Rare irAEs cases sharing: Linkuo CGMH experience

林口長庚紀念醫院

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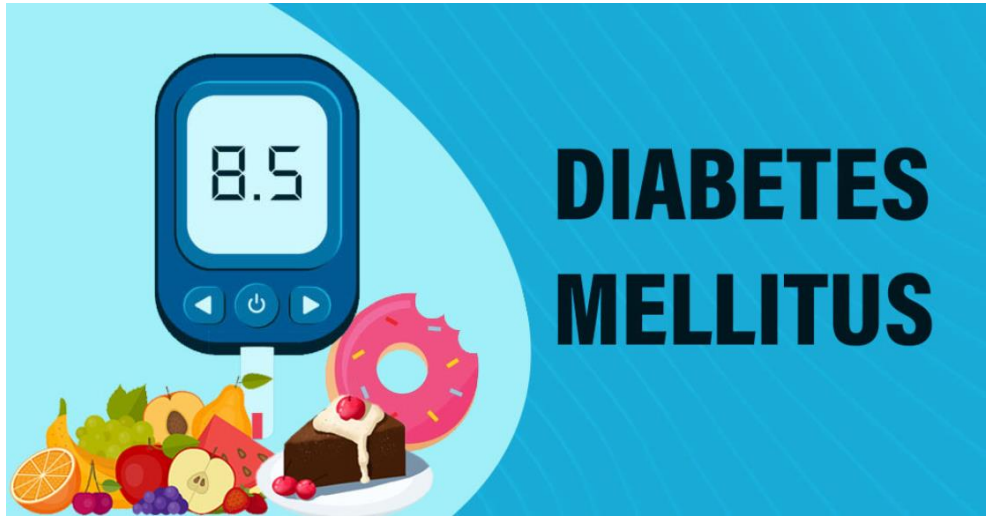
2022-04-16

Outline

- ICI-induced new onset of Type 1 DM
- Refractory irAE hepatitis
- Rechallenge ICI for a patient with ICI-induced SJS

ICI-induced new onset of Type 1 DM



Age (year)	Sex	Diagnosis	ICI	Cycle	Onset (month)	Sugar (mg/dL)	Antibody
75	M	Lung cancer	Nivolumab	42	18	1277	No data
61	F	Ovarian cancer	Pembrolizumab	2	3.5	533	No data
71	M	Melanoma	Nivolumab	20	10.5	496	No data
64	M	RCC	Nivolumab	21	9	1276	No data
66	M	Melanoma	Nivolumab	5	1.5	1032	IA2 Ab (-) GAD Ab (-) ZnT8 Ab (-)
V 88	F	Melanoma	Nivolumab	9	5	994	IA2 Ab (-) GAD Ab (-)

- 2016/06-2021/04; Linkuo CGMH; One doctor
- Male 4, Female 2
- Age (years): mean 71 (61-88)
- Onset: 1.5m-18m (Cycle: 2-42)
- Nivolumab 5, pembrolizumab 1
- All DKA presentation (sugar 496-1277)

✓GAD (glutamic acid decarboxylase)
✓ IA2 (Islet antigen 2)
✓ ZnT8 (Zinc transporter 8)

Patient baseline data

88y/o Female

- Height / Body weight 153cm / 61kg (BMI: 25)

- Underlying disease
  1. Alzheimer disease, regular outpatient department follow up
  2. HCV chronic infection

Cancer profile

April of 2018

- Left 2nd toe acral lentiginous melanoma, pT4aN0M0, stage IIB
  - Left popliteal sentinel lymph node negative
  - 2nd toe amputation on 2018/04/20
  - CT for follow up： Stationary

June of 2019

- Left popliteal mass → echo-guided biopsy on 2019/06/25
- PET result
  1. left second toe + left popliteal mass + bilateral inguinal
  2. left external and internal iliac lymph nodes
- Recurrent metastatic melanoma, TxN3M0, stage IIIC
  - Chemotherapy with DTIC x 5 cycles (2019/7/23 ~ 2019/12/20)

March of 2021

- Body weight lost
- CT on 2021/03/18

  Regrowth of melanoma in left external iliac lymph node

- Nivolumab x 9 cycles, 2021/04/15 ~ 2021/08/26
  - Grade 1: skin pruritus
  - After cycle 8： Grade 2, lichenoid dermatitis over trunk ~20%

2021/09/10

C.C. Lost of consciousness noted at night of 9/10

- The patient could not be woken up at night of 9/10

- Conscious level: E4V1M4
- Finger sugar show high
- Fever up to 38C

- SBP/DBP 85 / 55
- Tachycardia HR 154
- Tachypnea RR 32

項目	20210911 1445
WBC	7.4
Hemoglo...	13.7
Hematocrit	45.9
Platelets	182
Segment	85.4 H
Lymphocy...	6.6 L
Monocyte	7.2
Estimated...	
ALT/GPT	22
Total Bilir...	0.6
Lactate(B)	44.3 H
V Sugar	994 H
BUN	62.9 H
Creatinine	2.83 H
Osmolalit...	415 H

TEMP	37.0	
PH	7.308 L	
PCO2	43.4 H	
PO2	108.1 H	
HCO3	21.2	
SBE	-5.1	
SAT	97.5	
Po2(A-a)		
FIO2		
Temperat...		37
pH(Vein)		7.245 L
pCO2(Vein)		53.8
pO2(Vein)		20.7 L
cHCO3(Ve...		22.8
ctCO2(Vei...		24.5
BEecf(Vein)		-4.5
SAT(Vein)		26.4

V	BloodKet...	5.2 H
	CRP	40.21 H
	Cortisol	39.10 H

- DM induce HHS
- DKA
- Hypovolemic shock

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- DM induce HHS
- DKA
- Hypovolemic shock

• ANA	negative	
• IgG4	negative	
• IgE	267 H	
• Anti-GAD	negative	
• Anti-IA2	negative	(Islet Antigen 2 Antibody)
• C-peptide	0.25 ng/ml	(0.9-4.3)
• HbA1c	7.8%	

- Final diagnosis：

  IRAE induce DM, insulin dependent

Sugar and HbA1c records

Nivolumab: 2021/4/15 (C1) ~ 2021/8/26 (C9)

C9

	5/13	5/27	6/10	6/24	7/8	7/22	8/12	8/26	9/2	9/11	9/13
Sugar	127	142	131	87	117	121	119	127		994	
HbA1c			5.8						5.6		7.8

F/U

- 2021/10/8 CT show PR
- 2021/10/9 Discharge (Insulin detemir 38U hs, insulin aspart 16U tid)
- 2021/10/27 Expired (for certificate, ? cause of death)

PD-1/PD-L1 inhibitors-induced Type 1 DM

- Incidence ~1% (Diabetes 2018;67:1471-80)

Systematic Review or Meta-analysis

Immune checkpoint inhibitor-induced Type 1 diabetes: a systematic review and meta-analysis

H. K. Akturk[1], D. Kahramangil[1], A. Sarwal[2], L. Hoffecker[3], M. H. Murad[4] and A. W. Michels[1]

[1]Barbara Davis Centre for Diabetes, University of Colorado, School of Medicine, Aurora, CO, [2]Department of Biology, University of Colorado, Boulder, CO, [3]Health Sciences Library, University of Colorado, Aurora, CO, and [4]Evidence-Based Practice Centre, Mayo Clinic, Rochester, MN, USA

Diabet.Med. 2019;36:1075-1081.

	All cases (*n*=71)	Nivolumab (*n*=38)	Pembrolizumab (*n*=26)	anti-PD-L1* (*n*=7)
Age, years				
Mean (SD)	61.7 (12.2)	61.4 (12.8)	61.1 (11.4)	65.7 (10.8)
Median	62.0	62.5	61.0	66.5
Range	23–84	28–83	23–82	50–84
Gender				
Female, %	45.0	50.0	38.5	42.8
Cancer type, % (*n*)				
Melanoma	53.5 (38)	50.0 (19)	73.0 (19)	0 (0)
Lung	26.8 (19)	34.2 (13)	15.4 (4)	28.5 (2)
Renal cell	5.7 (4)	10.6 (4)	0 (0)	0 (0)
Head and neck	7.0 (5)	2.6 (1)	7.7 (2)	28.5 (2)
Urothelial carcinoma	4.2 (3)	0 (0)	0 (0)	43.0 (3)
Other	2.8 (2)	2.6 (1)	3.9 (1)	0 (0)
Duration to diabetes, days				
Mean (SD)	83.5 (88.5)	98.0 (102.1)	65.9 (72.1)	75.0 (39.7)
Median	49	73.5	42	84
Range	5-448	5-448	14-365	21-126
Diabetic ketoacidosis, % (*n*)				
Present	76.0 (54)	71.0 (27)	80.7 (21)	85.7 (6)
Severe	38.9 (21)	33.3 (9)	52.4 (11)	16.6 (1)
Moderate	20.4 (11)	22.2 (6)	14.3 (3)	33.3 (2)
Mild	11.1 (6)	3.7 (1)	14.3 (3)	33.3 (2)
Not able to assess	29.6 (16)	40.8 (11)	19.0 (4)	16.6 (1)
Blood glucose, mmol/l				
Mean (SD)	33.4 (11.5)	33.8 (12.1)	34.1 (9.5)	29.4 (13.8)
Median	32.2	31.7	34.2	22.8
Range	13.7–67.3	13.7–67.3	15.0–50.5	18.1–56.4
HbA_{1c}, mmol/mol				
Mean (SD)	62 (0.3)	60 (0.3)	64 (0.3)	66 (0.4)
Median	61	56	62	66
Range	40–93	40–88	40–93	46–84
Type 1 diabetes-associated antibodies, % (*n*)				
Present	50.7 (36)	44.7 (17)	57.7 (15)	57.1 (4)
Absent	49.3 (35)	55.3 (21)	42.3 (11)	42.9 (3)
Type 1 diabetes risk HLA genes†, % (*n*)				
Present	38.0 (27)	39.5 (15)	38.5 (10)	28.5 (2)
Absent	7.0 (5)	13.1 (5)	0 (0)	0 (0)
Not Reported	55.0 (39)	47.4 (18)	61.5 (16)	71.5 (5)
Ipilimumab (anti-CTLA-4) use‡, % (*n*)				
Present	31.0 (22)	31.5 (12)	38.5 (10)	0 (0)
Absent	69.0 (49)	68.5 (26)	61.5 (16)	100.0 (7)

HLA, human leukocyte antigen; PD-1, programmed cell death protein; PD-L1, programmed cell death protein-1 ligand.
*Atezolizumab, avelumab and durvalumab.
†HLA-DQ-DR risk genes include DR3, DR4, DQ2, DQ8.
‡Prior or concurrent use of ipilimumab with anti-PD-1/PD-L1 treatment.

Result

- N = 71 (Nivo 54%, Pembro 36%, anti-PD-L1 10%)
- Age (years) median 62.0; mean 61.7; range 23-84
- Male 55%
- DKA 76%
- Type 1 DM-associated antibody ~50% (anti-GAD is the most common)
- Blood glucose 600 mg/dL (mean)
- HbA_{1c} 7.8% (mean)
- At-risk HLA* 38%
- Prior or concurrent use of Ipilimumab ~30%
- Ipilimumab alone did not develop type 1 DM

GAD: glutamic acid decarboxylase

* HLA-DR3, DR4, DQ2, DQ8

Type 1 DM-associated antibody

■ Antibody against:

