Society for Immunotherapy of Cancer

Advances in Cancer Immunotherapy™

Patient Selection based on Safety Concerns

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Outline

- **Toxicity:**
  - Autoimmune conditions/Prior irAEs
  - Organ Transplants

- **Poor Functional Status:**
  - Performance Status 2
  - Elderly

- **'Untested' Populations:**
  - Paraneoplastic Syndromes

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Prior Autoimmune Conditions: The Melanoma Experience

PD-1

- 55/119 pts prior AID received anti-PD-1
- ORR= 33%
- 38% (20/119): AID flare
- 29% (15/119): other irAE
- 8% (4/119): stopped Tx

Overall, tolerable

CTLA-4

- 67/119 with prior CTLA-4 irAEs, received anti-PD-1
- 3% (2/67): same irAE
- 38% (23/67): new irAEs
- 12% (8/67): stopped Tx

Overall, tolerable

PD-1/CTLA-4

- 55 pts prior AID
- ORR= 55%
- 33% (18/55): AID flare
- 67% (37/55): other irAE
- 36% (30/55): stopped Tx

Not as Tolerable

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Menzies et al, *Ann Oncol* 2016; Brown et al, *J Immunother Cancer* 2021

Prior Autoimmune Conditions: The NSCLC Experience

56 pts NSCLC + AID

- ORR: 22%
- 23% AID flare (13% G3+)
- 38% other irAE (26% G3+)

- 6-mo cumulative incidence flare: 21%
- 18-mo cumulative incidence flare: 23%

21 patients with irAEs (23 irAEs)

- 29% G3+ irAEs
- 14% stopped PD-(L)1
- 5% flare + irAE

- No association baseline steroids & response
- No association flare & response

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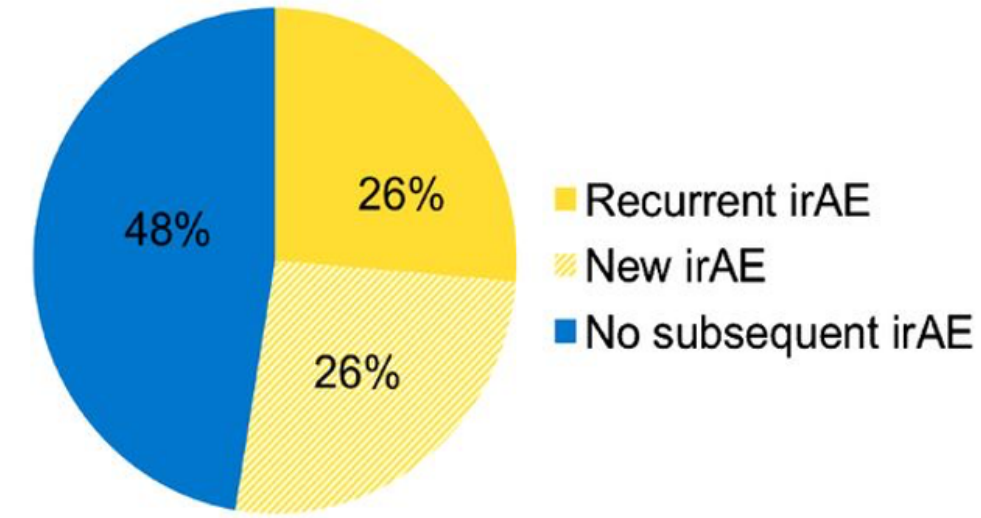
Leonardi et al, *J Clin Oncol* 2018

When to re-challenge?

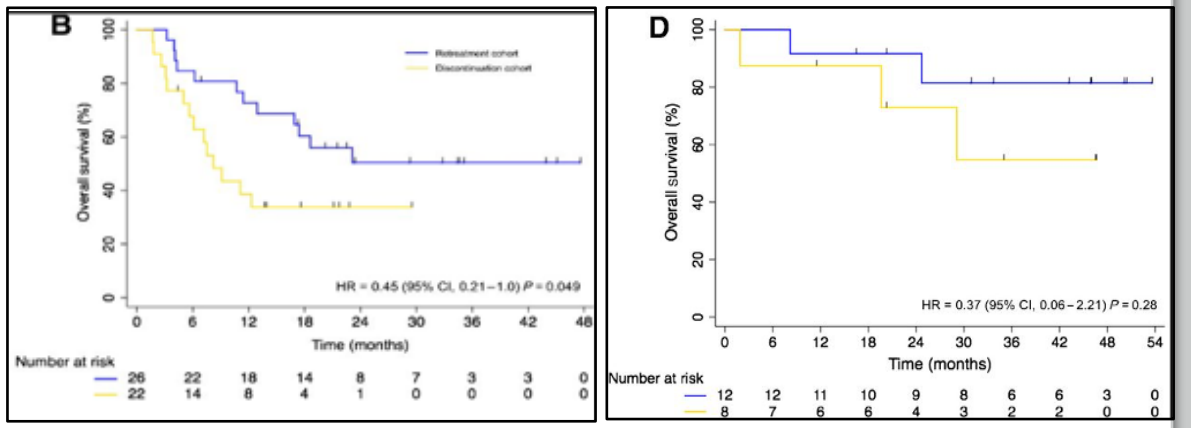
MSKCC Experience: 482 PD(L)1-treated NSCLC pts:

