免疫療法引起不良反應病例用藥討論

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2019.06.30

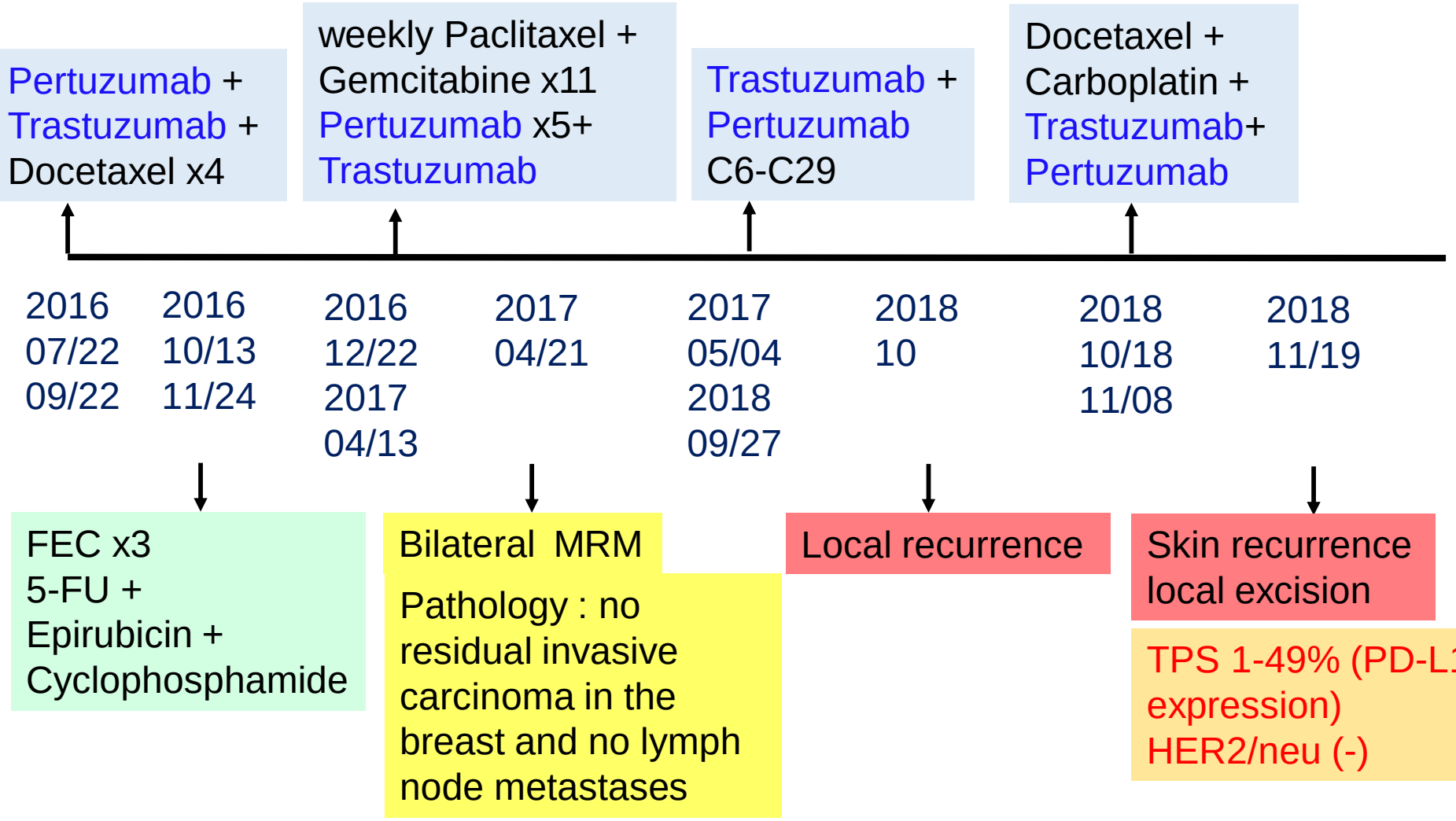
Case Report-1

Ms. Chang, 52 y/o, Height 144.8 cm, BW 46 kg

- **Subjective:**
- **PMH:**
- ✓ **Invasive ductal carcinoma of right breast, cT4AN3CM1 (with metastasis to left breast and bilateral lungs),stage IV, Ki-67 (MIB-1):45%,ER(-), PR(-), HER-2: FISH(+)**

