12th Challenges in Viral Hepatitis and Liver Disease

Diagnosis and Management of Immune Checkpoint Inhibitor-Induced Liver Injury

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Plan

- Background
- ICI mechanisms of action
- General overview of ICI toxicities
- ICI hepatotoxicity diagnosis
- ICI hepatotoxicity management
- Place for liver histology
- Refractory IRAEs management
- ICI re-challenge
- IRAEs and oncological outcomes
- Conclusions

Background

- **Antagonistic antibodies (mAbs) that block specific immune checkpoint molecules** (CTLA-4, PD-1 and its tumoral ligand PD-L1)
- **Targeting these checkpoints had led to long-lasting tumor responses in metastatic disease (First example: melanoma)**
- **These new immunotherapies also generate dysimmune toxicities, called immune-related adverse events** (IRAEs)

Michot JM et al. Eur J Cancer 2016

«Beginning of the story»

ORIGINAL ARTICLE

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

F. Stephen Hodi, M.D., Steven J. O'Day, M.D., David F. McDermott, M.D., Robert W. Weber, M.D., Jeffrey A. Sosman, M.D., John B. Haanen, M.D., Rene Gonzalez, M.D., Caroline Robert, M.D., Ph.D., Dirk Schadendorf, M.D., Jessica C. Hassel, M.D., Wallace Akerley, M.D., Alfons J.M. van den Eertwegh, M.D., Ph.D., et al.

RESULTS

The median overall survival was 10.0 months among patients receiving ipilimumab plus gp100, as compared with 6.4 months among patients receiving gp100 alone (hazard ratio for death, 0.68; P<0.001). The median overall survival with ipilimumab alone was 10.1 months (hazard ratio for death in the comparison with gp100 alone, 0.66; P=0.003). No difference in overall survival was detected between the ipilimumab groups (hazard ratio with ipilimumab plus gp100, 1.04; P=0.76). Grade 3 or 4 immune-related adverse events occurred in 10 to 15% of patients treated with ipilimumab and in 3% treated with gp100 alone. There were 14 deaths related to the study drugs (2.1%), and 7 were associated with immune-related adverse events.

Hodi FS et al. N Engl J Med 2010

ORIGINAL ARTICLE

Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma

James Larkin, M.D., Ph.D., Vanna Chiarion-Sileni, M.D., Rene Gonzalez, M.D., Jean Jacques Grob, M.D., C. Lance Cowey, M.D., Christopher D. Lao, M.D., M.P.H., Dirk Schadendorf, M.D., Reinhard Dummer, M.D., Michael Smylie, M.D., Piotr Rutkowski, M.D., Ph.D., Pier F. Ferrucci, M.D., Andrew Hill, M.D., et al.

Table 2. Response to Treatment.

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

* The best overall response was assessed by the investigator according to the Response Evaluation Criteria in Solid Tumors, version 1.1.
† Data included patients with a complete response and those with a partial response. The calculation of the confidence interval was based on the Clopper–Pearson method. These analyses were conducted with the use of a two-sided Cochran–Mantel–Haenszel test stratified according to PD-L1 status, *BRAF* mutation status, and metastasis stage.
‡ The comparison is with the ipilimumab group.

Larkin J et al. N Engl J Med 2015

Indications

Advanced-stage melanoma
Renal cell carcinoma
Microsatellite high instability (MSI)-cancers
Small-cell lung cancer (SCLC)
Non-small-cell lung cancer (NSCLC)

