Response Criteria on Checkpoint Inhibitors Treatment

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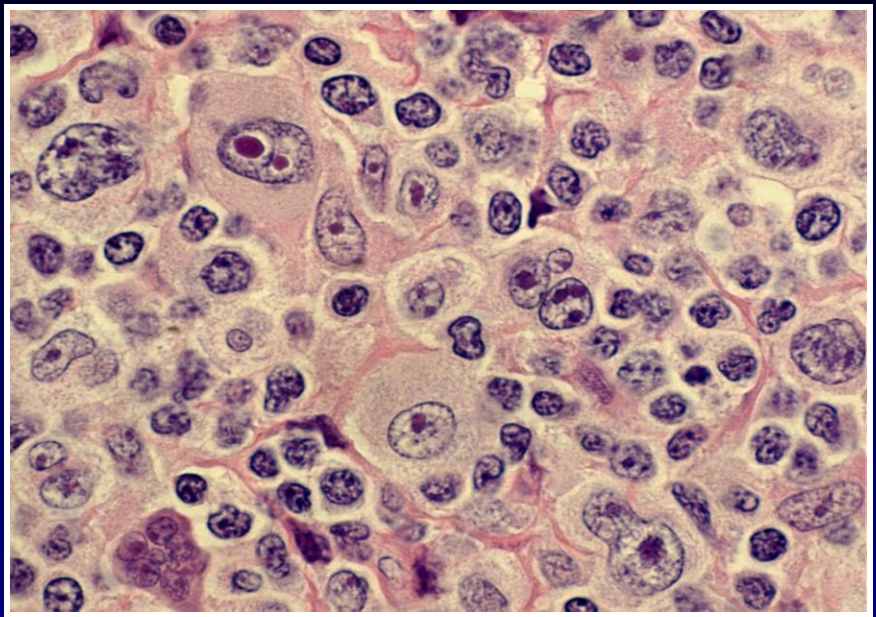
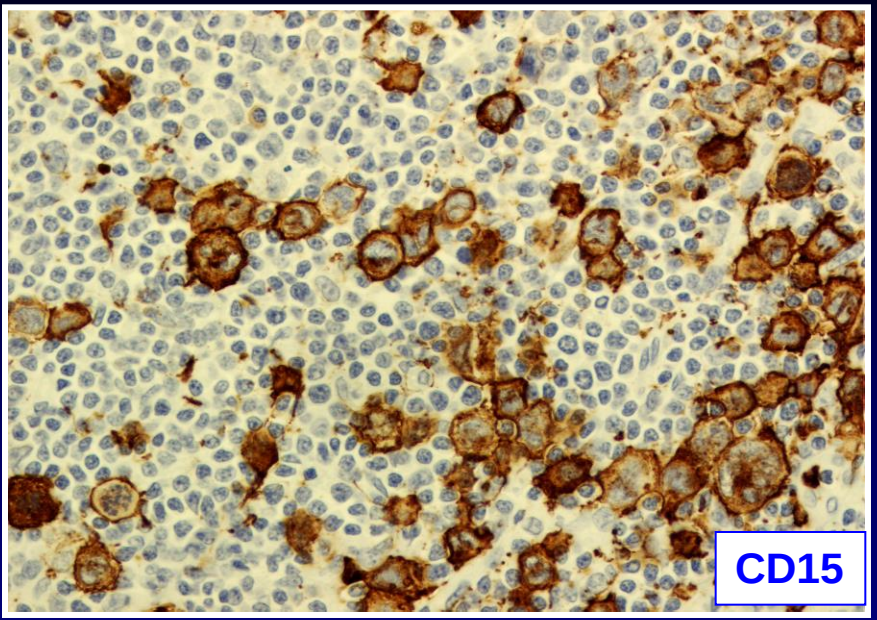
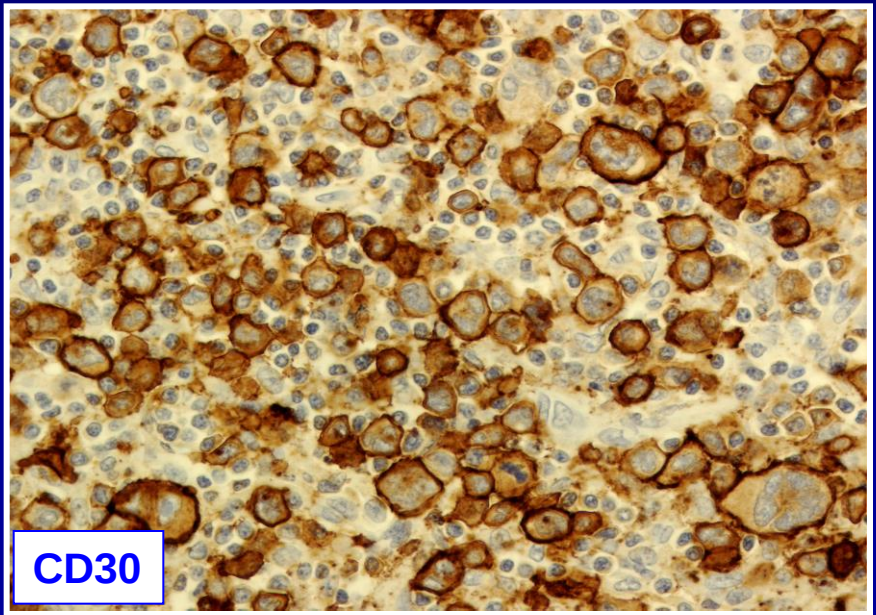