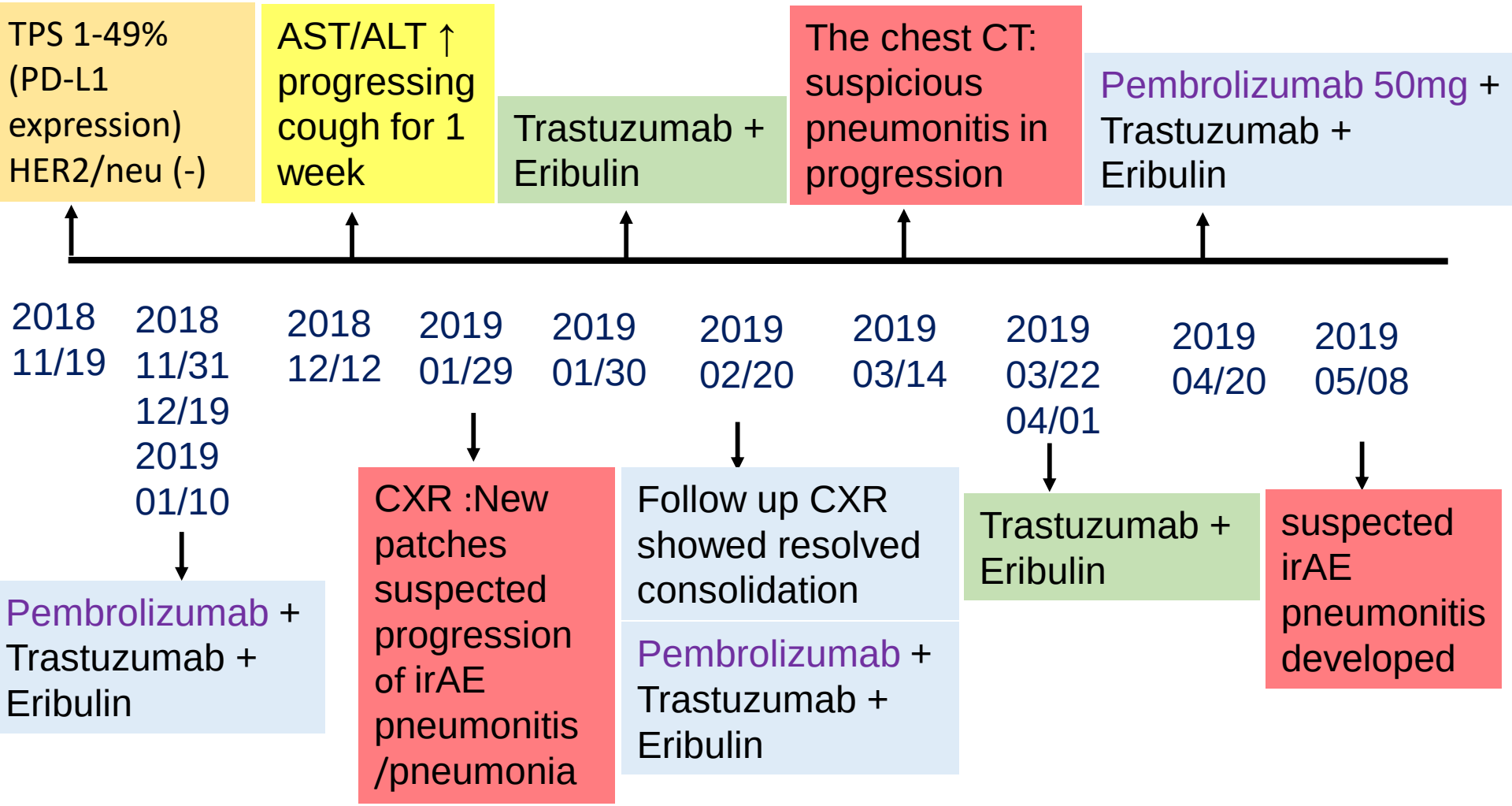
ER: estrogen receptor; PR: progesterone receptor
HER-2: human epidermal growth factor receptor 2
FISH: fluorescence in situ hybridization