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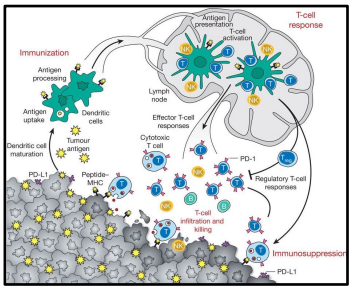
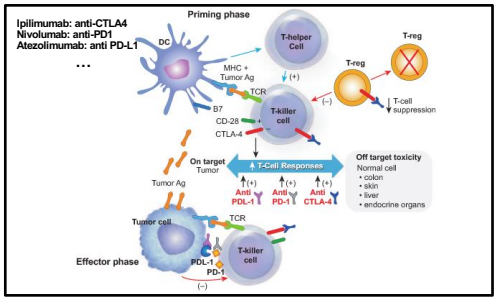
Mechanism of action



- Promotion of antigen presentation by dendritic cells
- Promotion of protective T-cell responses
- Overcoming immunosuppression in tumour bed

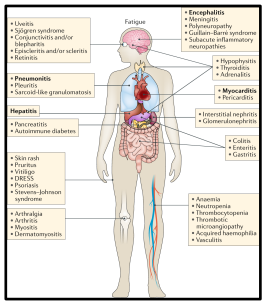
Mellman I, Coukos G and Dranoff G. Nature 2011

Mechanism of action



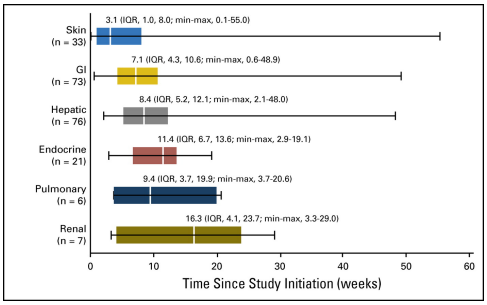
Suzman et al. Liver Int 2018

IRAEs



Martins F et al. Nat Rev Clin Oncol 2019

IAREs timing
combined ICI



Sznol M et al. J Clin Oncol 2017

IRAEs

- Agent
- Dose
- Combined therapy
- Characteristics of individual patients and tumor, preexistent autoimmune disease (AID)
- Fatal ICI-associated adverse events up to 1.3% in combined therapy

Martins F et al. Nat Rev Clin Oncol 2019

IRAEs in patients with AID

- Patients with pre-existing autoimmune diseases have been excluded from clinical trials of immune checkpoint inhibitors (ICIs) for cancer
- Retrospective data: significant increase of IRAEs/flare of preexistent AID disease
- Close monitoring is needed!
- Decision to introduce ICI should be based on risk-benefit evaluation for individual patient

Danlos FX et al. Eur J Cancer 2018;
Kehl KL et al. Cancer Immunol Immunother 2019;
Tison A et al. Arthritis Rheumatol 2019

Immune-related(ir)Hepatotoxicity

- IRH has emerged as a key target organ for ICIs toxicity
- Hepatotoxicity gradation is based on peak abdonormalities of serum liver biochemical indicators

	Grade 1	Grade 2	Grade 3	Grade 4
ALT (SGPT)	>1.25 - ≤3 X ULN	>3 - ≤5 X ULN	>5 - ≤10 X ULN	>10 X ULN
AST (SGOT)	>1.25 - ≤3 X ULN	>3 - ≤5 X ULN	>5 - ≤10 X ULN	>10 X ULN
Total bilirubin	>1.25 - ≤2 X ULN	>2 - ≤3 X ULN	>3 - ≤10 X ULN	>10 X ULN

Wang W et al. Int J Cancer 2017
National Cancer institute. Common Terminology Criteria for Adverse Events (CTCAE) v.5.0 2017