- 68 had irAE warranting therapy hold
- 30 permanently discontinued

38 patients rechallenged: Outcomes

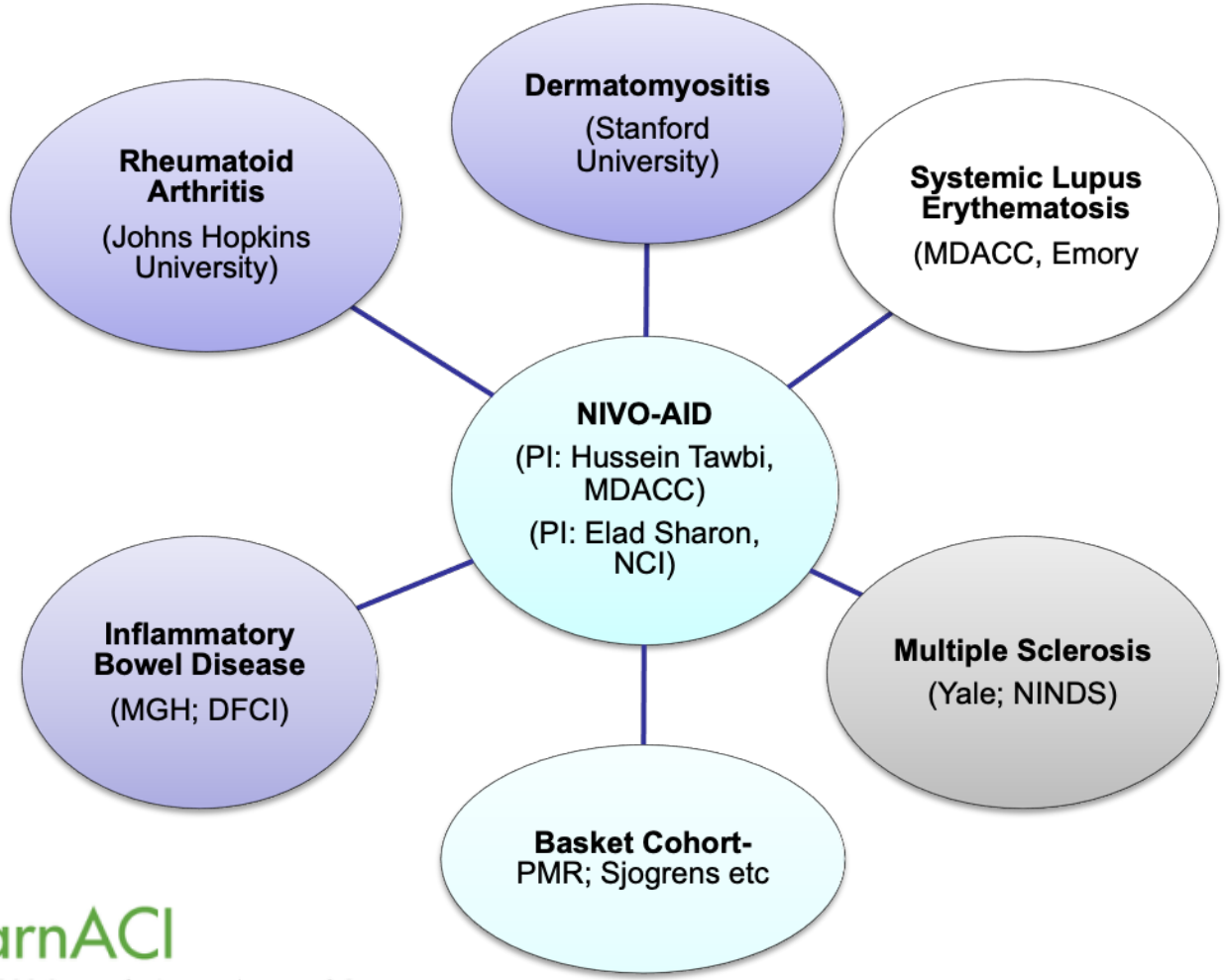


OS in those with v without ICI response prior to re-challenge



Santini et al, *Cancer Immunol Res* 2019

NCI-10204 (NIVO-AID): Nivolumab in patients with prior autoimmune disease



Primary Objective:

Establish safety, dose-limiting toxicity, associated with nivolumab in patients with varying severity of specific autoimmune diseases.