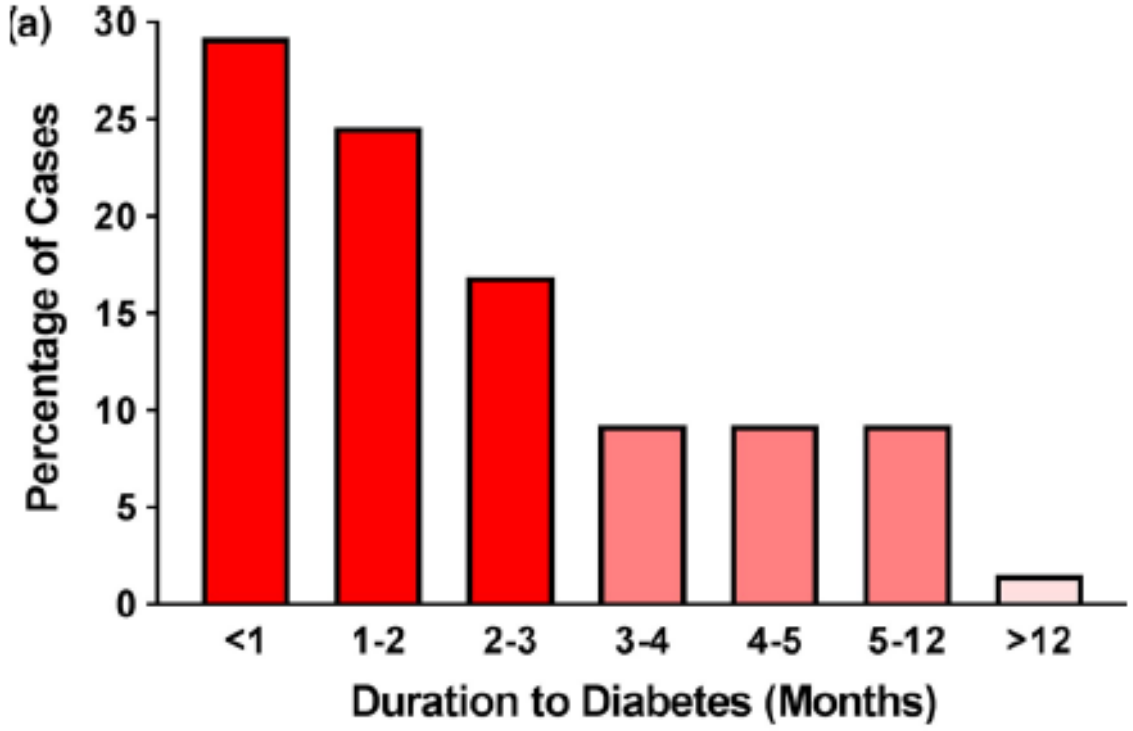
✓GAD

✓Islet cell

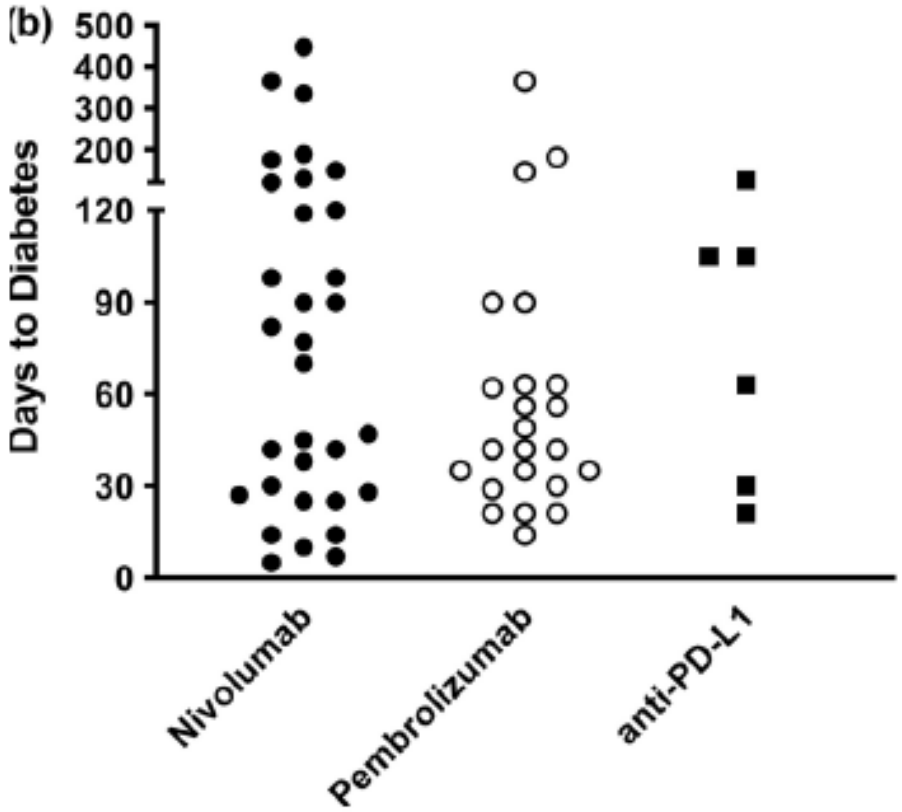
✓Islet antigen 2

✓Zinc transporter 8

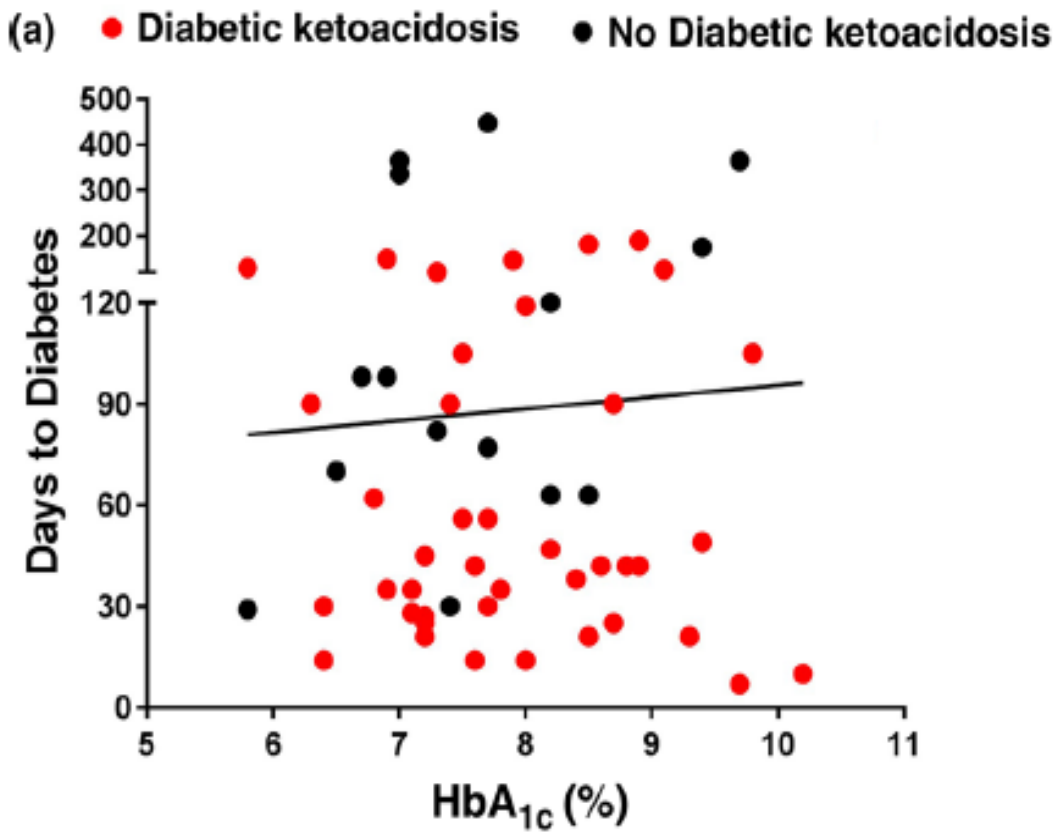
GAD (glutamic acid decarboxylase)
IA2 (Islet antigen 2)
ZnT8 (Zinc transporter 8)



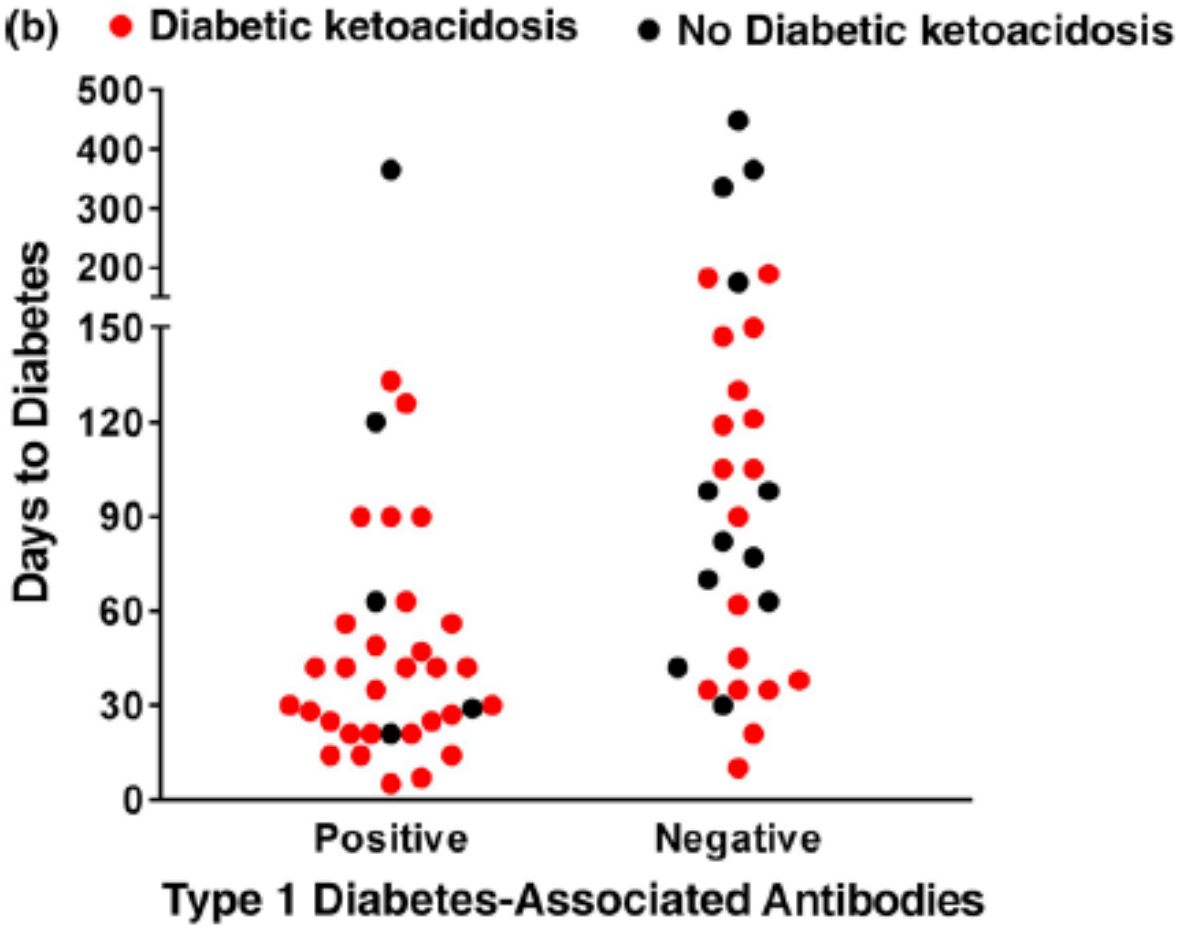
71% within first 3 months



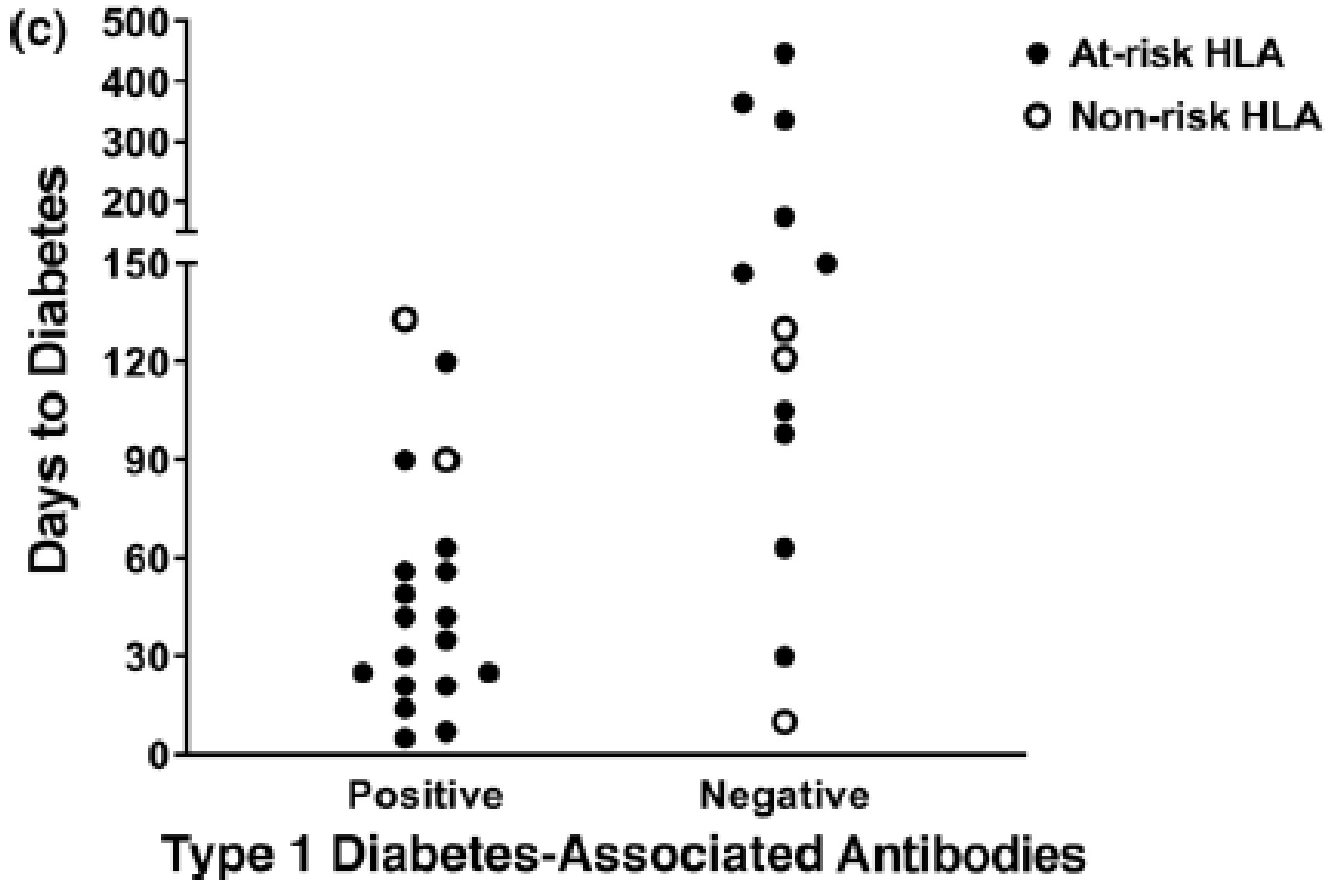
Median onset
nivolumab 73.5 day
pembrolizumab 42 day
anti-PD-L1 84 day



No correlation between HbA1c and onset



- ✓ Antibody (+) had faster onset (55 vs. 117 day, p=0.005)
- ✓ Antibody (+) had higher DKA incidence (86% vs. 60%, p=0.02)



✓ Type 1 diabetes risk HLA genes include DR3, DR4, DQ2, DQ8

✓ People with antibody (+) and at-risk HLA develop diabetes rapidly

Diabetes mellitus induced by immune checkpoint inhibitors: type 1 diabetes variant or new clinical entity? Review of the literature

V. Lo Preiato [1] · S. Salvagni [2] · C. Ricci [3] · A. Ardizzoni [2] · U. Pagotto [1] · C. Pelusi [1]

Reviews in Endocrine and Metabolic Disorders (2021) 22:337–349.