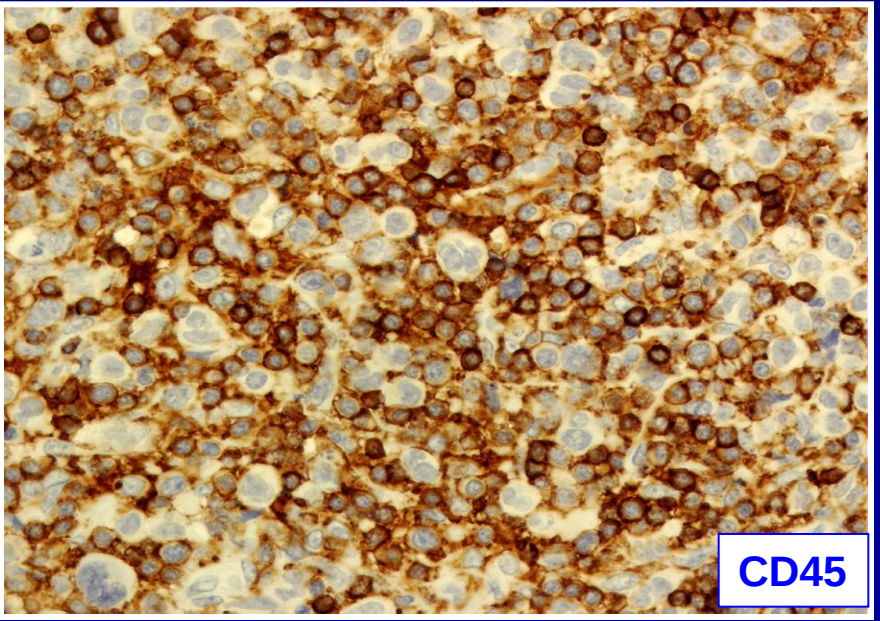
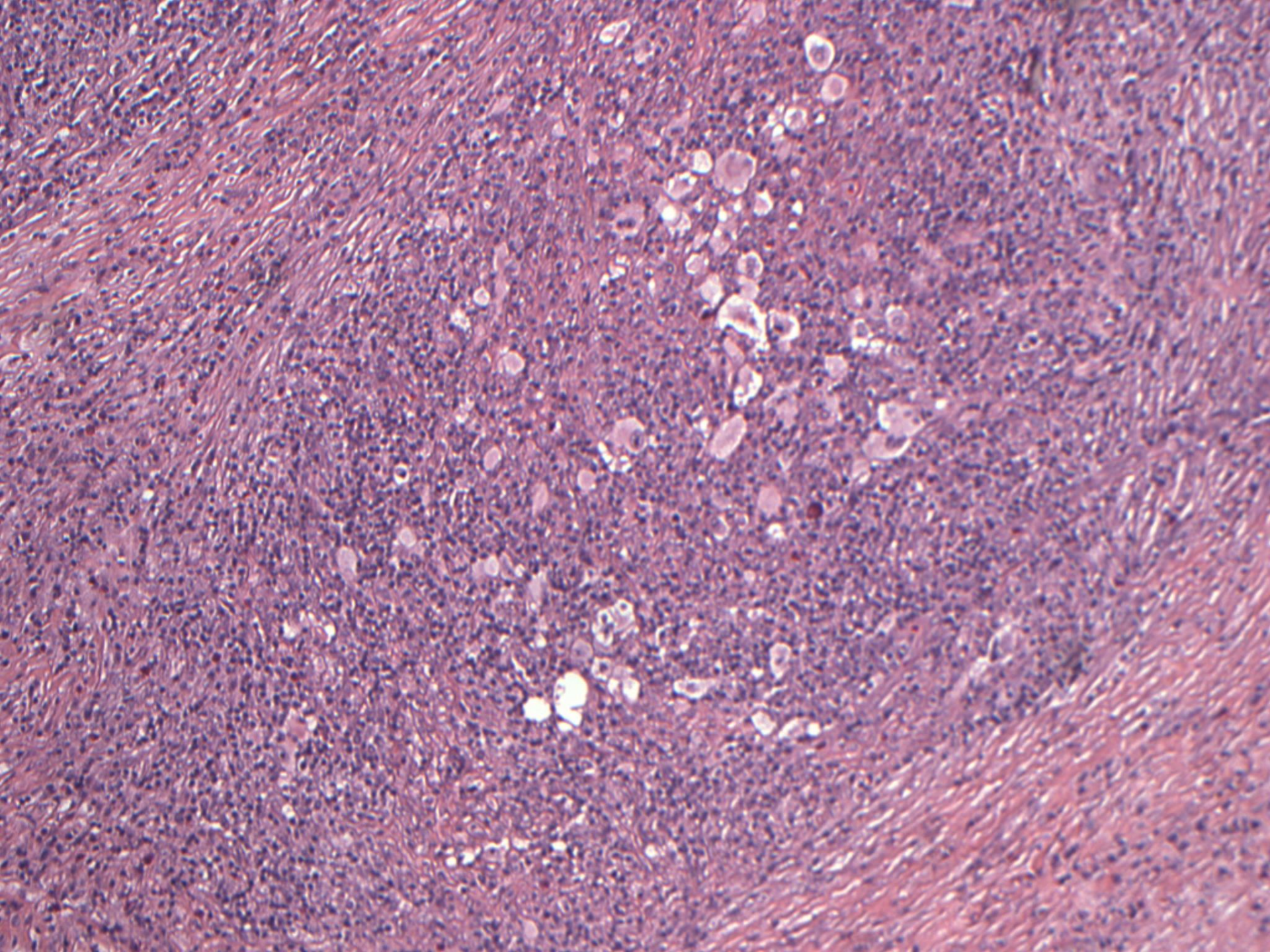
Classical Hodgkin's Lymphoma