Study Status:

Open and enrolling at 8 sites

Goal of 39 sites

Goal accrual 384 patients

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Organ Transplant
Response to ICI and Organ Rejection

Characteristic	Total	Rejection	No rejection	p
Median age (yrs)	63.8	63	65.5	0.48
Time to ICI since transplant (median yrs, range)	8 (0.75-32)	6 (0.75-27.6)	8 (0.75-32)	0.74
Solid Organ Transplant				
Kidney	39	18 (46)	21 (54)	0.34
Liver	19	6 (32)	13 (68)	
Heart	5	1 (20)	4 (80)	
Cornea	1	1 (100)	0 (0)	
Type of ICI				
CTLA-4	13	3 (23)	10 (77)	0.45
PD-(L)1	43	20 (47)	23 (53)	
Sequential	8	3 (37.5)	5 (62.5)	
Responder to ICI (all)	25	9 (37.5)	16 (62.5)	0.8
CTLA-4	7	1 (14)	6 (86)	
PD-(L)1	15	6 (40)	9 (60)	
Sequential	3	2 (66)	1 (33)	

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Kumar et al, *Oncologist* 2019

Clinical Trials of ICI+Transplant
Nivo+Ipi+Tacrolimus in Renal Transplant

Background

Solid organ transplant recipients
- +50x risk of selected cancers

ICI can be effective against cancers in chronically immunosuppressed

Transplant recipients excluded from ICI trials due to risk of allograft rejection/loss

Study Design

Investigator-initiated phase 1/2 clinical trial testing
nivolumab + tacrolimus + prednisone
Patients with progressive disease at 16 wks may receive ipilimumab

Study population:

Adult kidney transplant recipients
Melanoma, Basal cell, Cutaneous squamous cell, Merkel cell and MSI-high cancers

Primary objective:

Estimate % durable clinical benefit
(RECIST v1.1) without allograft loss at 16 wks

ETCTN Experimental Therapeutics Clinical Trials Network
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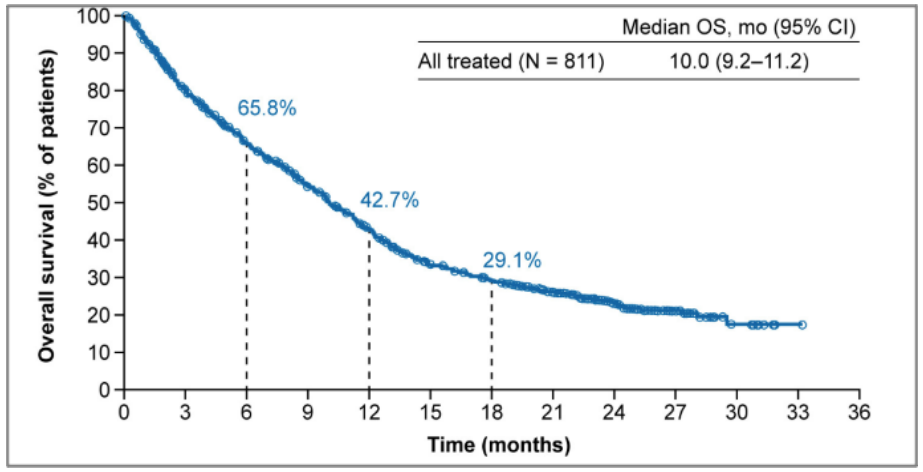
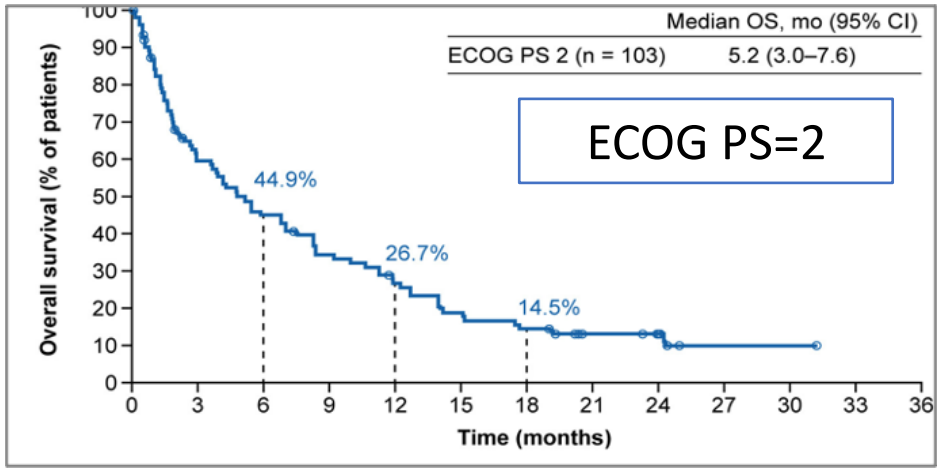
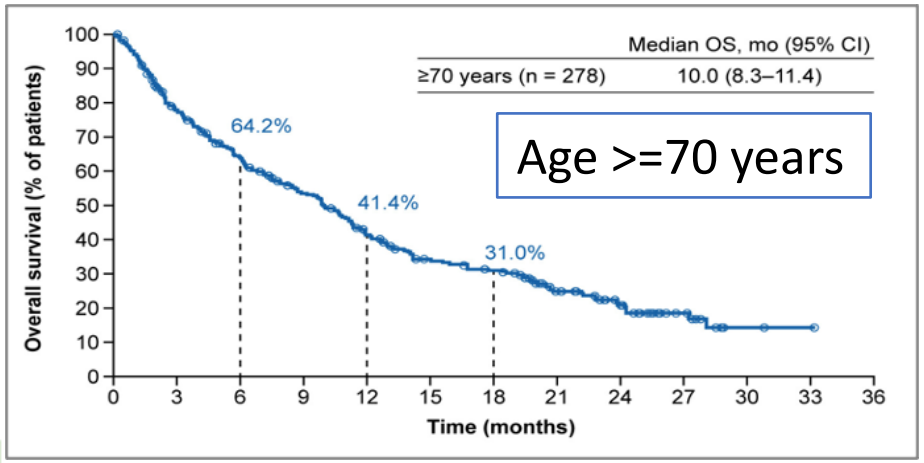
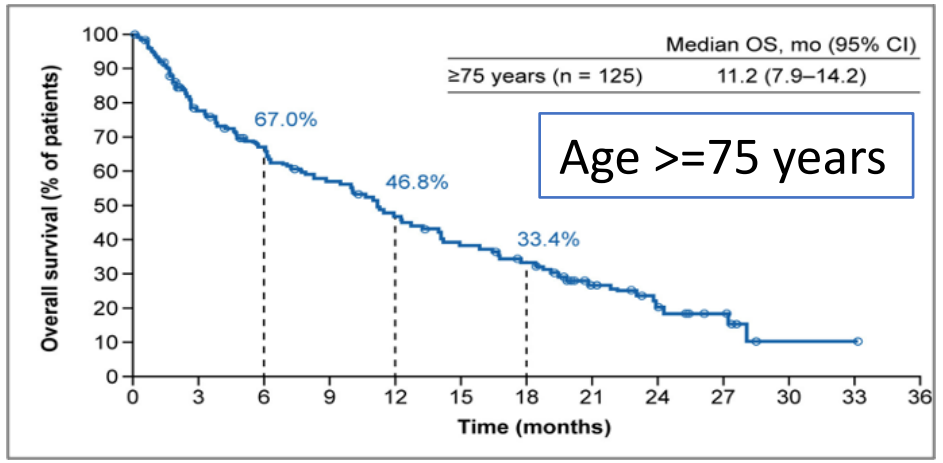
CM-171
Nivolumab in Squamous NSCLC: ECOG PS 2 + Elderly