Treatment course-1



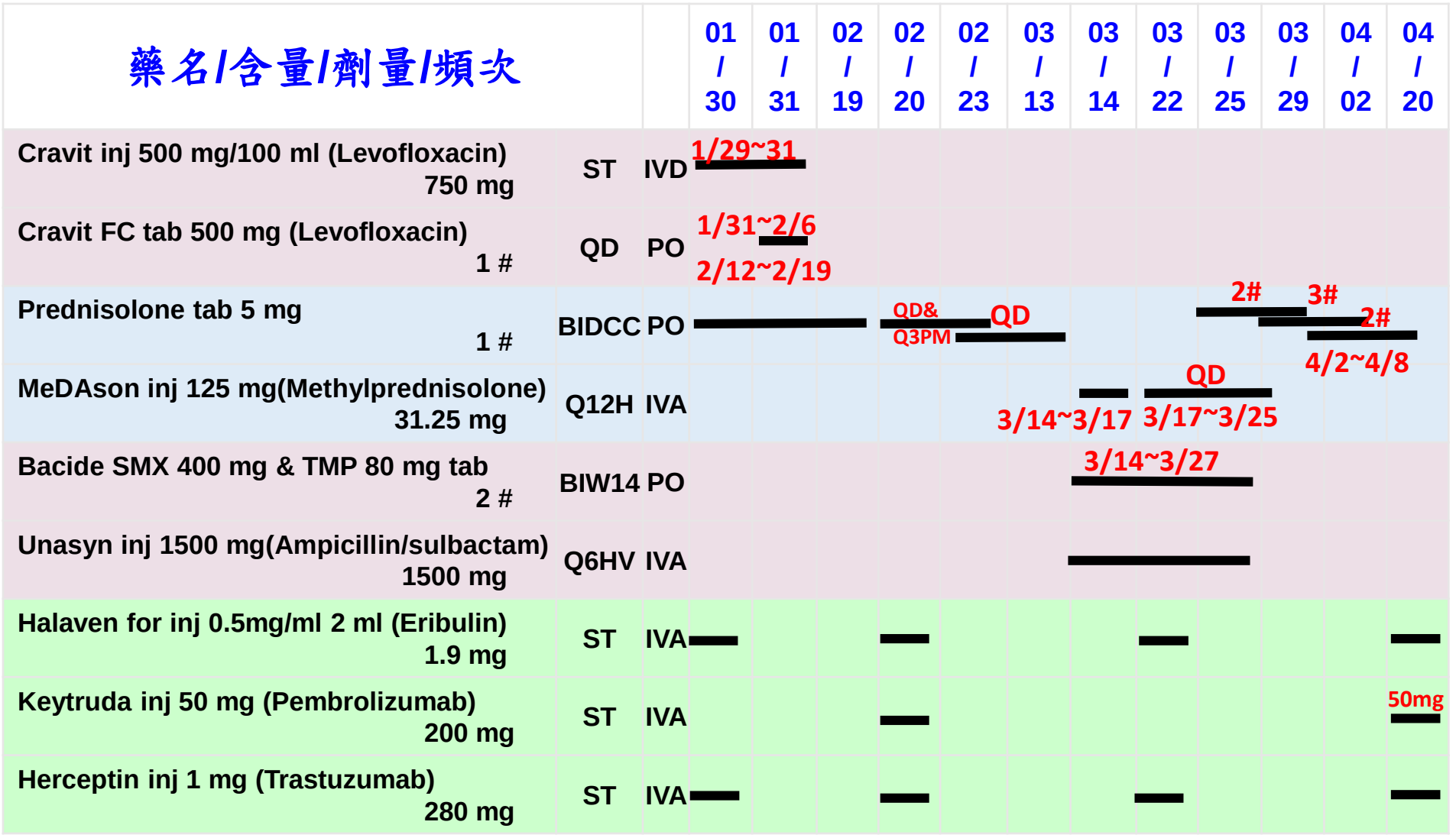
MRM: modified radical mastectomy
TPS: tumor proportion scores; PD-L1: programmed death-ligand 1