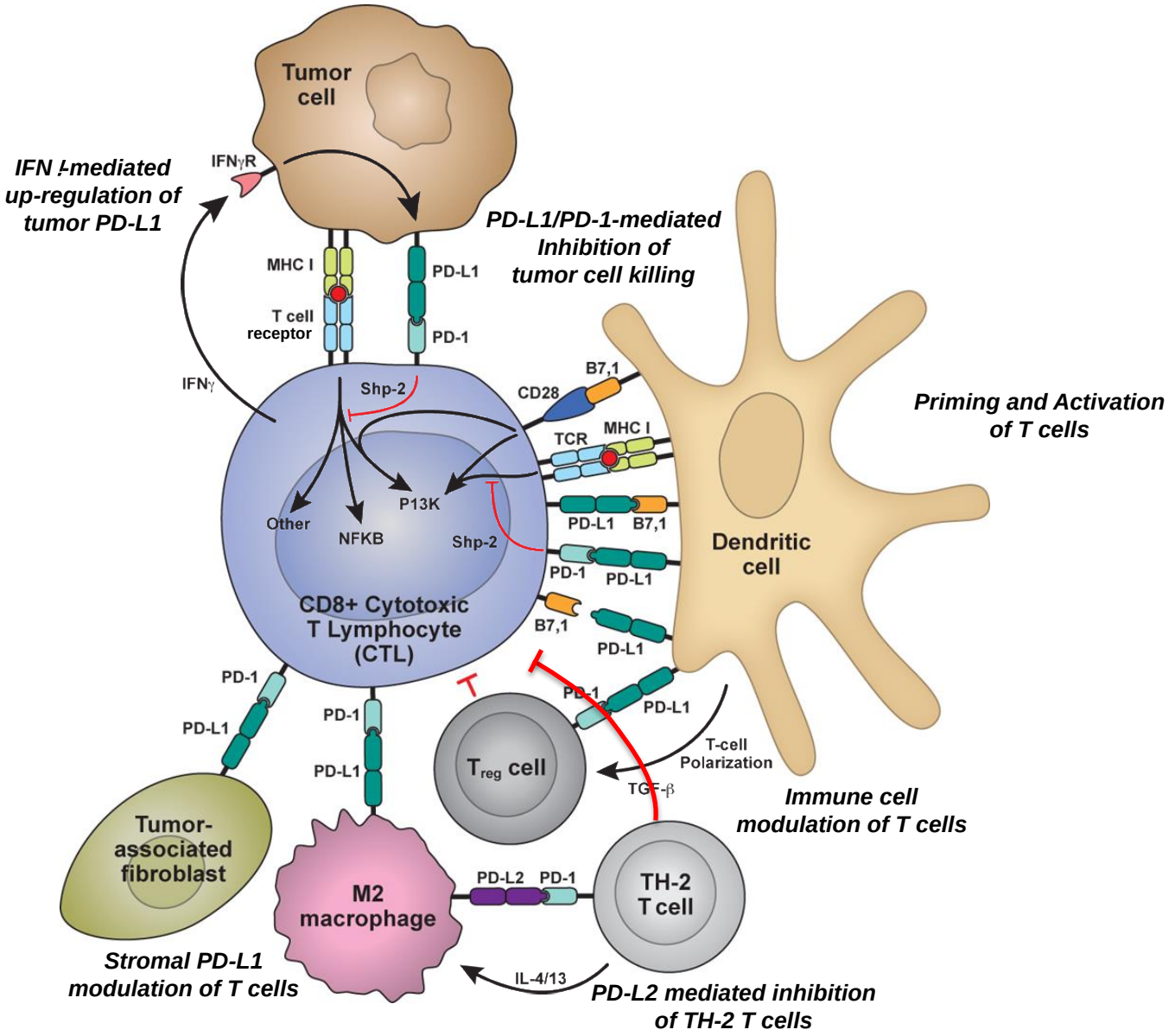








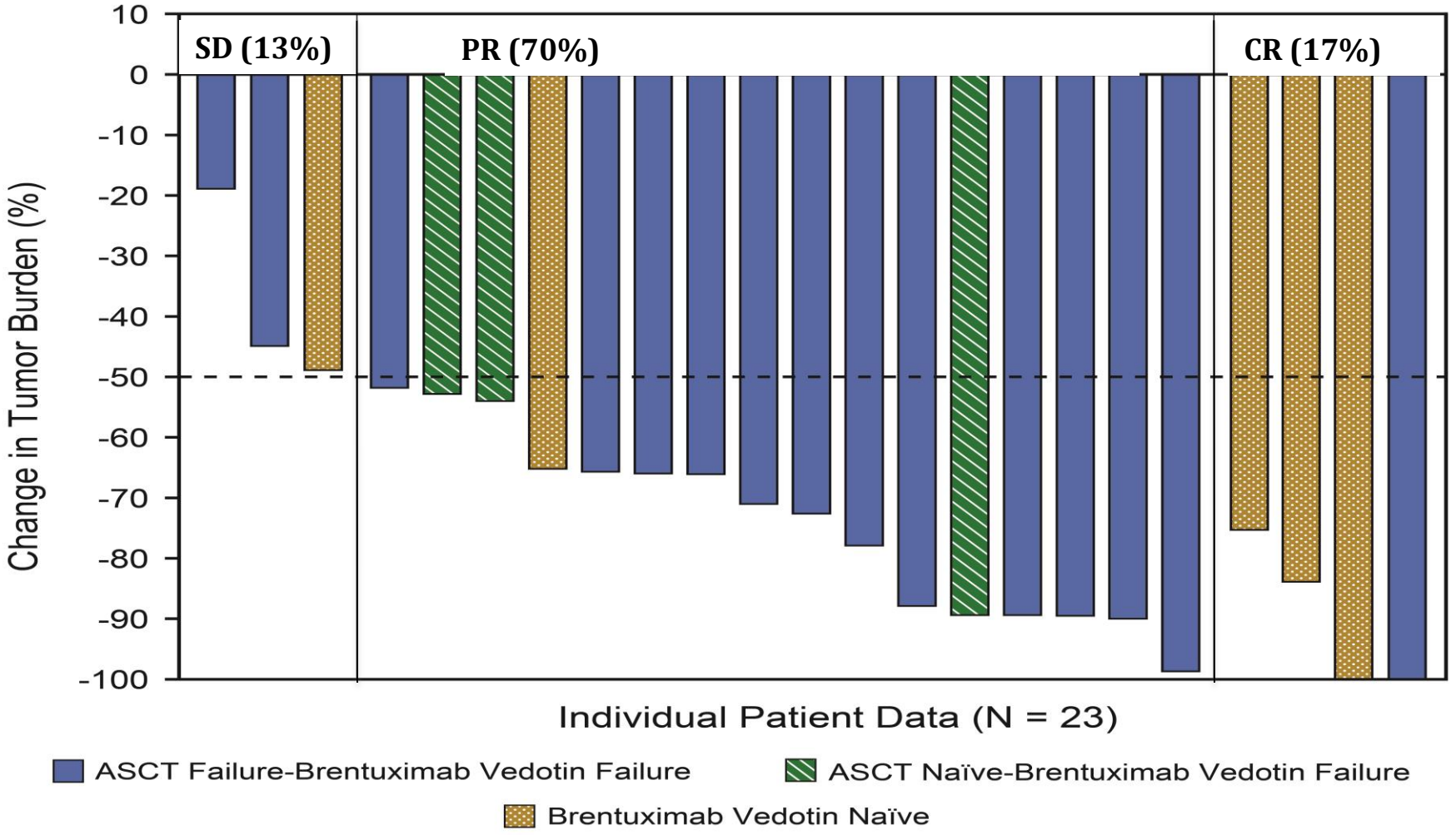




PD-L1 plays an important role in dampening the anti-tumor immune response

Chen DS, Irving BA, Hodi FS.
Clin Cancer Res. 2012;18:6580.