Felip et al, *Eur J Cancer* 2020

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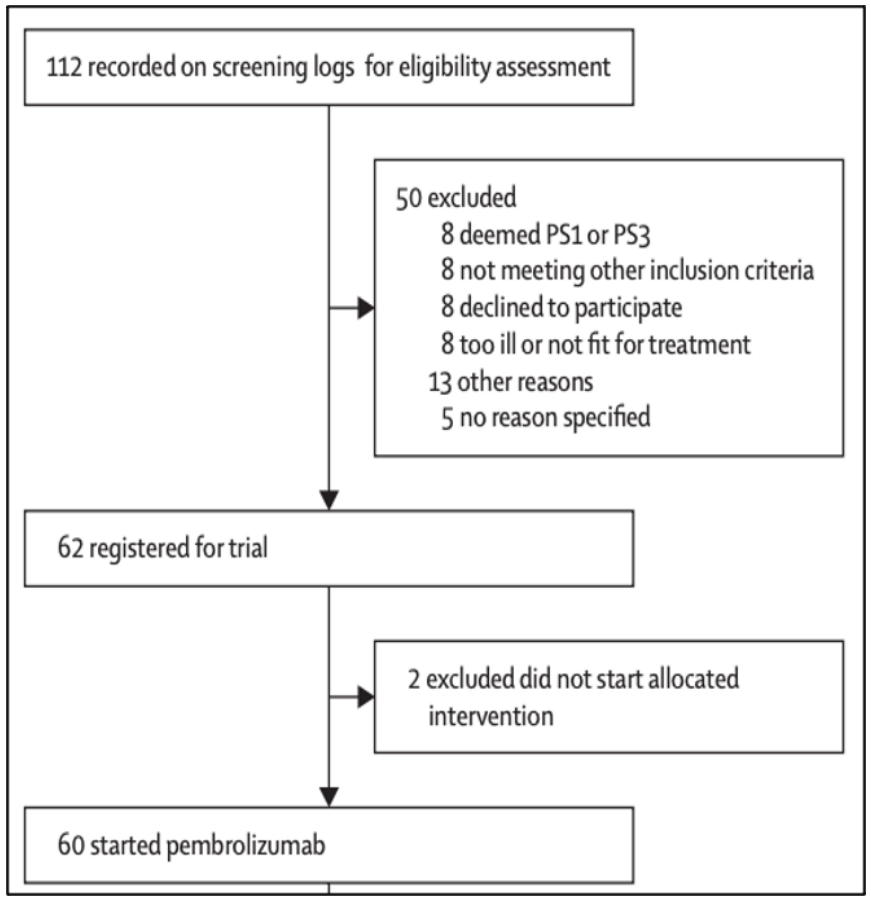
PePs2: Pembrolizumab in PD-L1>1% Advanced NSCLC ECOG PS 2