Treatment course-2



AST :aspartate aminotransferase; ALT :alanine aminotransferase
irAE :immune-related adverse event

Patient Drug Profile



Patient Drug Profile

藥名/含量/劑量/頻次			05/09	05/10	05/11	05/12	05/16	05/19	05/20	05/21	05/22	05/25
Maxipime inj 500 mg (Cefepime) 2000 mg	Q12H	IVA	5/9~5/14									
Cravit inj 500 mg/100 ml (Levofloxacin) 750 mg	QD	IVD										
Bacide SMX 400 mg & TMP 80 mg tab 2 #	BIW25	PO										
MeDAson inj 125 mg(Methylprednisolone) 62.5 mg	Q8H	IVA				31.25mg Q6H		31.25mg Q12H	31.25mg QD			
Solu-medrol inj 500 mg (Methylprednisolone) 500 mg	QD	IVA			5/11~5/13 steroid pulse therapy							
Metisone (Methylprednisolone) tab 4 mg 4 #	BIDCC	PO										3#

Case Report-2

- **Objective:**

日期	BUN	CREA	ALT	AST	BILIT	NA	K	WBC	SEG	LYM	Hgb	PLT
2018-11-30	14	0.71	16	23	0.43	141	3.9	3000	44.7	43.3	10.7	267000
2018-12-07	15	0.97	35	34	-	-	-	10800	50	27	12.2	351000
2018-12-12	16	0.99	82	66	-	-	-	28800	70	7	11.7	372000
2018-12-19	15	0.73	31	28	0.33	143	4.0	3300	31	47	11.7	331000

2019-01-31/03-14/05-08 CXR :favor immunotherapy related pneumonitis.

- **Assessment:**
  - **Immune-related adverse events (irAEs)**
  - ✓ **Hepatitis**
  - ✓ **Pneumonitis**
- **Plan to do:**
  - **Keep on current therapy.**
  - **Because repeated irAEs occurred, please avoid rechallenging pembrolizumab if possible.**

Discussion

- **The role of immunotherapy on breast cancer**

- **Immune-related adverse events (irAEs)**
  - **Most common irAEs**
  - **General principles of management**
  - ✓ **Hepatitis**
  - ✓ **Pneumonitis**
  - **Rechallenge**

Immunotherapy for breast cancer-1

- **Pembrolizumab (Keytruda®)**
  - **Advanced TNBC**
    - ✓ **Overall response rate(ORR):18.5%**

J Clin Oncol. 2016 Jul 20;34:2460-7

  - **mTNBC**
    - ✓ **PD-L1(+)→ ORR: 5.7%**

Disease control rate: 9.5%

    - ✓ **Durable antitumor activity & safety**

Ann Oncol. 2019 Mar 1;30:397-404

TNBC :triple-negative breast cancer
mTNBC :metastatic triple-negative breast cancer

Immunotherapy for breast cancer-2

- **Atezolizumab (Tecentriq®) + protein-bound paclitaxel (Abraxane®)**
  - **Locally advanced TNBC can't removed by surgery & metastatic TNBC**
  - **PD-L1(+)**
  - ✓ **Median overall survival ↑9.5 months(25.0 months (Tecentriq®+Abraxane®)v.s. 15.5 months(placebo+Abraxane®))**

TNBC :triple-negative breast cancer

N Engl J Med. 2018 Nov 29;379:2108-21

Immune-related adverse events (irAEs)