	Present review	Pharmacovigilance cohort[21]
Population number	N= 200	283
Male	62.5%	56.0%
Median age (yrs)	64	64
DKA at diagnosis	67.5%	50.2%
Fulminant Diabetes	59.3% (51/86)	N.A.
Median time to CPI-DM onset (weeks / cycle)	9/4	17 / N.A.
Range to CPI-DM onset (weeks / cycle)	1–94/1–42	1–113 / N.A.
Cancer type		
Melanoma	50.5%	43.3%
Lung	26.0%	32.3%
Renal Cell Carcinoma	7.0%	10.1%
Other	16.0%	14.3%
Not available	0.5%	–
CPI		
Nivolumab monotherapy	36.0%	52.7%
Pembrolizumab monotherapy	32.5%	23.3%
Anti PD-L1 monotherapy	7.0%	2.8%
Anti CTLA-4 monotherapy	0.5%	4.2%
Combination Therapy	23.5%	17.0%
Not available	0.5%	–

Fulminant diabetes (FD)

- Diagnostic criteria

DKA + blood glucose >228 mg/dL + HbA1c <8.7% + serum C-peptide < 0.3 ng/mL

- In Japan, FD represent 20% of all autoimmune DM; however, FD had rarely been reported in Caucasian subjects.
- FD in Asians show a low% of diabetes-associated auto-antibodies, and is associated with HLA-DR9 phenotype.
- ICI-induced Type 1 DM is very similar to FD: dramatic rapidly onset and low% detection of auto-antibodies

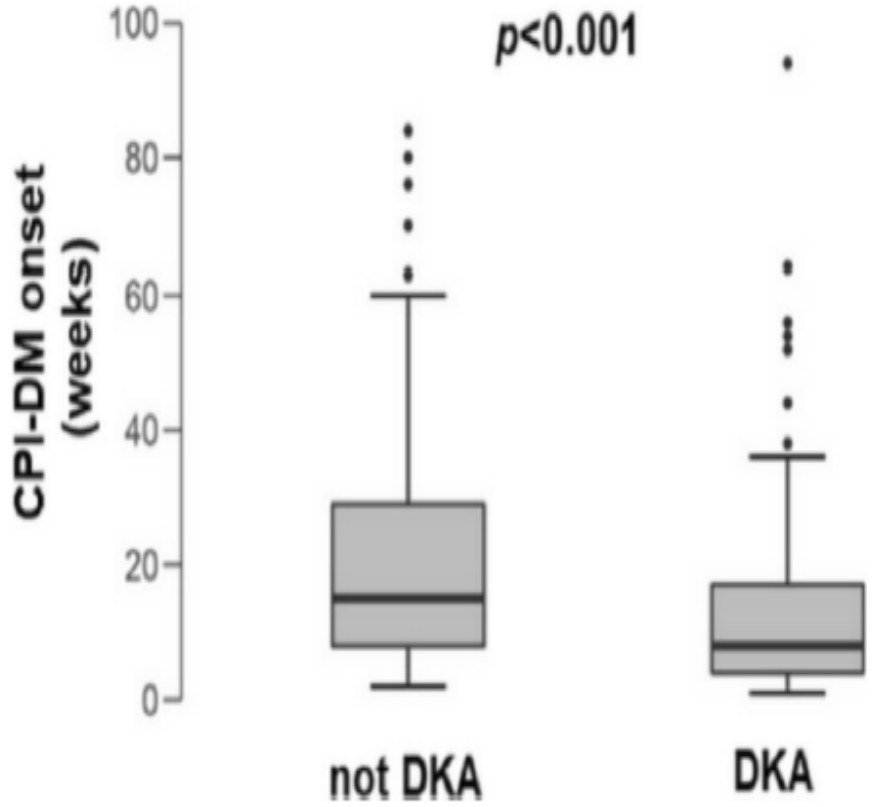


Fig. 2 Comparison of CPI-DM onset between subjects arose with or without DKA. CPI-DM with DKA arose before CPI-DM without DKA (median 8 weeks vs 15 weeks, $p < 0.001$); *CPI-DM* Diabetes Mellitus induced by Checkpoint Inhibitors; *DKA* Diabetic Ketoacidosis

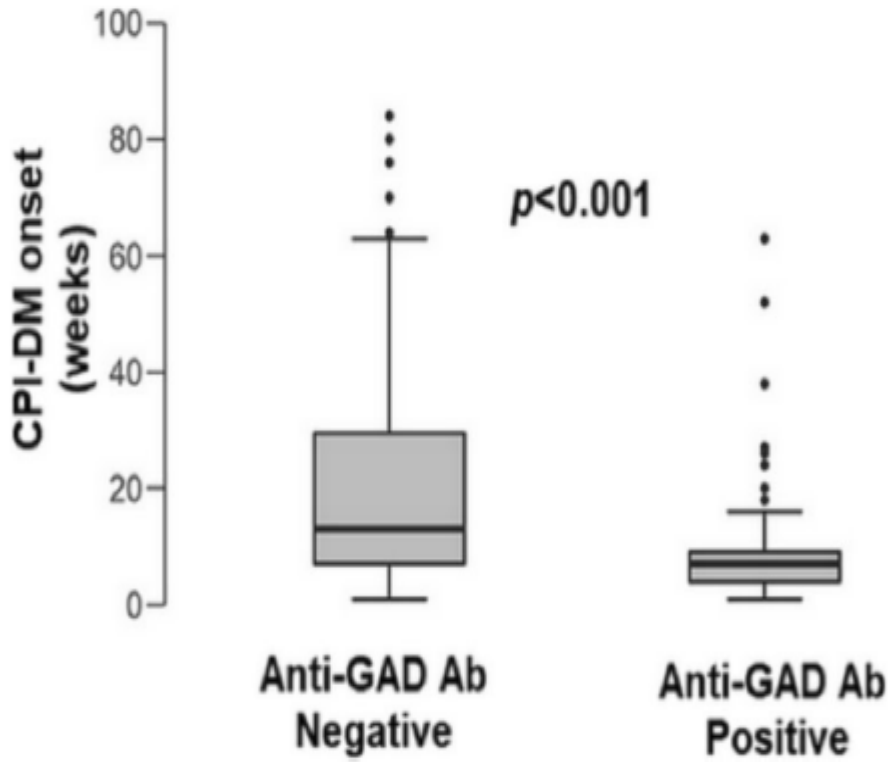
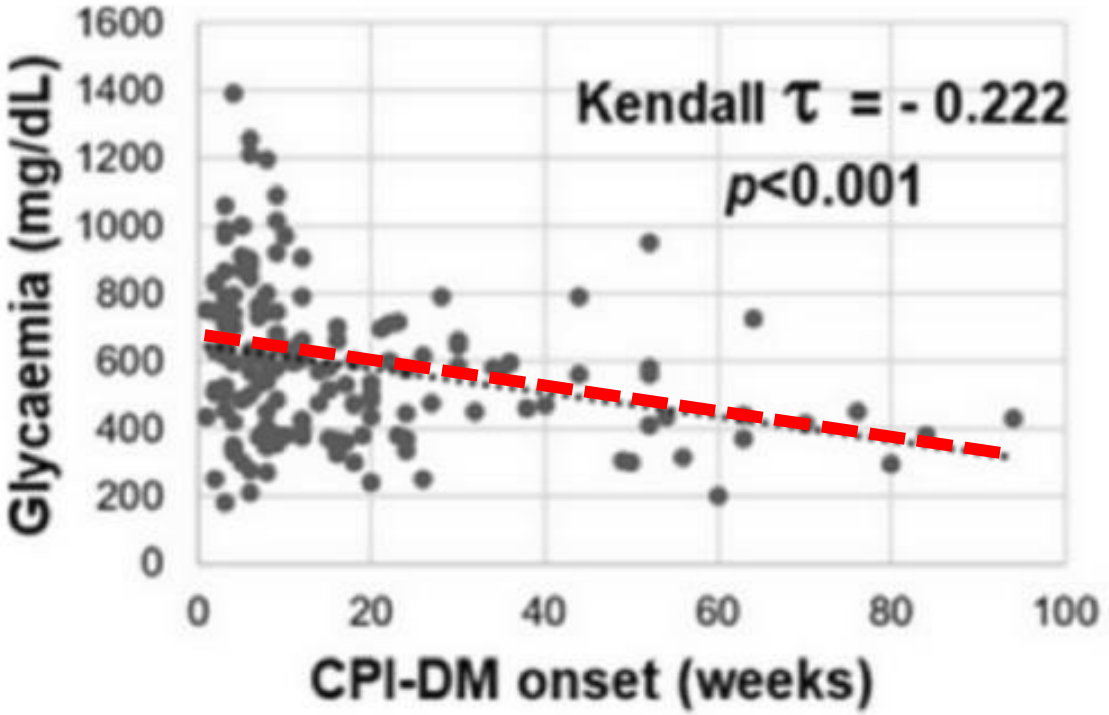
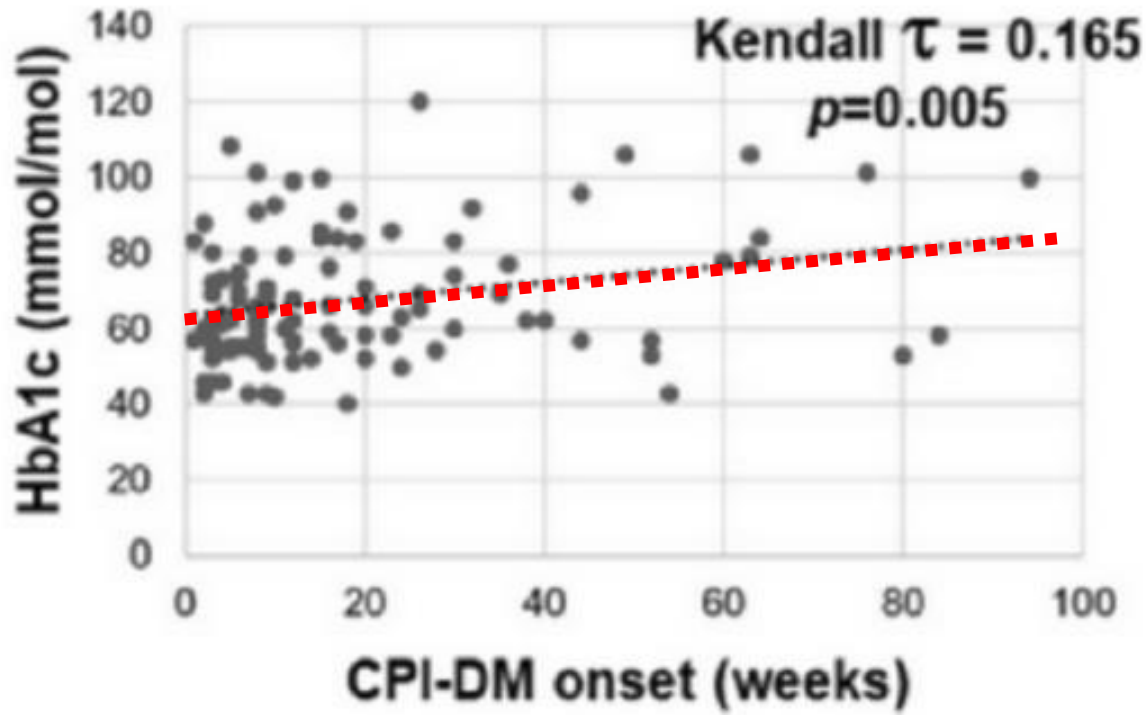
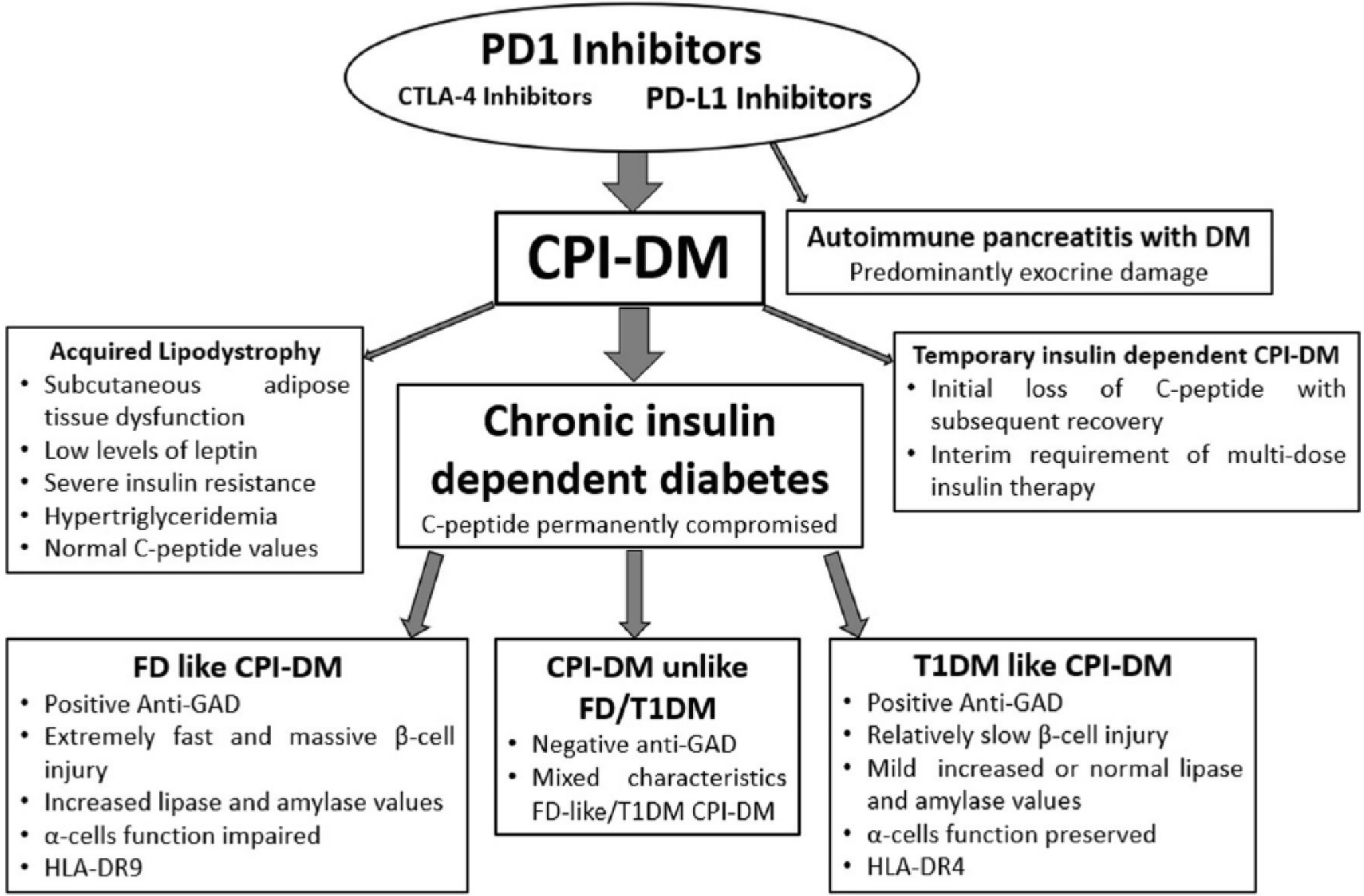