	Durable clinical benefit incidence	Toxicity incidence	Objective response incidence
All (n=60)	37% (22; 26–49)	28% (17; 19–41)	27% (16; 17–39)
Line of therapy			
First-line (n=24)	38% (9; 21–57)	29% (7; 15–49)	21% (5; 9–40)
Subsequent-line (n=36)	36% (13; 22–52)	28% (10; 16–44)	31% (11; 18–47)
PD-L1 tumour proportion score			
<1% (n=27)	22% (6; 11–41)	26% (7; 13–45)	11% (3; 4–28)
1–49% (n=15)	47% (7; 25–70)	13% (2; 4–38)	33% (5; 15–58)
≥50% (n=15)	53% (8; 30–75)	40% (6; 20–64)	47% (7; 25–70)
Unknown (n=3)	NE (n=1)	NE (n=2)	NE (n=1)

Middleton et al, *Lancet Respir Med* 2020

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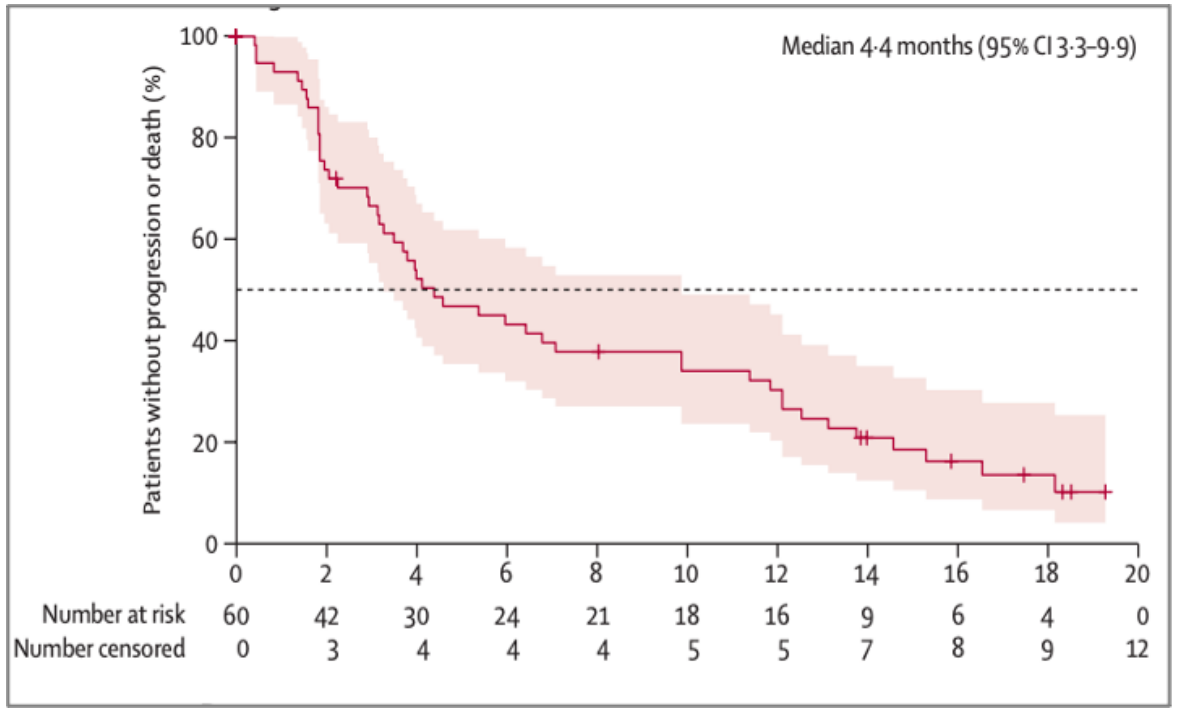
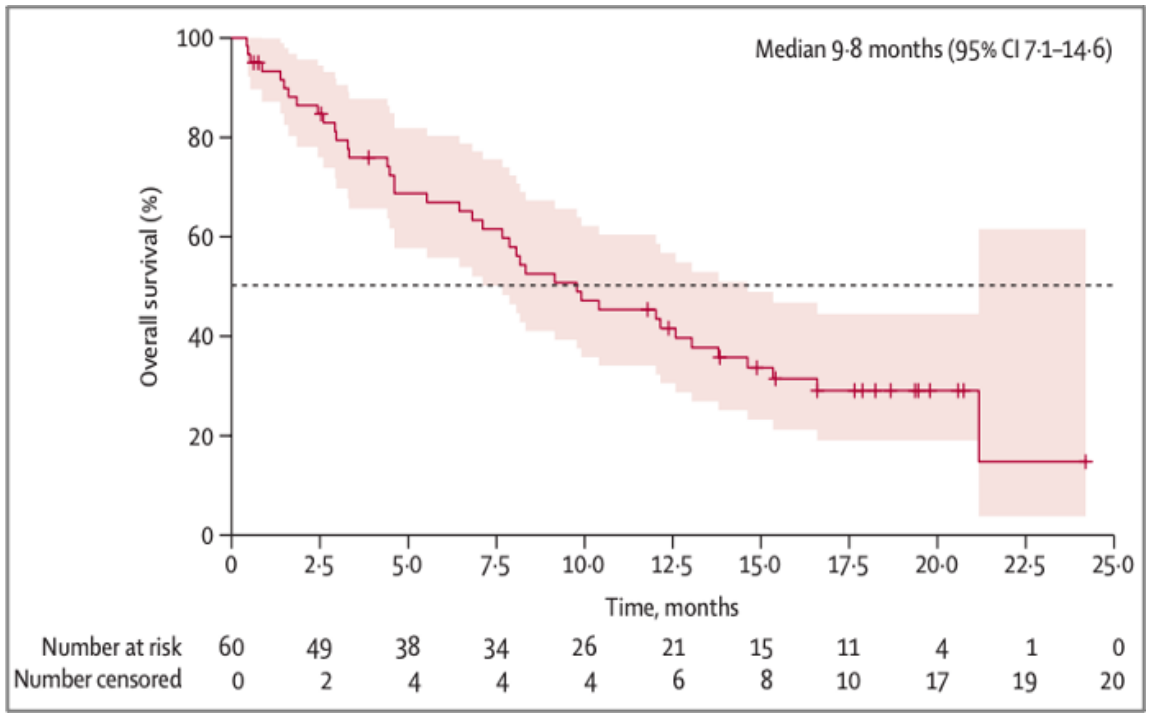
PePs2