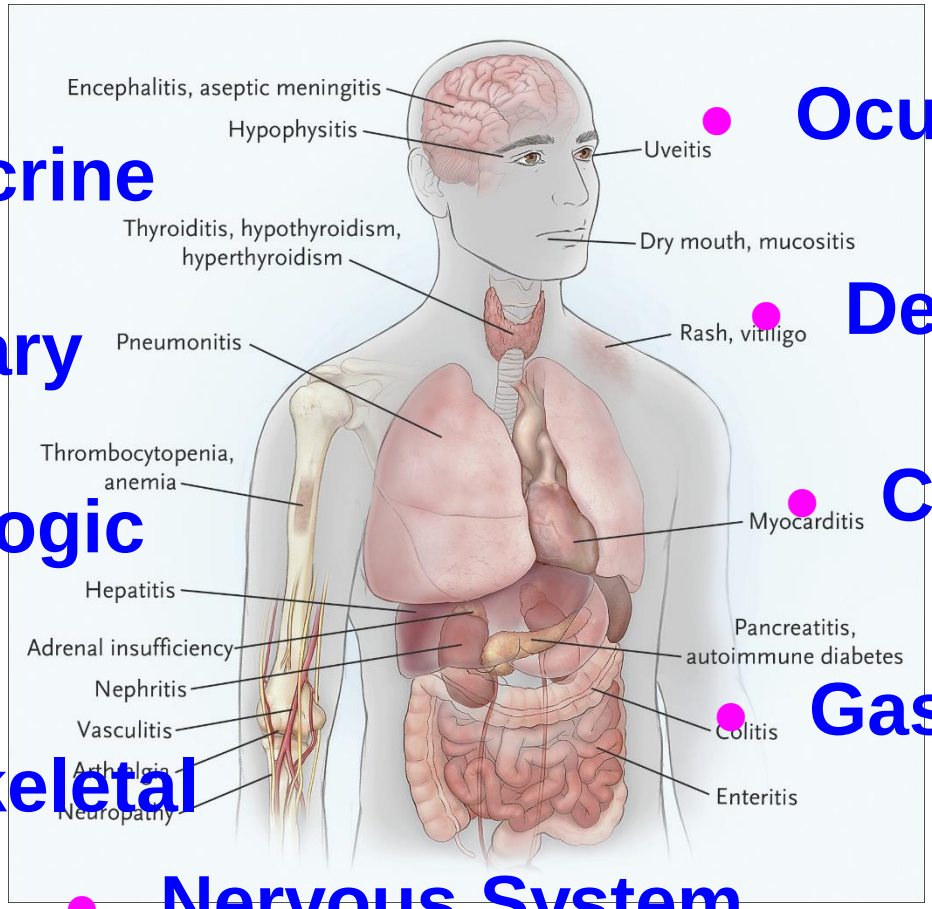
- **Precise pathophysiology**
  - **Unknown→immune checkpoints play in maintaining immunologic homeostasis**
- **Severity**
  - **Anti–CTLA-4 > anti–PD-1/PD-L1**
  - **Combination > alone**
- **When occur**
  - **Within the first few weeks to months after treatment but can occur anytime**

CTLA-4: cytotoxic T-lymphocyte–associated antigen 4
PD-1: programmed death 1

N Engl J Med. 2018 Jan 11;378(2):158-168

Most common irAEs

- Endocrine
- Pulmonary
- Hematologic
- Renal
- Musculoskeletal
- Ocular
- Dermatologic
- Cardiovascular
- Gastrointestinal
- Nervous System



N Engl J Med. 2018 Jan 11;378(2):158-168

General principles of management

- **No prospective trials have defined strategies for effectively managing specific irAEs**
- **Clinical practice remains variable**

Grade	Checkpoint inhibitor	Management
Grade 2 (Moderate)	Withheld Not be resumed until symptoms or toxicity is grade 1 or less	Corticosteroids (**prednisone 0.5 mg/kg/day or equivalent**) should be started if symptoms do not resolve within a week.
Grade 3 or 4 (Severe or life-threatening)	Permanently discontinued	• High doses of corticosteroids (**prednisone 1 ~2 mg/kg/day or equivalent**) should be given. • When symptoms subside to grade 1 or less→steroids gradually **tapered** over at least one month. • **Infliximab (5 mg/kg)** may be considered.