Ir Hepatotoxicity

Agent	Checkpoint target	Initial US approval* (monotherapy)	Tumour types	Incidence of hepatotoxicity*	Median time to onset* (months)
Ipilimumab (Yervoy)	CTLA-4	2011	Melanoma	4-11% (fatal in approximately 0.2%)	1.4 to 2
Pembrolizumab (Keytruda)	PD-1	2014	Melanoma Non-small cell lung cancer Head & neck squamous cell cancer Classical Hodgkin lymphoma Urothelial carcinoma Microsatellite instability-high/mismatch repairs deficient cancers Gastric cancer	0.7%	1.3
Nivolumab (Opdivo)	PD-1	2014	Melanoma Non-small cell lung cancer Renal cell carcinoma Classical Hodgkin lymphoma Head & neck squamous cell cancer Urothelial carcinoma Microsatellite instability-high/mismatch repair deficient colorectal cancer Hepatocellular carcinoma	1.8% (12% in combination with ipilimumab)	3.3 (2.1 in combination with ipilimumab)
Atezolizumab (Tecentriq)	PD-L1	2016	Urothelial carcinoma Non-small cell lung cancer	0.9-1.3% (fatal in <0.1%)	0.9-1.1
Avelumab (Bavencio)	PD-L1	2017	Merkel cell carcinoma Urothelial carcinoma	0.9% (fatal in approximately 0.1%)	3.2
Durvalumab (Imfinzi)	PD-L1	2017	Urothelial carcinoma Non-small lung cell cancer	1.1% (fatal in <0.1%)	1.7

Suzman D et al. Liver Int 2018

Ir Hepatotoxicity

- Multidisciplinary approach
- From the beginning…
- Hospitalization in grade ≥3 toxicities and even earlier depending on comorbidities and fraility

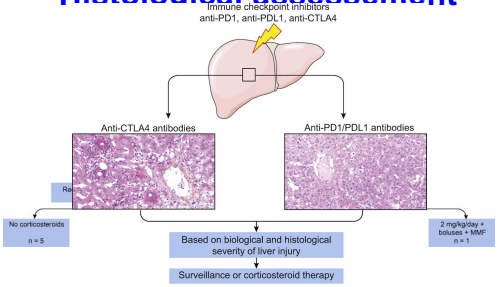
Hepatotoxicity CTCAE grade of severity	General recommendations*
Grade ≥2 (AST and/or ALT >3-5 times upper limit of normal (ULN) or total bilirubin >1.5-3 times ULN)	1. Institute corticosteroids (Minimum 0.5-1.0 mg/d prednisone equivalent) AND 2. Withhold ICI (Do not restart until return to Grade 1 or baseline) AND 3. Monitor for changes in liver function (General principals include: a. Recheck LTs/INR/albumin every 3 d b. Review all potential hepatotoxic medications c. Rule out alternative viral or autoimmune etiologies)
Grade ≥3 (AST and/or ALT >5 times ULN or total bilirubin >3 times ULN)	1. Institute corticosteroids (1-2 mg/kg/d prednisone equivalent)* AND 2. Permanent discontinuation

Suzman D et al. Liver Int 2018

Work-up

- Liver imaging: tumoral infiltration? Vascular complication? Other?
- HBsAg, anti-HCV, anti-HAV IgM, HEV PCR
- Total IgG, ANA, anti-SMA, anti-actin
- Medication history/phytotherapia
- Ferritin (oncological patients at risk for hemophagocytic syndrome)
- Biopsy!!!