Hodgkin Lymphoma - Response to Nivolumab

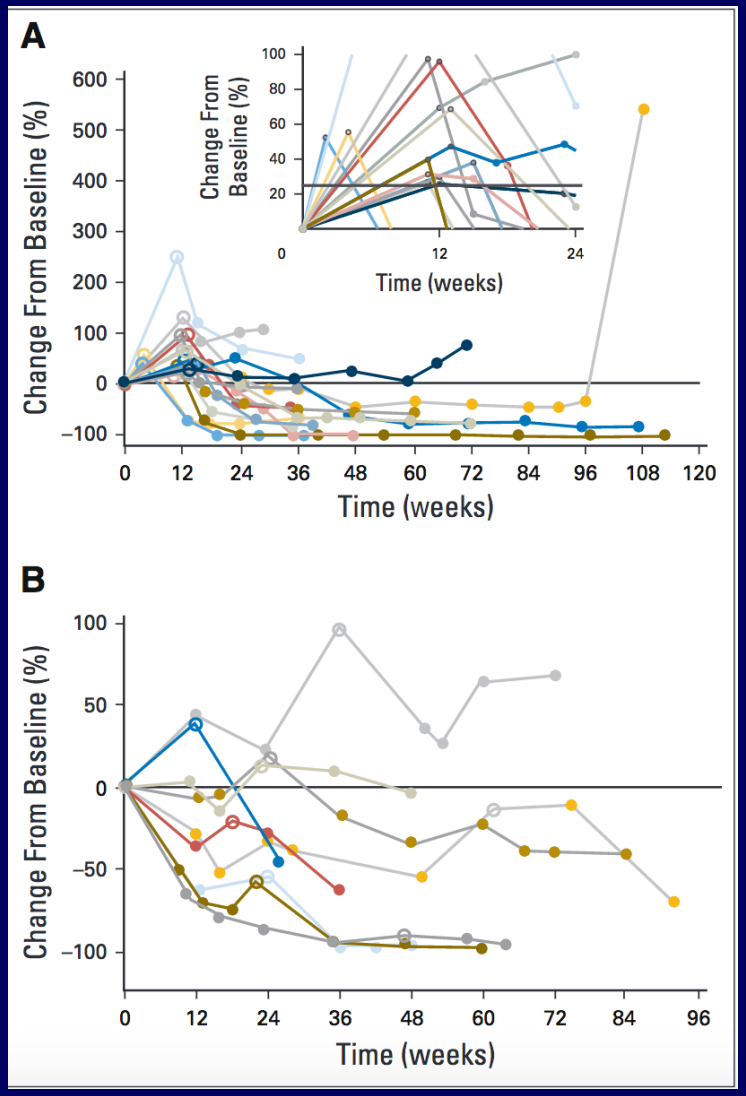


Ansell et al. N Engl J Med. 2014 Dec 6.