Fig. 4 Comparison of CPI-DM onset between subjects with or without Anti-GAD antibodies. CPI-DM with Anti-GAD antibodies arose before CPI-DM without Anti-GAD antibodies (median 7 weeks vs 13 weeks, $p < 0.001$); *CPI-DM* Diabetes Mellitus induced by Checkpoint Inhibitors; *Anti-GAD Ab* Anti-glutamic acid decarboxylase antibodies


Glycaemia (mg/dL)
1600
1400
1200
1000
800
600
400
200
0
0
20
40
60
80
100
CPI-DM onset (weeks)
Kendall τ = - 0.222
p<0.001


HbA1c (mmol/mol)
140
120
100
80
60
40
20
0
0
20
40
60
80
100
CPI-DM onset (weeks)
Kendall τ = 0.165
p=0.005


PD1 Inhibitors
CTLA-4 Inhibitors
PD-L1 Inhibitors
CPI-DM
Autoimmune pancreatitis with DM
Predominantly exocrine damage
Acquired Lipodystrophy
• Subcutaneous adipose tissue dysfunction
• Low levels of leptin
• Severe insulin resistance
• Hypertriglyceridemia
• Normal C-peptide values
Chronic insulin dependent diabetes
C-peptide permanently compromised
Temporary insulin dependent CPI-DM
• Initial loss of C-peptide with subsequent recovery
• Interim requirement of multi-dose insulin therapy
FD like CPI-DM
• Positive Anti-GAD
• Extremely fast and massive β-cell injury
• Increased lipase and amylase values
• α-cells function impaired
• HLA-DR9
CPI-DM unlike FD/T1DM
• Negative anti-GAD
• Mixed characteristics FD-like/T1DM CPI-DM
T1DM like CPI-DM
• Positive Anti-GAD
• Relatively slow β-cell injury
• Mild increased or normal lipase and amylase values
• α-cells function preserved
• HLA-DR4

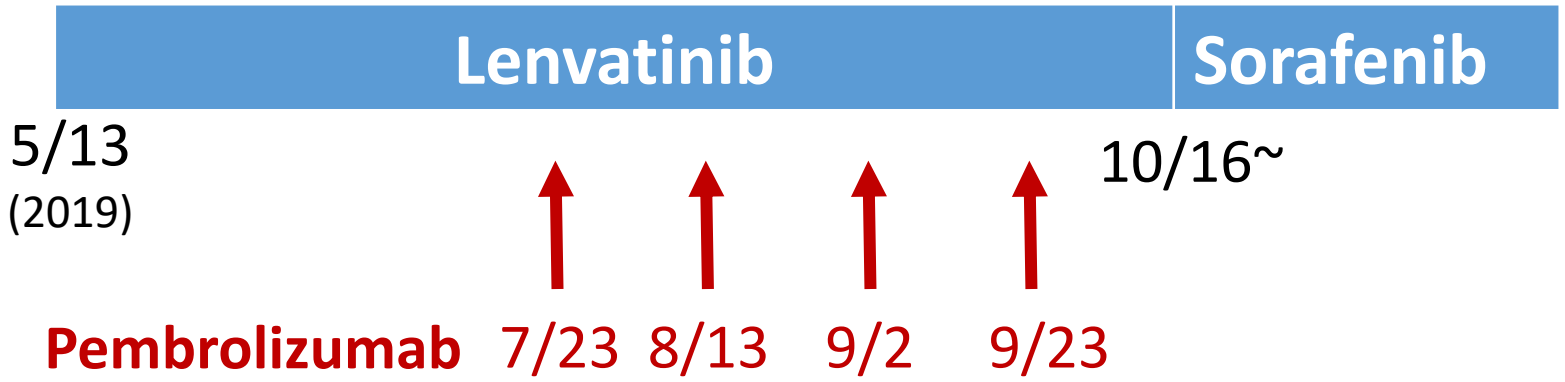
Clinical practice

- Highlight the importance of monitoring blood glucose and HbA_{1c} prior to initiating ICIs as well as during follow-up
- Risk factors: old age, nivolumab, at-risk HLA, anti-GAD(+)
- Develop a better risk prediction is needed

Refractory irAE hepatitis

Case

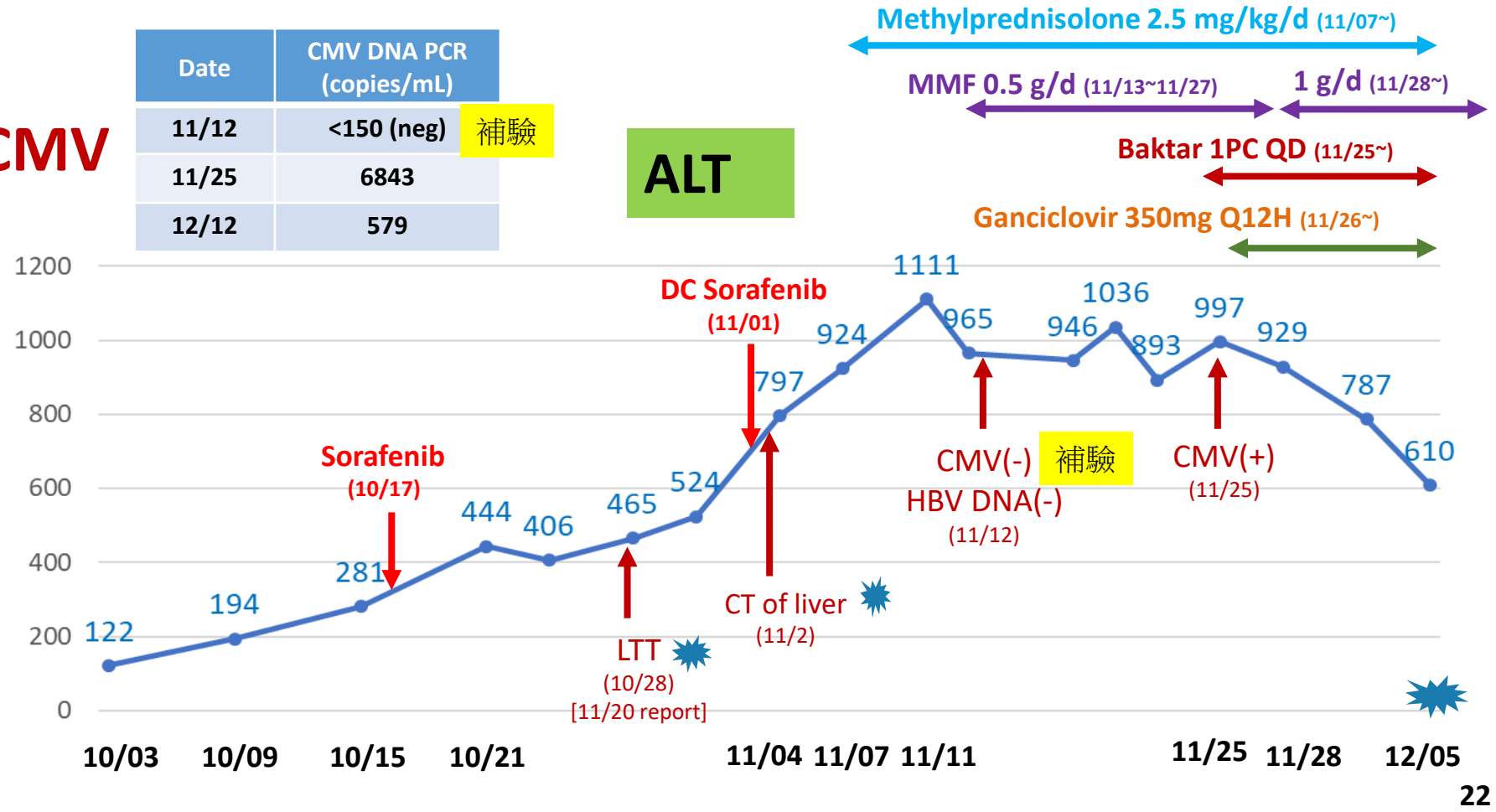
- A 58 years old male, 64 kg
- Diagnosed with metastatic hepatocellular carcinoma (HCC); non-B, non-C



Progress Note

CMV

Date	CMV DNA PCR (copies/mL)
11/12	<150 (neg) 補驗
11/25	6843
12/12	579



Lymphocyte transformation test (LTT)

AdrD 7934					
抽血日期 ： 20191028 實驗開始日期 ： 20191028 6*10E5/Well					
7 Days, 10X, +IL-7 (11/4-11/8)					
		GNLY		Granzyme B	
drug	clinical	(ng/mL)	fold	(pg/mL)	fold
PBS		6.49	1.00	271.38	1.00
Lenvatinib		7.40	1.14	352.37	1.30
Pembrolizumab		42.44	6.54	458.92	1.69
Sorafenib		97.44	15.01	539.50	1.99
PHA		12.40	1.91	176.86	0.65

抽血日期：2019/10/28
報告日期：2019/11/20

<報告內容> 收件號：19110239402
Clinical Information: HCC with multiple meta; under sorafenib

CT of the chest and liver with triphasic dynamic contrast enhancement:
(comparison 2019.9.2 JIAYI)

1. Compensated cirrhosis.
2. Embolized and resected HCC. No viable tumors
3. No biliary obstruction.
4. Patent portal vein.
5. No enlarged abdominal lymph nodes.
6. Bibasal partial atelectasis with mild effusion.
7. Progression of bone metastasis at left posterior chest (15.6-cm), right T12 transverse process (3-cm). Multiple osteolytic bone metastasis.

IMP: Compensated cirrhosis. No new/viable hepatic HCC. Progression of bone metastasis.

Management

- Methylprednisolone 11/7-12/13 (about 5 weeks)

  11/07-12/13 40 mg Q6H (2.5 mg/kg/day)
- Mycophenolate(250mg) 11/13-2020/01/10 (about 8 weeks)

  11/13-11/27 1# BID (500mg/day)→11/28-2020/01/10 2# BID (1g/day)
- Baktar tab(80/400) 11/25-2020/01/07 (about 6 weeks)

  11/25-12/4 1# QD→12/5-2020/01/10 2# QD
- Ganciclovir 5mg/kg q12h (11/26-12/16 about 3 weeks)