Progression-Free Survival



Overall Survival



Middleton et al, *Lancet Respir Med* 2020

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CM817: Nivo/Ipi in First-line Advanced NSCLC and ECOG PS 2

- Multi cohort ph III/IV study
- Cohort A1 (n=198): ECOG PS 2 or ECOG PS 0–1 with 1 of: Asymptomatic brain metastases, Hepatic, Renal impairment, HIV.
- Cohort A (n=391) ECOG PS 0–1.
- Nivo 240 mg Q2W + Ipi 1 mg/kg Q6W x 2 years or until disease progression/toxicity
- Safety and efficacy endpoints

CheckMate 817 safety	Cohort A1			Cohort A
	All treated (n=198)	ECOG PS 2 (n=139)	AOSP[b] (n=59)	All treated[1] (n=391)
TRAEs n, (%) Any grade Grade 3–4	 132 (67) 54 (27)	 86 (62) 34 (24)	 46 (78) 20 (34)	 295 (75) 123 (31)
TRAEs leading to discontinuation, n (%) Any grade Grade 3–4	 30 (15) 23 (12)	 20 (14) 16 (12)	 10 (17) 7 (12)	 69 (18) 52 (13)
Treatment-related deaths, n	2[c]	2[c]	0	2[d]
CheckMate 817 efficacy	**Cohort A1**			**Cohort A**
Objective response rate n/N % 95% CI	 50/198 25 19.4–31.9	 28/139 20 13.8–27.8	 22/59 37 25.0–50.9	 136/391 35 30.1–39.7