IR Hepatotoxicity Histological assessement

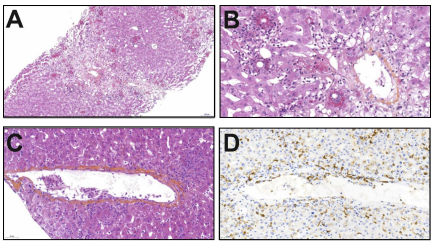


De Martin E et al. J Hepatol 2018

Histological patterns: anti-CTLA4

Centilobular confluent necrosis

Fibrin ring granulomas
Sinusoidal infl. infiltrates

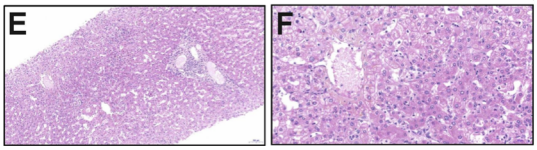


Endothelitis

Perivenular subendothelial CD8 T lymphocytes

De Martin E et al. J Hepatol 2018

Histological patterns: anti-PD1



Mild hepatitis
Mild periportal and lobular activity

Lobular lymphocytes and histocytes
No plasmocytes

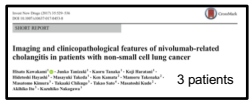
De Martin E et al. J Hepatol 2018

Histological assessment

- Liver injury resulting from ICI is not typical of what is seen in classical AIH
- High heterogenicity
- Very informative regarding severity
- Evolution toward chronicity: fibrosis!
- Helpful for <u>tailoring management</u> which does not require systematic corticosteroids…

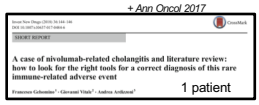
De Martin E et al. J Hepatol 2018

Immunotherapy-related cholangitis

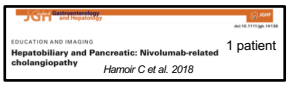

Imaging and clinicopathological features of nivolumab-related cholangitis in patients with non-small cell lung cancer

3 patients

+ Ann Oncol 2017

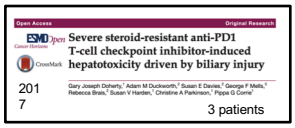

A case of nivolumab-related cholangitis and literature review: how to look for the right tools for a correct diagnosis of this rare immune-related adverse event

1 patient


EDUCATION AND IMAGING
Hepatobiliary and Pancreatic: Nivolumab-related cholangiopathy

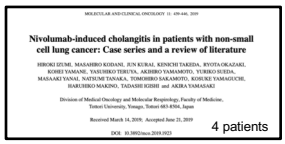
1 patient

Hamoir C et al. 2018


Severe steroid-resistant anti-PD1 T-cell checkpoint inhibitor-induced hepatotoxicity driven by biliary injury

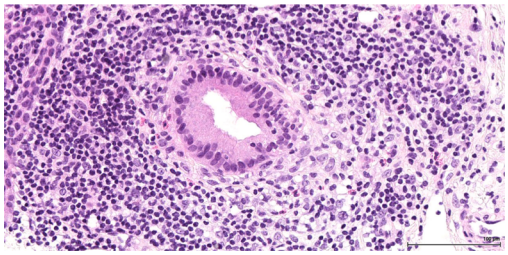
201 7

3 patients


Nivolumab-induced cholangitis in patients with non-small cell lung cancer: Case series and a review of literature