Follow-up

- 2020/01/13: AST/ALT 29/48
- Last f/u date: 2020/10/30

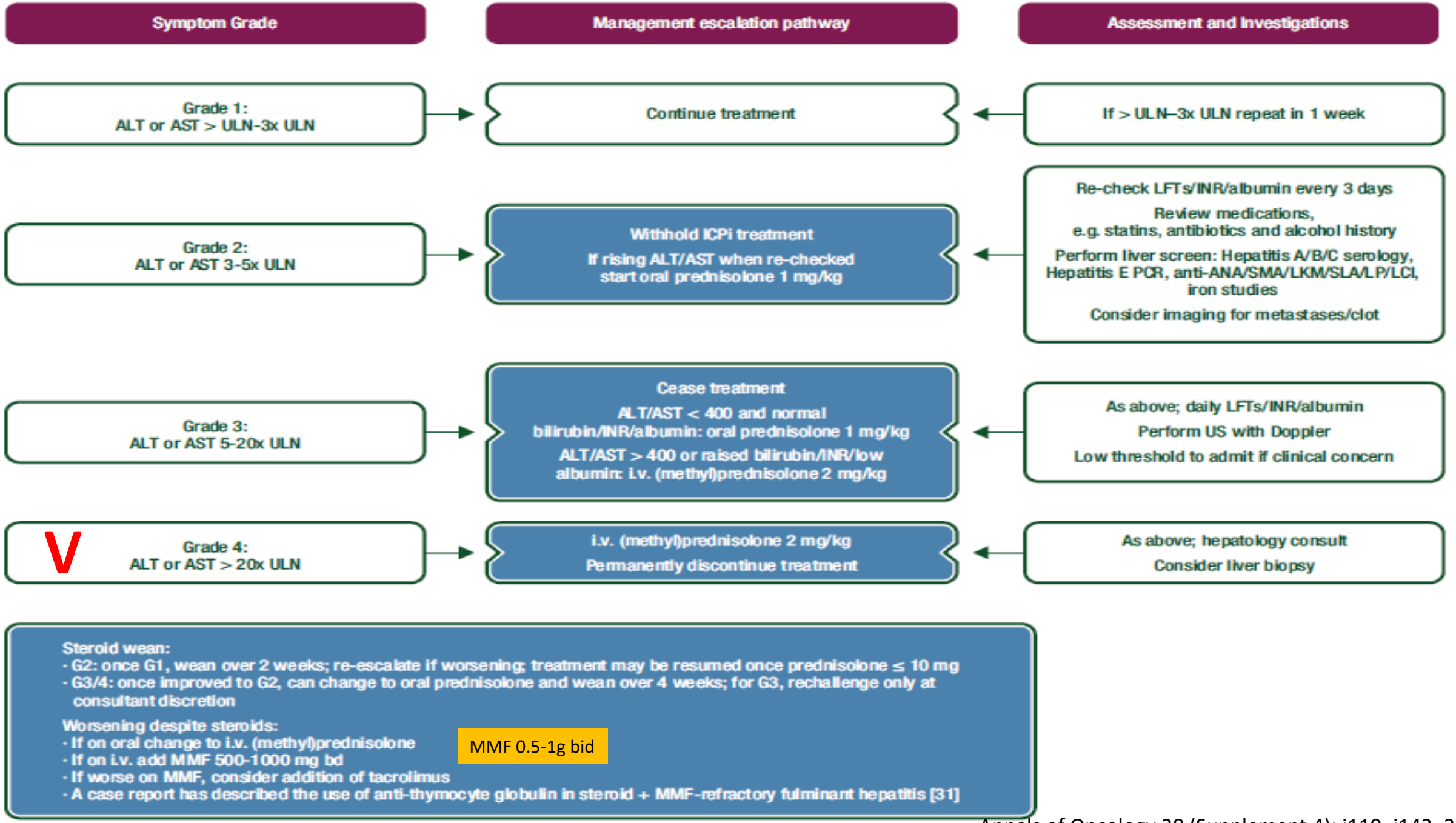
Annals of Oncology 28 (Supplement 4): i119–i142, 2017
doi:10.1093/annonc/mdx225

CLINICAL PRACTICE GUIDELINES

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[4], S. Peters[5], J. Larkin[6] & K. Jordan[7], on behalf of the ESMO Guidelines Committee*

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



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

Hepatitis usually resolves within 4–6 weeks with appropriate treatment but in the event that it does not resolve, other contributory causes should be reconsidered and the initial diagnostic work repeated as necessary, particularly bearing in mind the concomitant administration of other hepatotoxic drugs (including herbal medications and those purchased over the counter) and cytomegalovirus (CMV) reactivation.

(ESMO Guideline 2017)

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

Rechallenge ICI for a patient with ICI-induced SJS

Stevens Johnson Syndrome

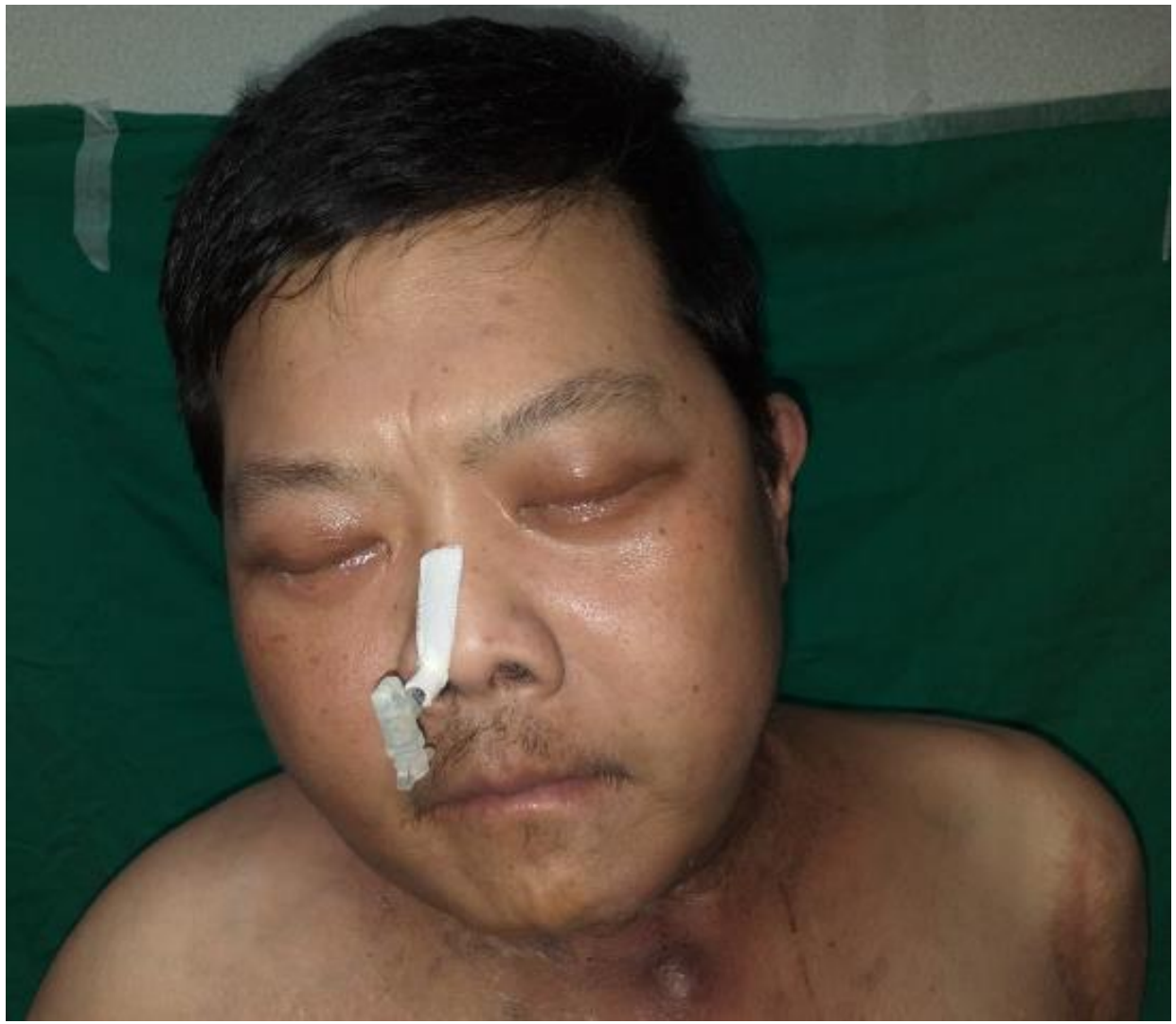
General Data

- 42-year-old, Male, 72 kg
- Tongue SCC, pT4aN3bM0 (Stage IVb)
  - 2019/6/13 total glossectomy and bilateral modified radical neck dissection
  - 2019/7/23-2019/9/09 post-OP CCRT (chemo with cisplatin)
  - 2019/11/13-2020/1/17 Docetaxel, Cisplatin and Cetuximab
  - post Tipifarnib clinical trial (oral Tipifarnib in HRAS mutant HNSCC)
  - disease progression, start Pembrolizumab 100 mg and Erlotinib 150 mg QD since 2020/7/10
- Right axilla LN metastasis with wound infection

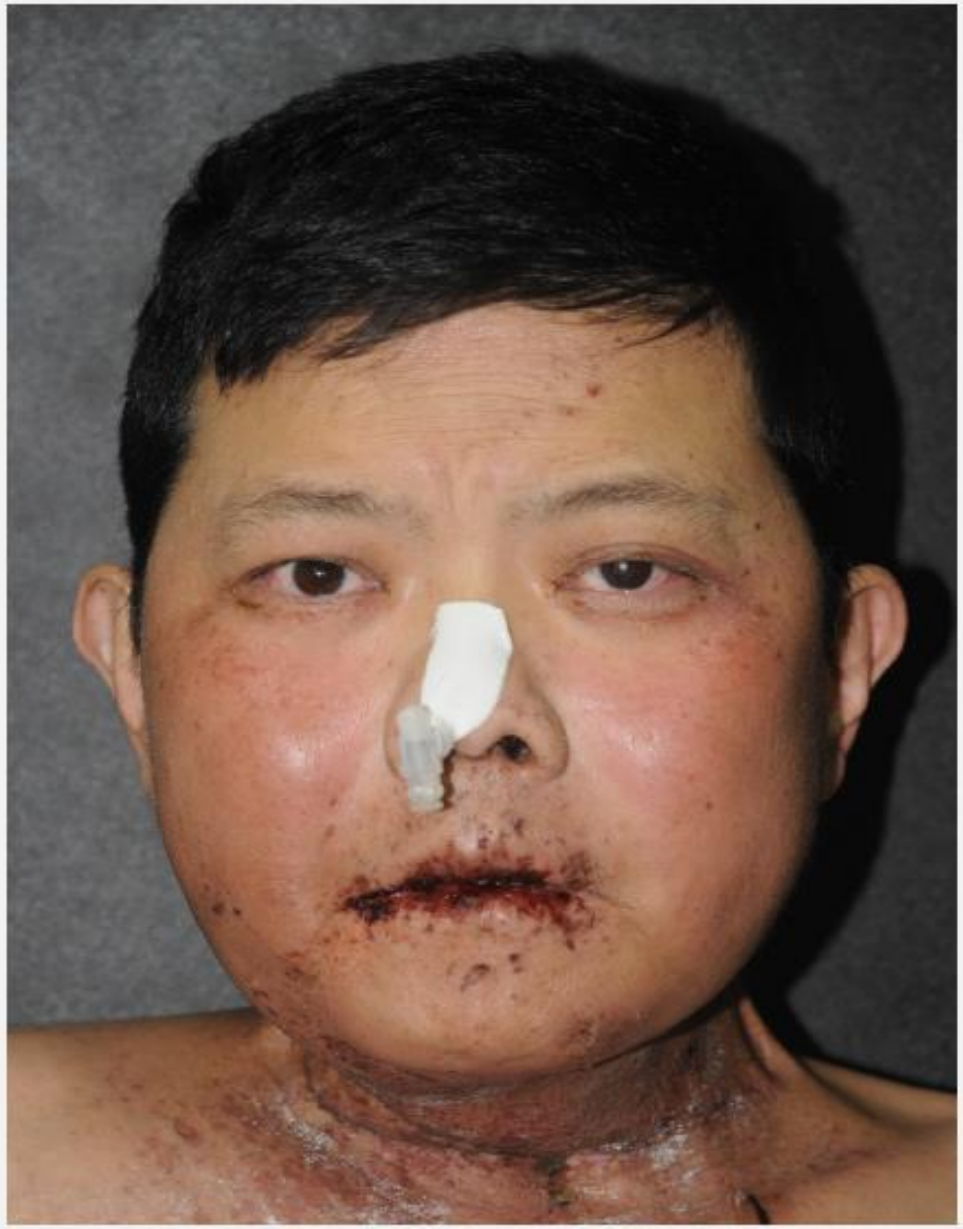
Present Illness

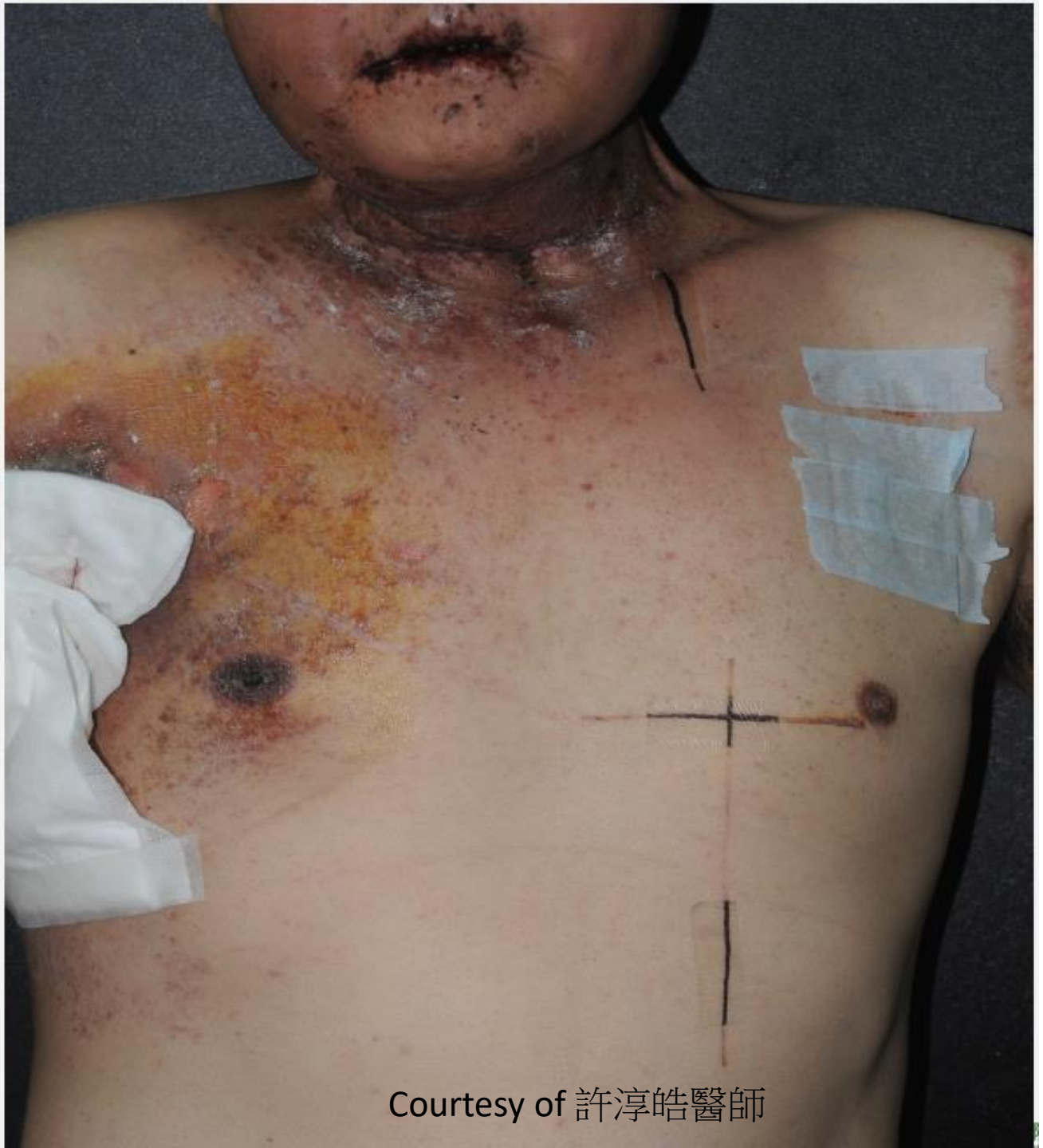
- He visited our ER on 7/24 for fever up to 39.1 degree(7/17) and eye redness for days (7/22~).
- Multiple skin rashes and oral ulcer developed since 7/22 (D1).
- Ophthalmologist diagnosed with Stevens-Johnson Syndrome, grade 3, OU.
- Dermatologist diagnosed with Stevens-Johnson Syndrome
- Under the impression of Steven-Johnson Syndrome, the patient was admitted to our ward on 2020/7/26 for further management and care.