A New Problem

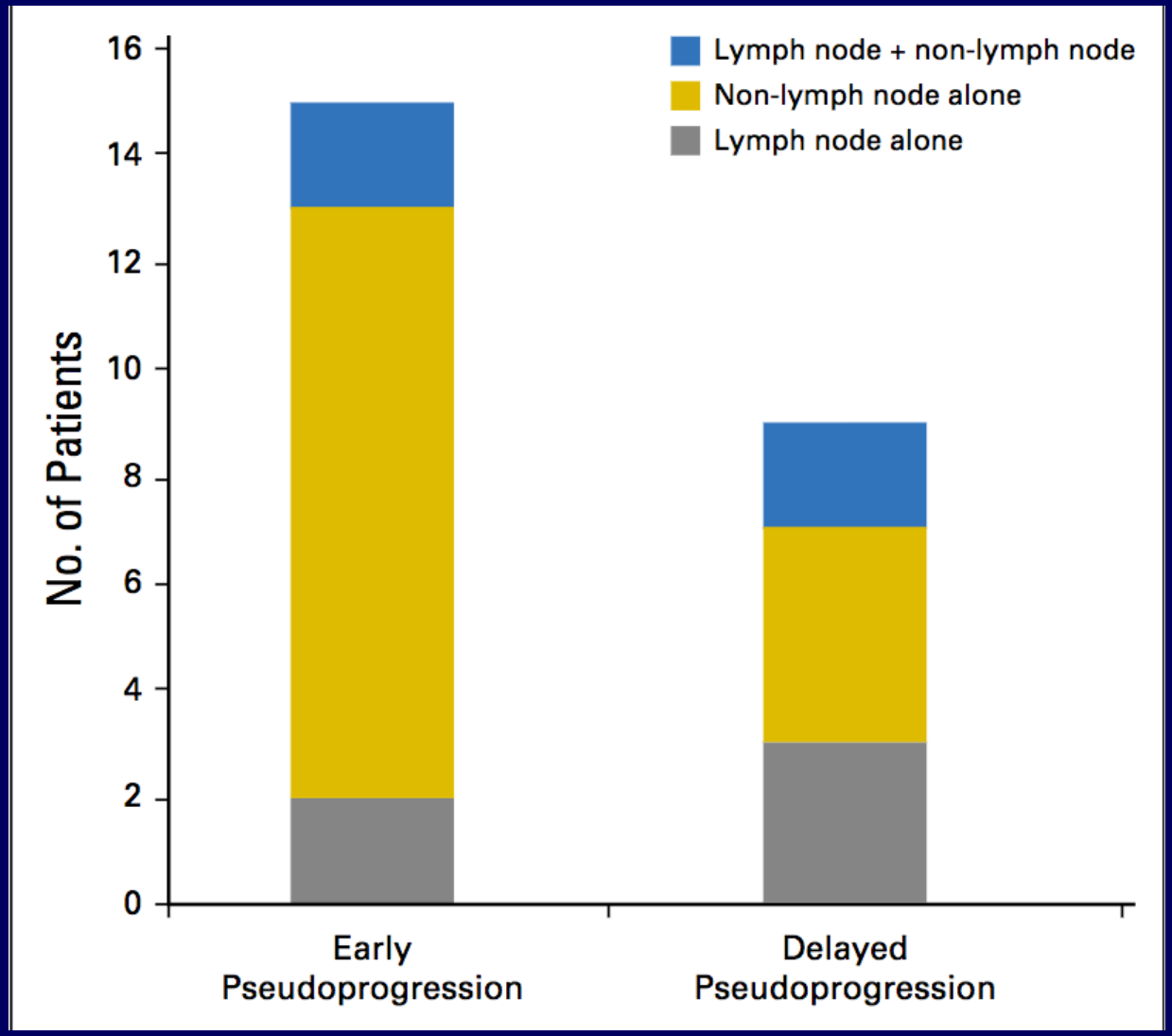
- ~15% of solid tumor pts have a flare response on immunomodulatory agents (CPIs)
- Confused with PD
- Result in premature termination

Percent Change from Baseline of Early (A) vs Late (B) Pseudoprogression



Hodi et al JCO 34:1510, 2016

Distribution of Lesions with Atypical Responses



Hodi et al JCO 34:1510, 2016

Core Concepts of IRC

- Confirmation of progression via a subsequent scan to detect delayed responses (time point to be determined by characteristics of the disease)
- Measuring new lesions to include in total tumor volume
- Accounting for durable SD as benefit
- Treating beyond conventional PD if clinically appropriate