Barlesi et al, *J Thoracic Oncol* 2019

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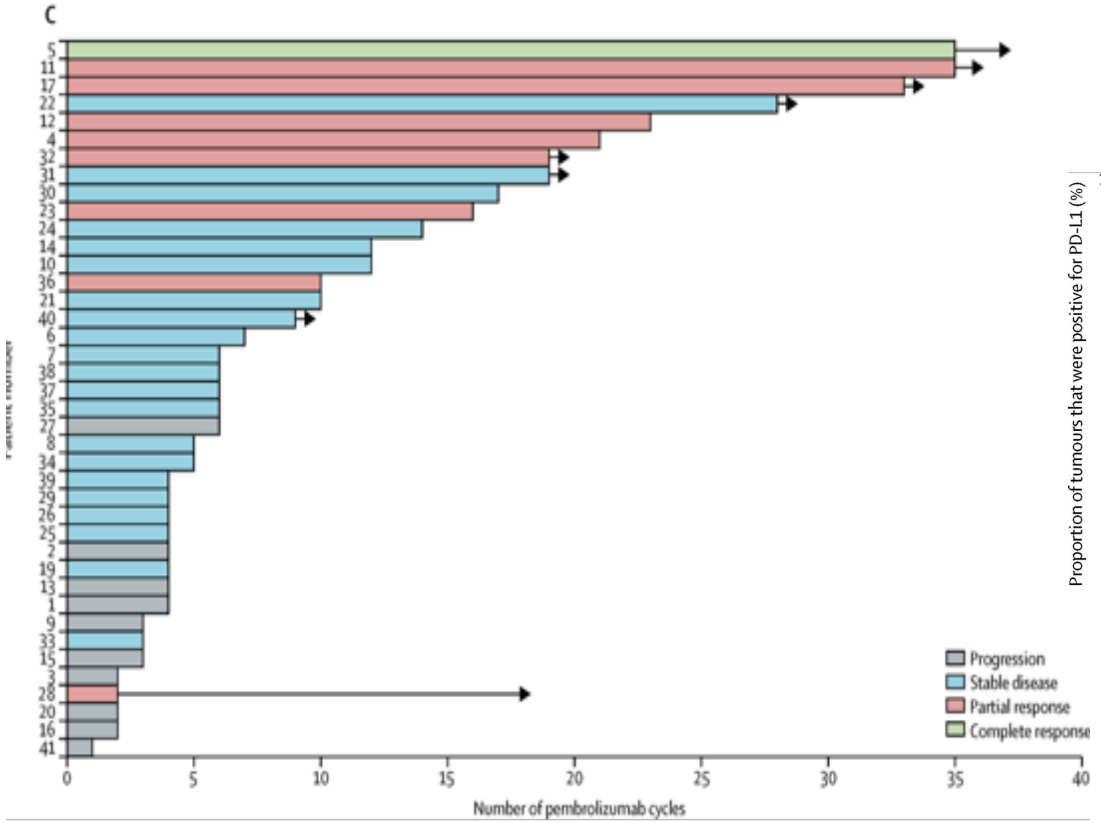
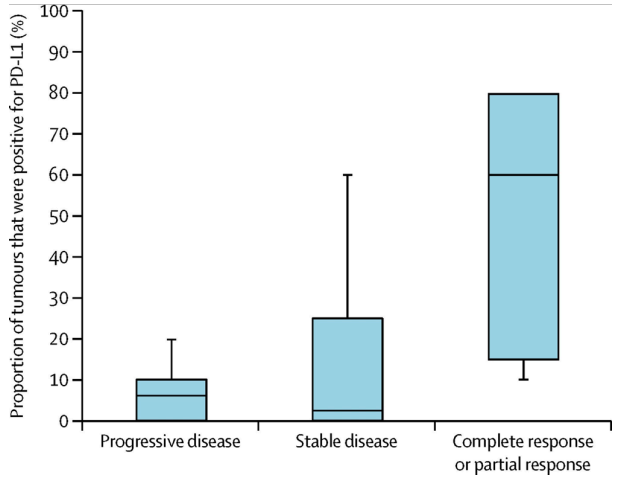
Untested Populations
Paraneoplastic Syndromes





- 15% (6/20 pts) developed severe autoimmune toxicity:
  - myocarditis
  - polymyositis
- Patients with MG or Pure Red Cell Aplasia excluded
- Safety of administering ICIs in those with known paraneoplastic syndromes is unknown