SJS, grade 3, OU.



Courtesy of 許淳皓醫師





Courtesy of 許淳皓醫師

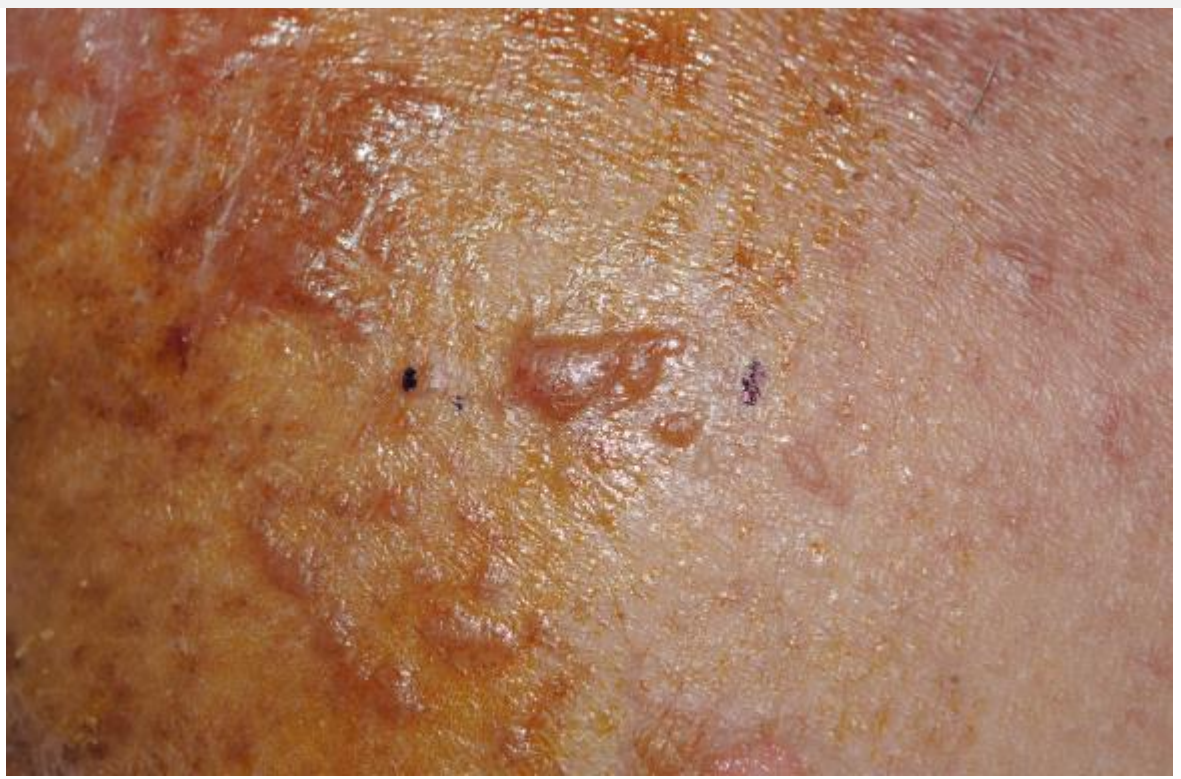
PATHOLOGY (2020/07/29, D8)

DX:

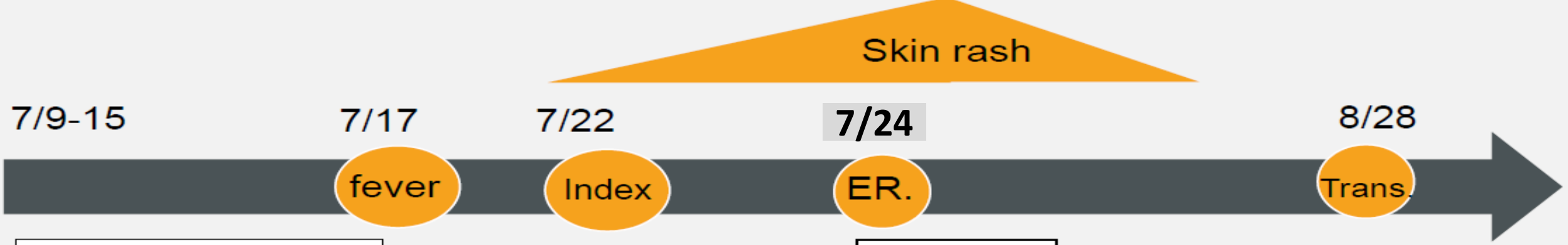
Skin, chest, biopsy

---- epidermal necrosis and mild interface change

----consistent with the spectrum of EM/SJS/TEN



Courtesy of 許淳皓醫師



. admitted for immunotherapy

7/16-20
RT for right axilla

. Maculopapular exanthema with atypical targets over upper chest
. Red eye and oral erosions
. Nikolsky sign (-)

Biopsy

Ophtha. - SJS, grade3 OU
-> aminiotic membrane graft 7/29

Dexa 5mg Q8H IV(7/27-29)
MTP 20mg BID IV(7/30-31)
20mg QD IV(8/1-3)
12mg BID PO (12/3-
Etanercept 1# (7/25.28.30

Enbrel 50 mg x 3

- Pemborlizumab (7/10)
- Erlotinib 150mg QD (7/10-24)
- Teicoplanin 600mg Q12H (7/11-14)
- Ceftriaxone 1mg Q12H (7/11-14)
- Ciprofloxacin 500mg Q12H (7/14-21)

Tazocin (7/26-8/9)
Colistin (8/4-
Brosym (8/9-11)
Teicoplanin (8/11-21)

. **Trunk rash:** Fluocinonide BID
. Lip erosion: tetracycline
. Wound: Salfasil and Neomycin BID

抽血日期 ： 20200727 實驗開始日期 ： 20200727 5*10E5 溶血				
7 Days, 10X, +IL-7 (8/3-8/7)				
	GNLY		Granzyme B	
drug	(pg/mL)	fold	(pg/mL)	fold
DMSO	427.16	1.00	218.56	1.00
Ciprofloxacin	552.10	1.29	320.22	1.47
Erlotinib	602.58	1.41	339.32	1.55
Diclofenac	627.14	1.47	411.84	1.88
Pembrolizumab	226.20	0.53	195.76	0.90
Ciprofloxacin + Pembrolizumab	305.10	0.71	301.26	1.38
PHA	517.52	1.21	210.12	0.96
14 Days, 10X, +IL-7 (8/10-8/14)				
DMSO	103.67	1.00	301.30	1.00
Ciprofloxacin	315.72	3.05	309.82	1.03
Erlotinib	514.56	4.96	453.32	1.50
Diclofenac	158.64	1.53	367.42	1.22
Pembrolizumab	2664.80	25.70	2024.4	6.72
Ciprofloxacin + Pembrolizumab	215.148	2.08	256.26	0.85
PHA	201.636	1.94	471.32	1.56

F/U

- Second dose of Pembrolizumab 100 mg: 2020/8/21
  - Last Enbrel on 7/30.
  - Etanercept: half-life 115 hr (range 98-300 hr; about 4-12 days)
- Re-start erlotinib 150 mg QOD since 2020/8/28
- Start weekly paclitaxel/cisplatin: 2020/9/21, 9/29
- No SJS recur
- Expired on 2020/10/1 (BP drop and then apnea)

Patient/Family Teaching

- Instruct patient to take eszopiclone immediately before going to bed, as directed. May result in short-term memory impairment, hallucinations, impaired coordination, and dizziness. Do not take eszopiclone if consumed alcohol that evening. Do not increase dose or discontinue without notifying health care professional. Dose may need to be decreased gradually to minimize withdrawal symptoms. Rebound insomnia and/or anxiety may occur upon discontinuation and usually resolves within 1–2 nights. Advise patient to read *Medication Guide* before starting therapy and with each Rx refill in case of changes.
- May cause daytime and next-day drowsiness. Caution patient to avoid driving or other activities requiring alertness until response to medication is known.
- Caution patient that eszopiclone may cause complex sleep behaviors (sleep walking, sleep-driving, making and eating food, talking on the phone, having sex) while unaware. Patient may not remember anything done during the night; increased risk with alcohol or other CNS depressants. Discontinue eszopiclone immediately and notify health care

in patients who are candidates for systemic therapy or phototherapy.

Action

Binds to tumor necrosis factor (TNF), making it inactive. TNF is a mediator of inflammatory response.

Therapeutic Effects: Decreased pain and swelling with decreased rate of joint destruction in patients with rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, and ankylosing spondylitis. Reduced severity of plaques.

Pharmacokinetics

Absorption: 60% absorbed after subcut administration.

Distribution: Unknown.

Metabolism and Excretion: Unknown.

Half-life: 115 hr (range 98–300 hr).

TIME/ACTION PROFILE (symptom reduction)

ROUTE	ONSET	PEAK	DURATION
Subcut	2–4 wk	unknown	unknown

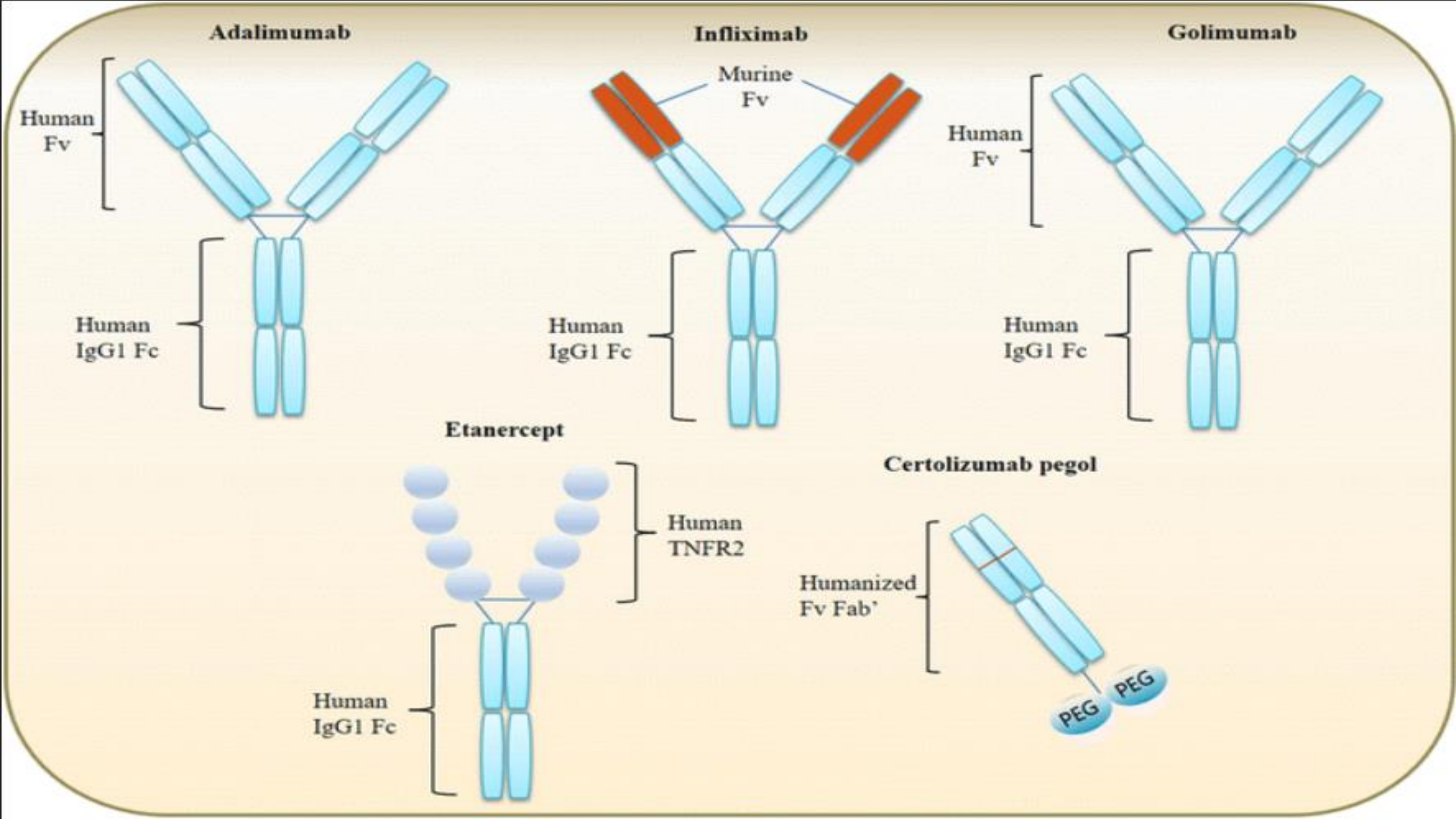
Etanercept

Davis's Drug Guide for Nurses 2020,page 538.

