 (20)	9 (82)	6 (55)
ALT increased	2 (67)	2 (67)	1 (20)	1 (20)	6 (55)	3 (27)
AST increased	2 (67)	2 (67)	1 (20)	1 (20)	6 (55)	2 (18)
ALP increased	2 (67)	0	0	0	3 (27)	2 (18)
Diarrhea	1 (33)	0	1 (20)	0	6 (55)	1 (9)
Arthralgia	1 (33)	0	0	0	2 (18)	0
Nausea	0	0	0	0	4 (36)	0
Fatigue	0	0	0	0	4 (36)	0
Hypokalemia	0	0	0	0	3 (27)	2 (18)
Decreased appetite	0	0	0	0	3 (27)	0
Headache	0	0	0	0	2 (18)	0
Hepatotoxicity	2 (67)	2 (67)	2 (40)	1 (20)	6 (55)	5 (45)

A lower dose sotorasib lead-in produced a tolerable AE profile

Li B et al, IASLC WCLC 2022

Increased hepatotoxicity with sotorasib immediately following ICI exposure

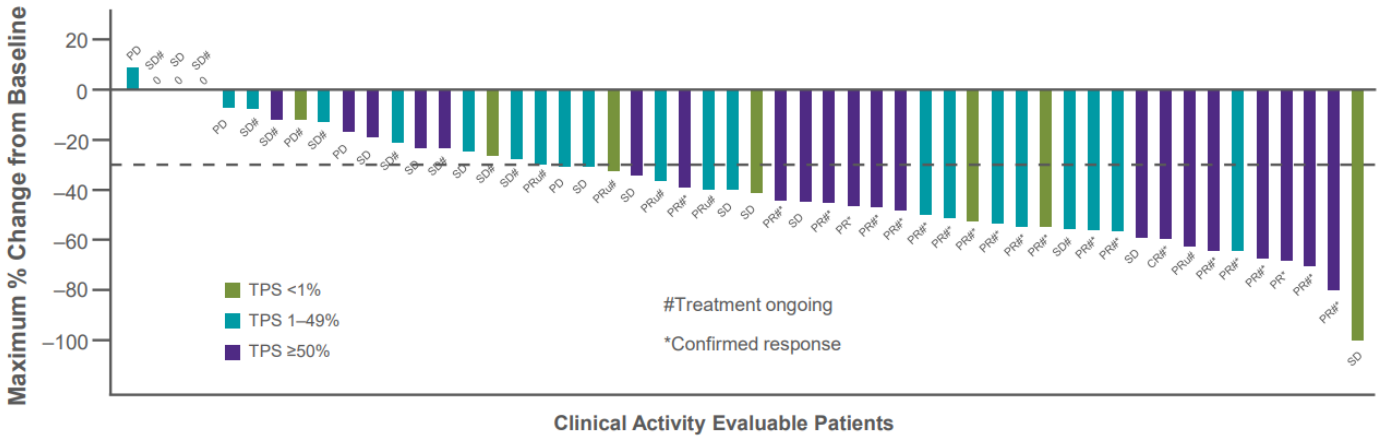




Chour et al. J Thorac Oncol. 2023;

Adapted from Thummalapalli et al JCO Precis Oncol 2023

KRYSTAL-7: First-line Adagrasib + Pembrolizumab in KRAS G12C+ NSCLC



Unconfirmed ORR (all PD-L1 scores) 49%

- ***Combination with acceptable side effect profile***
- ***10-14% rate of G3+ AST, ALT increase***

Most Frequent Liver TRAEs, %	Concurrent 400 mg BID Adagrasib + Pembrolizumab (N=148)				
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4
ALT increase	38	15	13	9	1
AST increase	32	10	8	13	1
Hepatitis	4	0	2	2	0
Hepatotoxicity[a]	1	0	1	1	0
Liver injury	1	0	1	0	0
Drug-induced liver injury	1	1	0	0	0
Hepatic failure	1	0	0	1	0
Acute hepatitis	1	0	1	0	0
Immune-mediated hepatitis	1	0	0	1	0

Jänne et al, ESMO IO 2022

Take Away Points

- The use of oncogene-targeted therapies in the initial months following checkpoint inhibitor immunotherapy can carry increased risk of toxicity. This risk appears greatest in the first three months following ICI treatment.

- Risk assessment likely must be assessed at the drug level rather than by drug target

- **Identifying actionable oncogenes prior to immunotherapy initiation remains essential to avoid treatment with ineffective regimens and reduce risk of toxicity**