UpToDate 2019

Hepatitis

- **Manifestations**
  - **↑ AST and ALT；↑total bilirubin (rarely)**
  - **Asymptomatic laboratory abnormalities (most episodes)± fever**
  - **Anti–CTLA-4＜10%；0.7~1.8% anti–PD-1/PD-L1**
  - **Onset**
  - ✓ **5 ~6 weeks from start of treatment but can occur months later**

AST :aspartate aminotransferase
ALT :alanine aminotransferase

Liver Int 2018;38:976-987
NCCN Guideline V2.2019
Ann Oncol. 2018 Oct 1;29(Supplement_4):iv264-iv266

Hepatitis

- **Management**

Grade	Checkpoint inhibitor	Management
Grade 1 AST/ALT >3X ULN and/or BILIT>1.5 X ULN	Continue with close monitoring	Monitor laboratories 1~2 times weekly. **Ms.Chang: 2018-12-12 ALT 82 ; AST 66** **2018-12-19 ALT 31; AST 28**
Grade 2 AST/ALT 3~5X ULN and/or BILIT>1.5~3 X ULN	Withheld; Not be resumed until symptoms or toxicity is grade 1 or less	If symptoms do not resolve within a week: Corticosteroids (**prednisone 0.5~1 mg/kg/day** or equivalent)
Grade 3 AST/ALT 5~20 X ULN and/or BILIT>3~10 X ULN	Permanently discontinued	• Corticosteroid **1~2 mg/kg methylprednisolone** or equivalent. • Corticosteroid refractory or no improvement after 3 days: consider **mycophenolate mofetil** or **azathioprine** • Infliximab should not be given to patients with immune-mediated heapatitis.
Grade 4 AST/ALT >20 X ULN and/or BILIT>10 X ULN		

ULN: upper limited normal
BILIT：total bilirubin

Ann Oncol. 2018 Oct 1;29(Supplement_4):iv264-iv266

Pneumonitis

- **Manifestations**
  - **Onset: median 2.8 months (9 days~19 months)**
  - **Common presenting symptoms : dyspnea(53%) cough (35%) ; 1/3 asymptomatic**

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4
Pneumonitis	Asymptomatic; confined to one lobe of the lung or <25% of lung parenchyma; clinical or diagnostic observations only	Symptomatic; **≥ 1 lobe of the lung or 25~50% of lung parenchyma**; medical intervention indicated; limiting instrumental ADL	Severe symptoms; hospitalization required; involves **all lung lobes or >50% of lung parenchyma**; limiting self-care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (intubation)

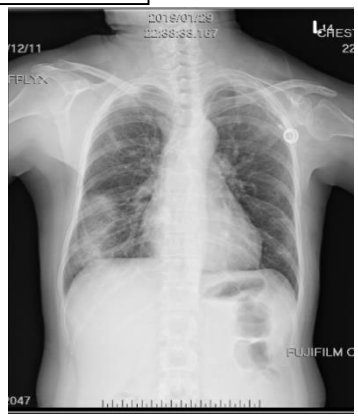
Pneumonitis is characterized by inflammation focally or diffusely affecting the lung parenchyma.
ADL: activities of daily living.