TNF inhibitor

- Etanercept (Enbrel): a fusion protein
- Adalimumab
- Infliximab: second-line choice for irAE management
- Golimumab
- Certolizumab

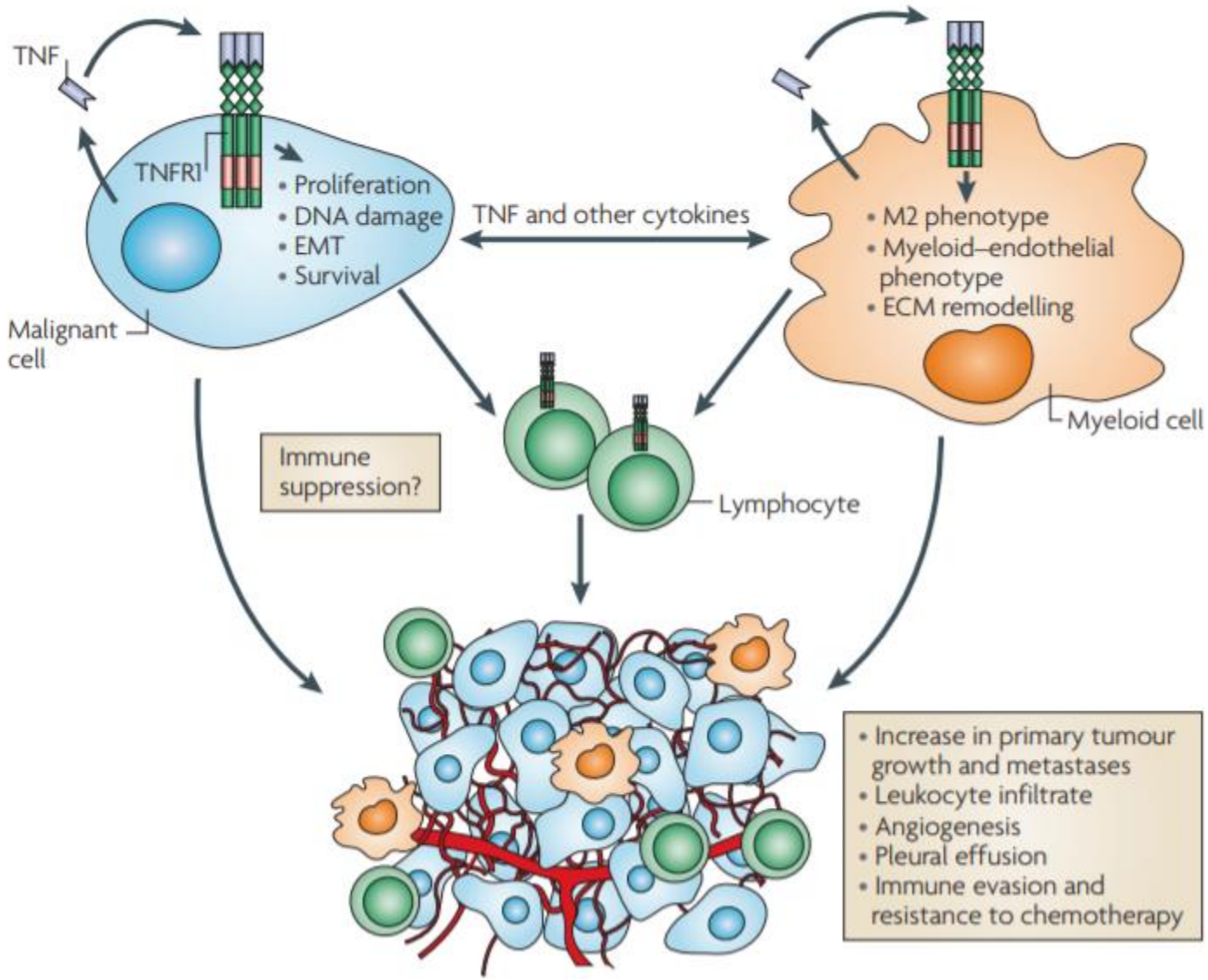
TNF: tumor necrosis factor


Adalimumab
Human
Fv
Human
IgG1 Fc
Infliximab
Murine
Fv
Human
IgG1 Fc
Golimumab
Human
Fv
Human
IgG1 Fc
Etanercept
Human
TNFR2
Human
IgG1 Fc
Certolizumab pegol
Humanized
Fv Fab'
PEG
PEG

irAE management

- First-line: steroid
- Second-line: TNF inhibitor (eg, infliximab)

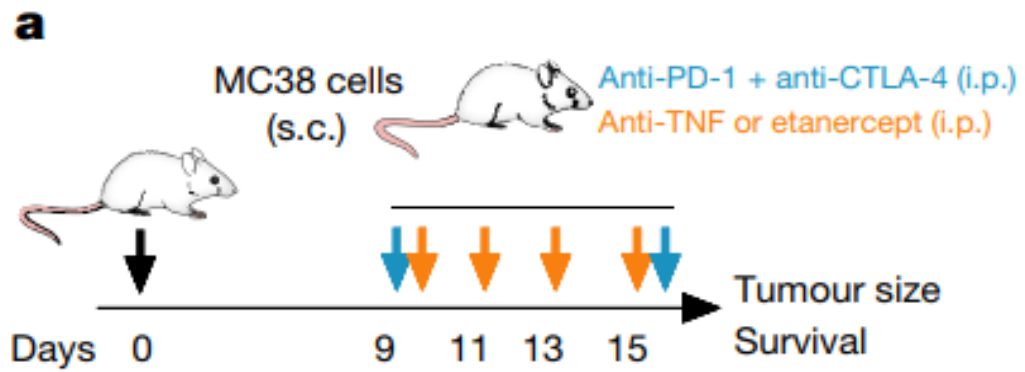
Pro-tumor actions of TNF in the tumor microenvironment

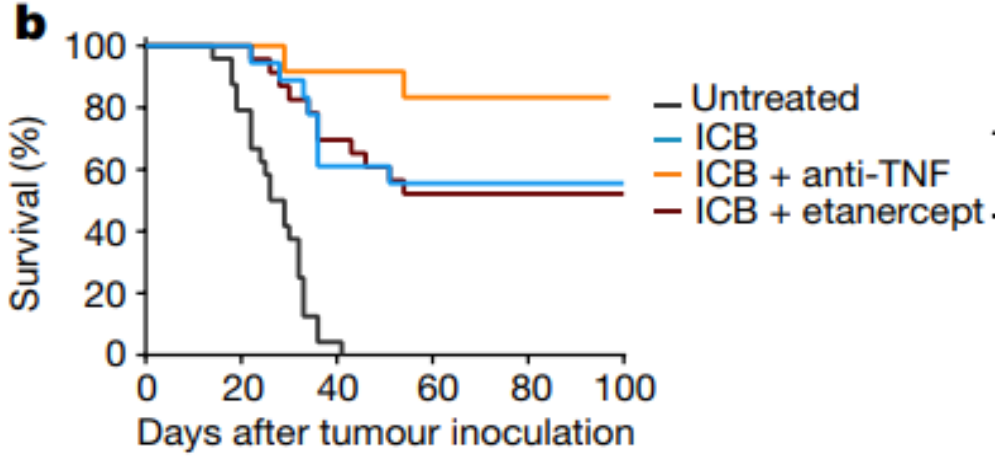


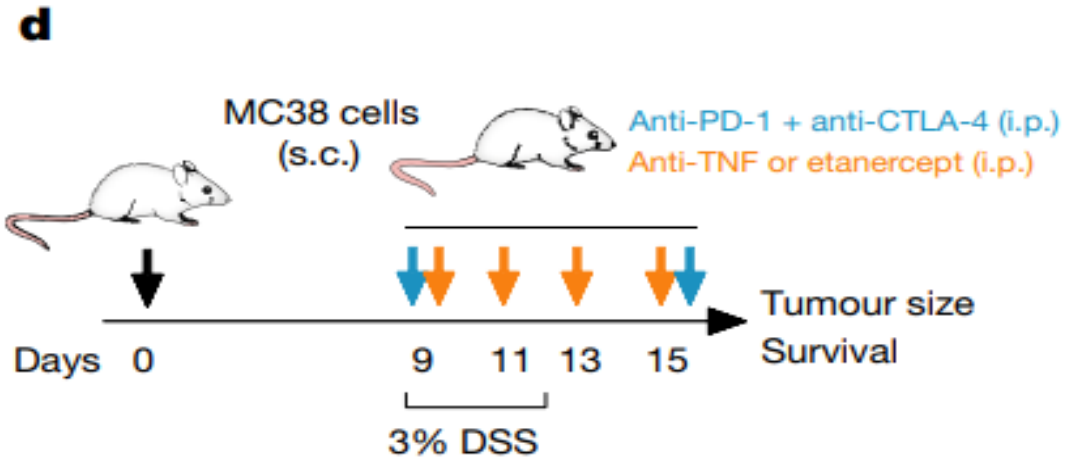
Nat Rev Cancer 2009;9:361–71.

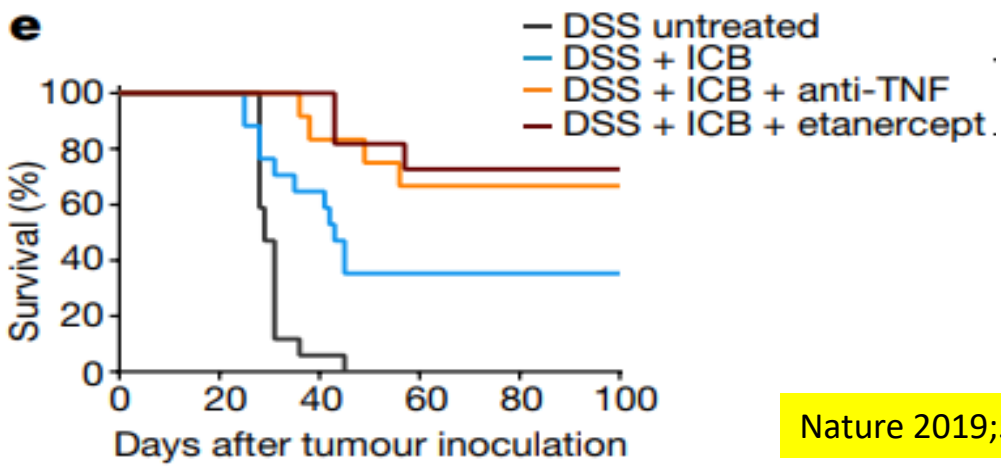
Prophylactic TNF blockade uncouples efficacy and toxicity in dual CTLA–4 and PD–1 immunotherapy

Elisabeth Perez-Ruiz[1,2,3,4,5], Luna Minute[1,2], Itziar Otano[1,2], Maite Alvarez[1,2], Maria Carmen Ochoa[1,2,6], Virginia Belsue[1,2], Carlos de Andrea[2,7], Maria Esperanza Rodriguez-Ruiz[1,3], Jose Luis Perez-Gracia[2,3,6], Ivan Marquez-Rodas[6,8], Casilda Llacer[9], Martina Alvarez[5,10,11], Vanesa de Luque[5,10], Carmen Molina[1,2], Alvaro Teijeira[1,2,6], Pedro Berraondo[1,2,6,13]* & Ignacio Melero[1,2,3,6,12,13]*









Nature 2019;569:428–32.

Prophylactic TNF blockade uncouples efficacy and toxicity in dual CTLA-4 and PD-1 immunotherapy

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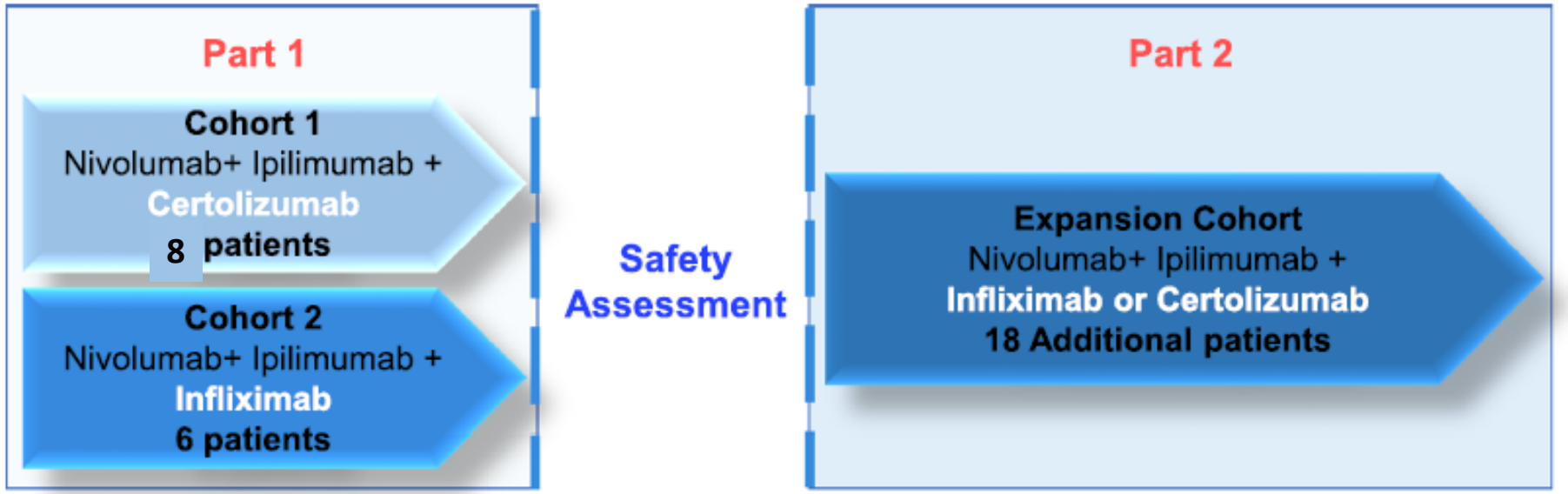
Treating mice with TNF inhibitors concomitantly with anti–CTLA-4 and anti–PD-1 not only improves ICI efficacy, but also reduces colitis and hepatitis in melanoma and colon cancer models.