Giaccone et al, *Lancet Oncol* 2018

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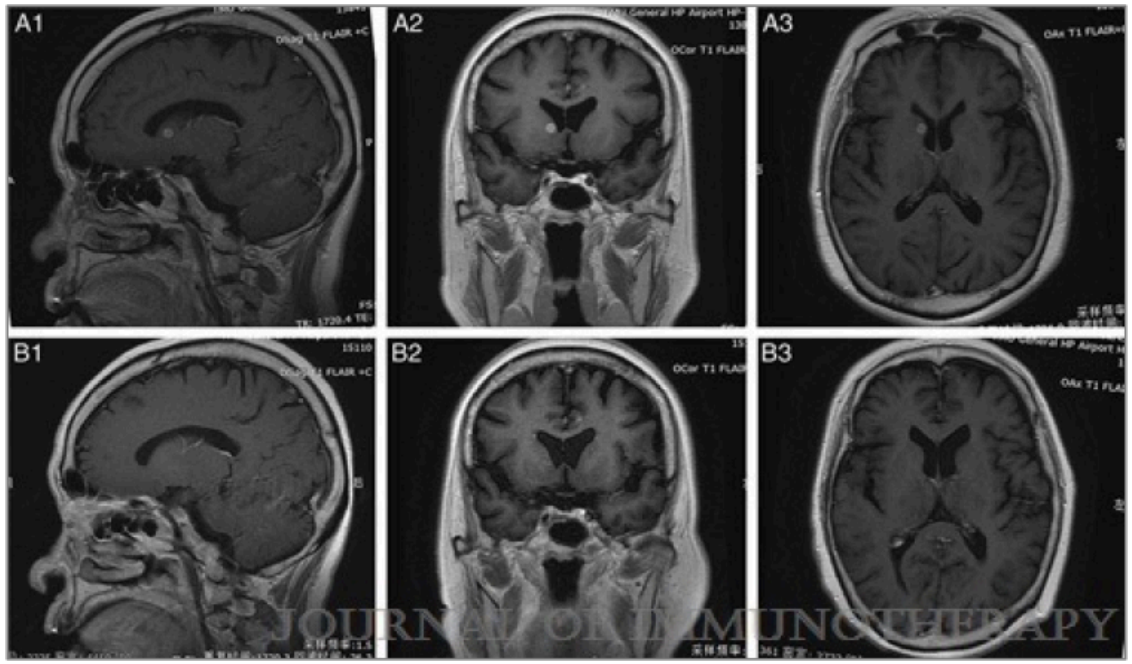
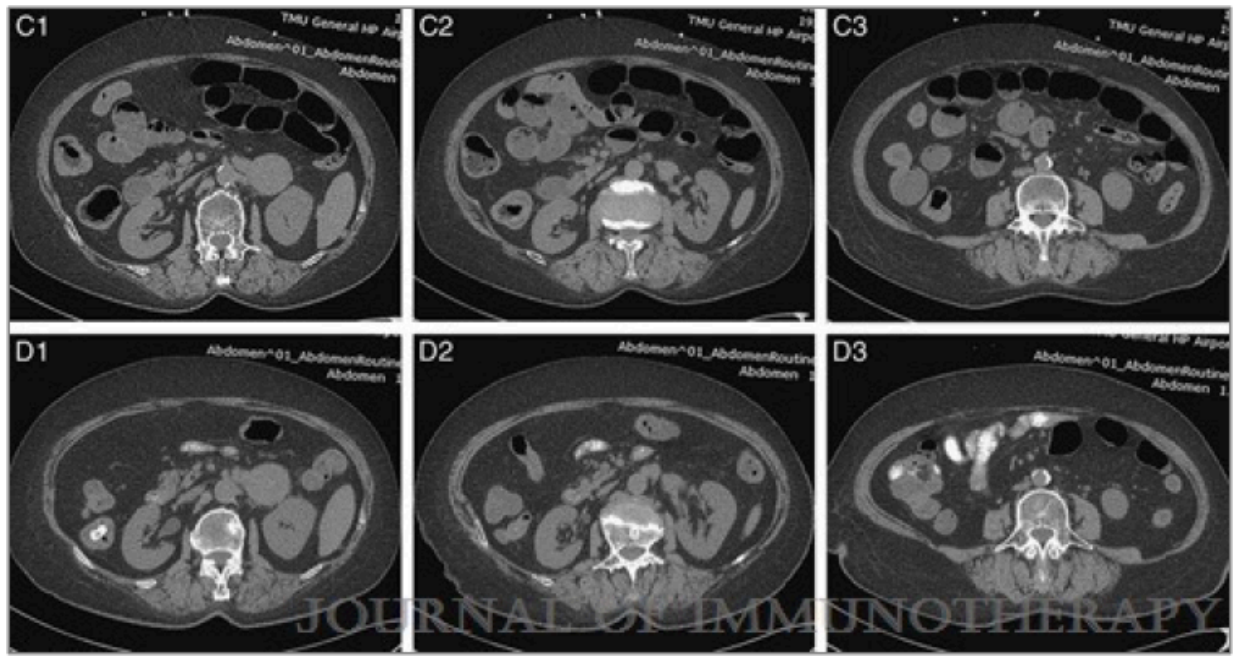
Untested Populations
Paraneoplastic Syndromes

Anti-Hu antibody induced encephalitis & enteric neuropathy in SCLC treated with sintilimab





Kang et al, *J Immunotherapy* 2020

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Patient Selection for ICI based on Safety

Toxicity: - Autoimmune conditions/Prior irAEs - Organ Transplants	- AIDs/prior irAEs do not preclude ICI, tolerability poorer with PD-1/CTLA-4 - Organ Transplant= high rejection risk
Poor Functional Status: - Performance Status 2 - Elderly	- PD-1 and PD-1/CTLA4 may be effective in ECOG PS2, elderly, other high-risk groups (CM171, 817, PePs2)
Untested Populations: - Paraneoplastic Syndromes	- Risk of irAEs/poor outcomes in pts with paraneoplastic syndromes unknown

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Colleagues and Collaborators

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