J Clin Oncol. 2018 Jun 10;36:1714-68

Ann Oncol. 2018 Oct 1;29(Supplement_4):iv264-iv266

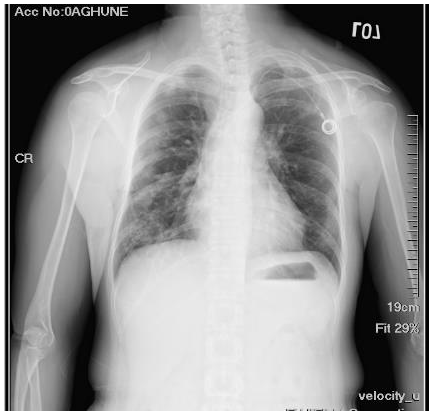
Pneumonitis

Ms.Chang:



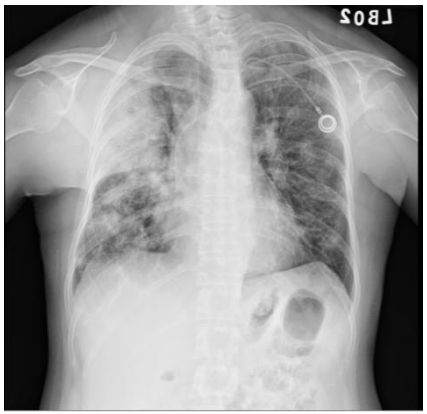
1st (2019-01-29):
Ill-define opacities at bilateral upper lung, Developement of RML consolidation, suspected post-RT change or consolidative pneumonitis.

Grade 2~3



2nd (2019-03-14):
Multiple ill-define consolidative patches and increased infiltration at bilateral lung fields, limited at subpleural regions, may compatible with immunotherapy-induced pneumonitis. In progressive change as compared the study on 20190129

Grade 3



3rd (2019-05-08):
Large consolidative patch at RUL and bilateral lung fields, with air-bronchogram, most likely pneumonia, such as bacterial or atypical infection.

Grade 3

RML:right middle lobe RUL:right upper lobe

Pneumonitis

- **Management**

Grade	Checkpoint inhibitor	Management
Grade 1	Hold with radiographic evidence of pneumonitis progression	If no improvement→treat as Grade 2
Grade 2	Withheld Not be resumed until symptoms or toxicity is Grade 1 or less	• Prednisone 1~2 mg/kg/day and taper by 5 ~10 mg/week over 4~6 weeks. • Consider **empirical antibiotics.** • No clinical improvement after 48~72 hrs of prednisone→treat as Grade 3
Grade 3 or 4	Permanently discontinued	• **Empirical antibiotics** • Methylprednisolone IV 1~2 mg/kg/day • 48 hrs no improve: **infliximab** 5 mg/kg; **mycophenolate mofetil** IV 1 g BID;**IVIG** *5 days ; **cyclophosphamide** • Taper steroids over 4~6 weeks

IVIG: intravenous immune globulin

Ann Oncol. 2018 Oct 1;29(Supplement_4):iv264-iv266

Rechallenge

- **Principles:**
  - **Assess patient's tumor status prior to rechallenge**
  - **If re-challenged and toxicity returns, permanently discontinue class of immunotherapy.**

Organ-Specific	Management
Liver	• Transaminitis without elevated bilirubin: following a Grade 2 irAE →resumption of immunotherapy after ALT/AST return to baseline and steroids, if used, have been tapered to ≤10 mg prednisone equivalent daily. • **Grade 3–4 hepatitis:** Permanent discontinuation is warranted
Lung	• **Progressive grade 1 pneumonitis** requiring a hold: Consider resuming upon radiographic evidence of improvement. • **Grade 2:** Resume once pneumonitis has resolved to ≤ Grade 1 and patient is off steroids. • **Grade 3–4 pneumonitis:Permanent** discontinuation

Ms.Chang 1st:

Ms.Chang 2nd:

NCCN Guideline V2.2019

Take Home Massage

- **Commen irAEs**
  - **Skin;GI tract;Lungs;Endocrine;Musculoskeletal; Renal;Nervous;Hematologic;Cardiovascular;Ocular**
- **Hepatitis**
  - **Moderate: Withheld; Corticosteroids (0.5~1 mg/kg/day)**
  - **Severe or life-threatening: Permanently discontinued**
  - **Infliximab should not be given**
- **Pneumonitis**
  - **Moderate: Empirical antibiotics; steroid (1~2 mg/kg/day)**
  - **Severe or life-threatening: Permanently discontinued**

Thanks for Your Attention