Both reduce irAE and improve ICI efficacy in pre-clinical study

Nature 2019;569:428–32.

Phase Ib TICIMEL trial

TNF-Inhibitor as Immune Checkpoint Inhibitor for Advanced MELanoma (TICIMEL)
Clinical Trial Identifier: NCT03293784



	Induction Phase				Maintenance Phase			
Week	**0**	**3**	**6**	**9**	**12**	**14**	**16**	**Continued…**
Day	**1**	**22**	**43**	**64**	**85**	**99**	**112**	
Nivolumab (IV)	1 mg/kg	1 mg/kg	1 mg/kg	1 mg/kg	3 mg/kg	3 mg/kg	3 mg/kg	3 mg/kg **Q2W**
Ipilimumab (IV)	3 mg/kg	3 mg/kg	3 mg/kg	3 mg/kg	-	-	-	-
Certolizumab (SC)	400 mg	400 mg	400 mg	200 mg	200 mg	200 mg	200 mg	200 mg **Q2W**
Infliximab (IV)	5 mg/kg	5 mg/kg	5 mg/kg	-	-	5 mg/kg	-	5 mg/kg **Q8W**

End of DLT period evaluation

Journal for Immunotherapy of Cancer 2019;7:303

Combining Nivolumab and Ipilimumab with Infliximab or Certolizumab in Patients with Advanced Melanoma: First Results of a Phase Ib Clinical Trial

Anne Montfort[1,2], Thomas Filleron[3,4], Mathieu Virazels[1,2], Carine Dufau[1,2,5], Jean Milhès[1,2], Cécile Pagès[4,6], Pascale Olivier[7], Maha Ayyoub[1,4,5], Muriel Mounier[3,4], Amélie Lusque[3,4], Stéphanie Brayer[1,2,6], Jean-Pierre Delord[1,4,5], Nathalie Andrieu-Abadie[1,2], Thierry Levade[1,2,5,8], Céline Colacios[1,2,5], Bruno Ségui[1,2,5], and Nicolas Meyer[1,2,4,5,6]

Triple therapy: TNF inhibitor + CTLA-4 inhibitor + anti-PD1 inhibitor

- N = 14 (8 I+N+certoli; 6 I+N+inflixi)
- Between Jan. 2018 and Sep. 2019 enrolled
- Median f/u duration: 13.3 months (the last f/u date Dec. 6, 2019)
- Tumor responses were assessed every 12 weeks (3 months)
- Primary endpoint: DLI (dose-limiting toxicity) incidence
- Secondary endpoint: TRAE, ORR, PFS

Clin Cancer Res 2021;27:1037–47

	Certolizumab *N* (%)	Infliximab *N* (%)
Sex (*N* = 14)		
Male	5 (62.5)	5 (83.3)
Female	3 (37.5)	1 (16.7)
Age at inclusion (*N* = 14)		
Median	49.5	61
Range	(33:73)	(50:75)
ECOG Performance status (*N* = 14)		
ECOG 0	7 (87.5)	4 (66.7)
ECOG 1	1 (12.5)	2 (33.3)
LDH (U/L) (*N* = 14)		
Normal	2 (25)	3 (50)
ANCS	6 (75)	3 (50)
AJCC stage at screening (*N* = 14)		
Stage IIIc	2 (25)	2 (33)
Stage IV	6 (75)	4 (66.7)
Number of metastatic sites (if stage IV at screening) (*N* = 10)		
1 site	1 (16.7)	0 (0)
2 sites	2 (33.3)	2 (50)
3 sites	2 (33.3)	2 (50)
5 sites	1 (16.7)	0 (0)
BRAF V600 (*N* = 14)		
Mutated	5 (62.5)	1 (16.7)
NRAS (*N* = 13)		
Mutated	1 (14.3)	1 (16.7)
Missing	1	0
Prior adjuvant therapy (*N* = 14)		
No	8 (100)	5 (83.3)
Yes[a]	0 (0)	1 (16.7)

DLI

- Certolizumab cohort: No DLT

- Infliximab cohort:

only 1 patient (16.7%) developed a DLT of LVEF alteration

TRAE

	Total N = 14		Certolizumab cohort N = 8		Infliximab cohort N = 6	
	All N (%)	Grade 3–4 N (%)	All N (%)	Grade 3–4 N (%)	All N (%)	Grade 3–4 N (%)
At least one treatment-related AE	13 (92.9)	9 (64.3)	7 (87.5)	6 (75)	6 (100)	3 (50)
General disorders and administration site conditions	10 (71.4)	0 (0)	7 (87.5)	0 (0)	3 (50)	0 (0)
Gastrointestinal disorders	9 (64.3)	4 (28.6)	4 (50)	3 (37.5)	5 (83.3)	1 (16.7)
Skin and subcutaneous tissue disorders	9 (64.3)	1 (7.1)	6 (75)	1 (12.5)	3 (50)	0 (0)
Hepatobiliary disorders	6 (42.9)	4 (28.6)	4 (50)	3 (37.5)	2 (33)	1 (16.7)
ALAT	2 (14.3)	1 (7.1)	2 (25)	1 (12.5)	0 (0)	0 (0)
ASAT	2 (14.3)	2 (14.3)	1 (12.5)	1 (12.5)	1 (16.7)	1 (16.7)
Endocrine disorders	4 (28.6)	0 (0)	3 (37.5)	0 (0)	1 (16.7)	0 (0)
Nervous system disorders	4 (28.6)	0 (0)	3 (37.5)	0 (0)	1 (16.7)	0 (0)
Metabolism and nutrition disorders	3 (21.4)	1 (7.1)	3 (37.5)	1 (12.5)	0 (0)	0 (0)
Respiratory, thoracic, and mediastinal disorders	3 (21.4)	0 (0)	2 (25)	0 (0)	1 (16.7)	0 (0)
Musculoskeletal and connective tissue disorders	2 (14.3)	0 (0)	2 (25)	0 (0)	0 (0)	0 (0)
Vascular disorders	2 (14.3)	0 (0)	1 (12.5)	0 (0)	1 (16.7)	0 (0)
Blood and lymphatic system disorders	1 (7.1)	0 (0)	1 (12.5)	0 (0)	0 (0)	0 (0)
Cardiac disorders	1 (7.1)	0 (0)	0 (0)	0 (0)	1 (16.7)	0 (0)
Psychiatric disorders	1 (7.1)	0 (0)	1 (12.5)	0 (0)	0 (0)	0 (0)

	Total N=14	Certolizumab N=8	Infliximab N=6
Best Overall response (n=14)			
Complete	5 (35.7%)	4 (50%)	1 (16.7%)
Partial	5 (35.7%)	3 (37.5%)	2 (33.3%)
Progression	3 (21.4%)	0 (0%)	3 (50%)
Not evaluable	1 (7.1%)	1 (12.5%)*	0 (0%)
Objective response (n=14)			
No	3 (21.4%)	0 (0%)	3 (50%)
Yes	10 (71.4%)	7 (87.5%)	3 (50%)
Non evaluable	1 (7.1%)	1 (12.5%)	0 (0%)

ORR 87.5% 50%

	Total N=14	Certolizumab N=8	Infliximab N=6
Non progression at 6 months (n=14)			
No	3 (21.4%)	0 (0%)	3 (50%)
Yes	7 (50%)	6 (75%)	1 (16.7%)
Non evaluable	4 (28.6%)	2 (25%)	2 (33.3%)

* One patient (Certolizumab) progressed and initiated a new therapy before the first tumor assessment

Phase 3 CheckMate 067 Trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma

J. Larkin, V. Chiarion-Sileni, R. Gonzalez, J.J. Grob, C.L. Cowey, C.D. Lao, D. Schadendorf, R. Dummer, M. Smylie, P. Rutkowski, P.F. Ferrucci, A. Hill, J. Wagstaff, M.S. Carlino, J.B. Haanen, M. Maio, I. Marquez-Rodas, G.A. McArthur, P.A. Ascierto, G.V. Long, M.K. Callahan, M.A. Postow, K. Grossmann, M. Sznol, B. Dreno, L. Bastholt, A. Yang, L.M. Rollin, C. Horak, F.S. Hodi, and J.D. Wolchok

N Engl J Med 2015;373:23-34

Event	Nivolumab (N=313)		Nivolumab plus Ipilimumab (N=313)		Ipilimumab (N=311)	
	Any	Grade 3 or 4	Any	Grade 3 or 4	Any	Grade 3 or 4
	number of patients with event (percent)					
Any adverse event	311 (99.4)	136 (43.5)	312 (99.7)	215 (68.7)	308 (99.0)	173 (55.6)
Treatment-related adverse event†	257 (82.1)	51 (16.3)	299 (95.5)	172 (55.0)	268 (86.2)	85 (27.3)
Diarrhea	60 (19.2)	7 (2.2)	138 (44.1)	29 (9.3)	103 (33.1)	19 (6.1)
Fatigue	107 (34.2)	4 (1.3)	110 (35.1)	13 (4.2)	87 (28.0)	3 (1.0)
Pruritus	59 (18.8)	0	104 (33.2)	6 (1.9)	110 (35.4)	1 (0.3)
Rash	81 (25.9)	2 (0.6)	126 (40.3)	15 (4.8)	102 (32.8)	6 (1.9)
Nausea	41 (13.1)	0	81 (25.9)	7 (2.2)	50 (16.1)	2 (0.6)
Pyrexia	18 (5.8)	0	58 (18.5)	2 (0.6)	21 (6.8)	1 (0.3)
Decreased appetite	34 (10.9)	0	56 (17.9)	4 (1.3)	39 (12.5)	1 (0.3)
Increase in alanine amino-transferase level	12 (3.8)	4 (1.3)	55 (17.6)	26 (8.3)	12 (3.9)	5 (1.6)
Vomiting	20 (6.4)	1 (0.3)	48 (15.3)	8 (2.6)	23 (7.4)	1 (0.3)
Increase in aspartate amino-transferase level	12 (3.8)	3 (1.0)	48 (15.3)	19 (6.1)	11 (3.5)	2 (0.6)
Hypothyroidism	27 (8.6)	0	47 (15.0)	1 (0.3)	13 (4.2)	0
Colitis	4 (1.3)	2 (0.6)	37 (11.8)	24 (7.7)	36 (11.6)	27 (8.7)
Arthralgia	24 (7.7)	0	33 (10.5)	1 (0.3)	19 (6.1)	0
Headache	23 (7.3)	0	32 (10.2)	1 (0.3)	24 (7.7)	1 (0.3)
Dyspnea	14 (4.5)	1 (0.3)	32 (10.2)	2 (0.6)	13 (4.2)	0
Treatment-related adverse event leading to discontinuation	24 (7.7)	16 (5.1)	114 (36.4)	92 (29.4)	46 (14.8)	41 (13.2)

Variable	Nivolumab (N=316)	Nivolumab plus Ipilimumab (N=314)	Ipilimumab (N=315)
Best overall response — no. (%)*			
Complete response	28 (8.9)	36 (11.5)	7 (2.2)
Partial response	110 (34.8)	145 (46.2)	53 (16.8)
Stable disease	34 (10.8)	41 (13.1)	69 (21.9)
Progressive disease	119 (37.7)	71 (22.6)	154 (48.9)
Could not be determined	25 (7.9)	21 (6.7)	32 (10.2)
Objective response†			
No. of patients with response	138	181	60
% of patients (95% CI)	43.7 (38.1–49.3)	57.6 (52.0–63.2)	19.0 (14.9–23.8)
Estimated odds ratio (95% CI)‡	3.40 (2.02–5.72)	6.11 (3.59–10.38)	—
Two-sided P value	<0.001	<0.001	—
Time to objective response — mo			
Median	2.78	2.76	2.79
Range	2.3–12.5	1.1–11.6	2.5–12.4

ORR

	Ipi + Nivo	Ipi + Nivo + Infliximab	Ipi + Nivo + Certolizumab
Gr 3/4 TRAE (%)	55	50	75
CR (%)	11.5	16.7	50
PR (%)	46.2	33.3	37.5
ORR (%)	57.7	50	87.5

The same thing?

- ICI + TNFi initiallly
- ICI → irAE → ICI + TNFi

Summary

- Rapid onset of Type 1 diabetes can result with the use of ICIs. The best management is early recognition of DM symptoms and on periodically blood sugar monitoring. Future studies are warranted to identify risk factors associated with ICI-DM.
- CMV infection must be considered for refractory irAE hepatitis cases.
- For a patient had developed ICI-SJS, successfully rechallenge ICI may be achieved with adding TNF inhibitor.
- High response rate in Ipi/Nivo/certolizumab cohort deserves further studies.


The End