4 patients

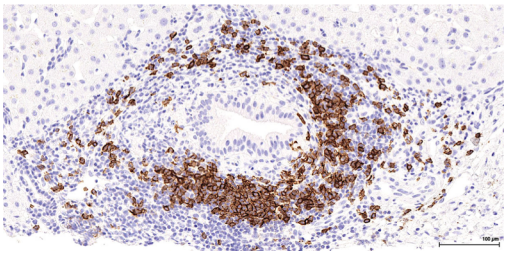
Immunotherapy-related cholangitis



Courtesy of Christine Sempoux

Immunotherapy-related cholangitis

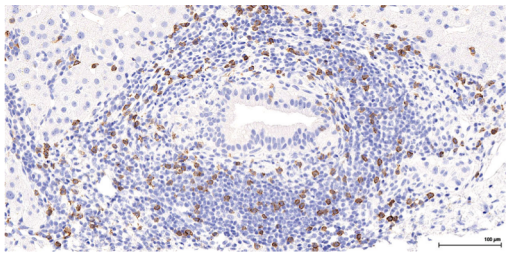
CD20



Courtesy of Christine Sempoux

Immunotherapy-related cholangitis

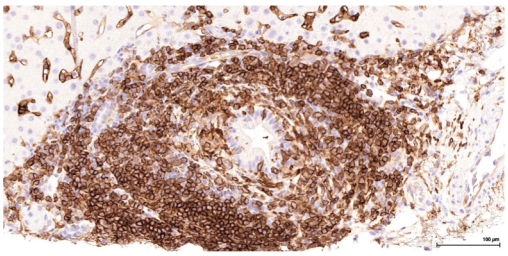
CD8



Courtesy of Christine Sempoux

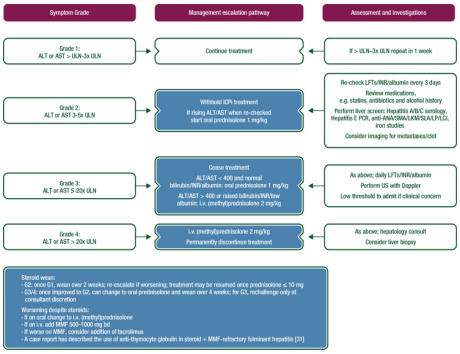
Immunotherapy-related cholangitis

CD4



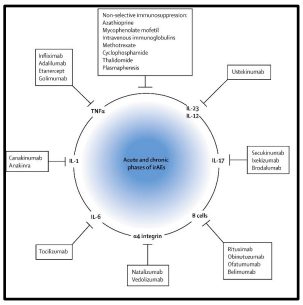
Courtesy of Christine Sempoux

Management ESMO CPG



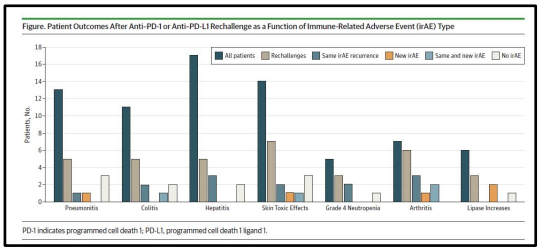
ESMO CPG. Ann Oncol 2017

New therapeutic perspectives for refractory cases



Martins F et al. Lancet Oncol 2019

Re-challenge



The second IRAEs were not found to be more severe than the first
Close monitoring is mandatory

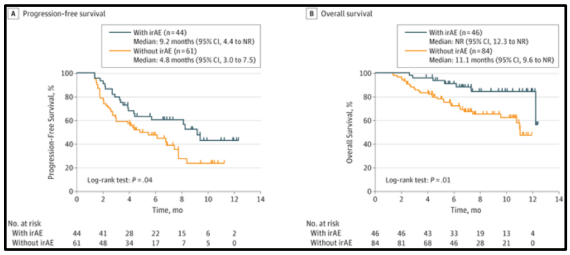
Simonaggio A et al. JAMA Oncol 2019

Re-challenge

- **A decision to reintroduce ICIs following discontinuation owing IRAEs should be made on an individual basis**
- **Permanent discontinuation of ICIs is generally advocated in patients with high-grade ocular, hepatic, pancreatic and/or pulmonary IRAEs**

Martins F et al. Nat Rev Clin Oncol 2019

IRAEs and oncological outcomes



Haratani K et al. JAMA Oncol 2018

IRAEs and oncological outcomes

- Meta-analysis, including 48 studies
- 7936 patients
- Objective tumoral response rate was positively correlated with the incidence of IRAEs across multiple neoplasms
- However, not confirmed for severe (IRAEs ≥Grade 3) even with potential deleterious effect on prognosis

Xing P et al. J Immunother Cancer 2019

Conclusions

- ICI are reshaping the prognosis of many cancers
- Increasing number of patients will be exposed
- New spectrum of toxicities, potentialy letal
- Multidisciplinary approach
- Close monitoring of ICIs treated patients
- Personalised approach going beyond systematic corticosteroid use
- Key role of histology in liver toxicity

Conclusions

- Many opened questions:
  - Re-challenge
  - Optimal immunosuppression
  - AID patients (prospective studies needed)

Questions?