Wolchok et al, Clin Cancer Res 15:7412, 2009

Agents That Induce Flare Reactions in Lymphoma

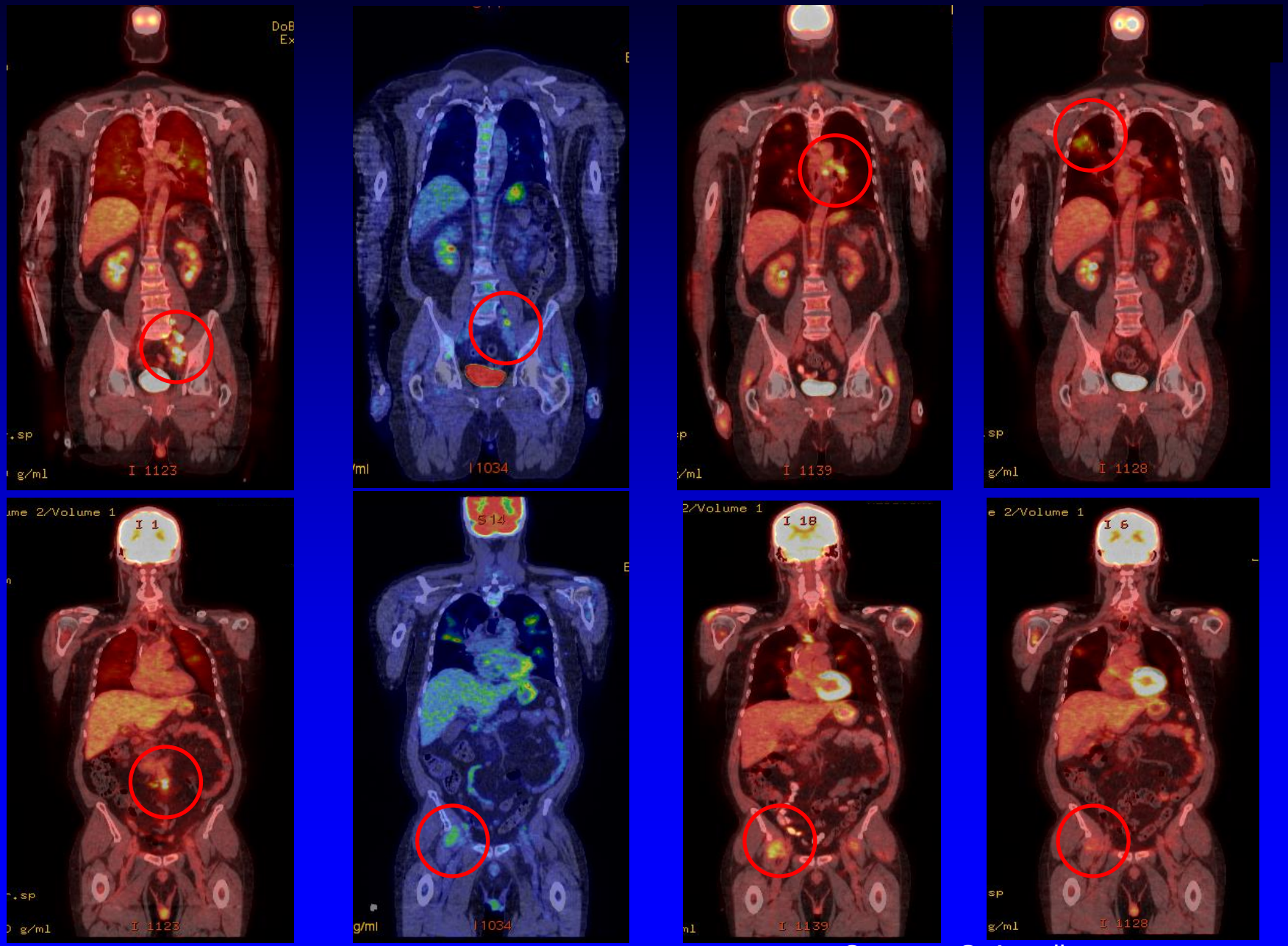
- Lenalidomide
- Rituximab
- Brentuximab vedotin
- Ibrutinib
- Check point inhibitors
- Potential agents
  - Bispecific antibodies
  - Engineered T-cells

May 2015

August 2015

October 2015

December 2015



Courtesy S. Ansell

Immune Response Criteria (IRC)*

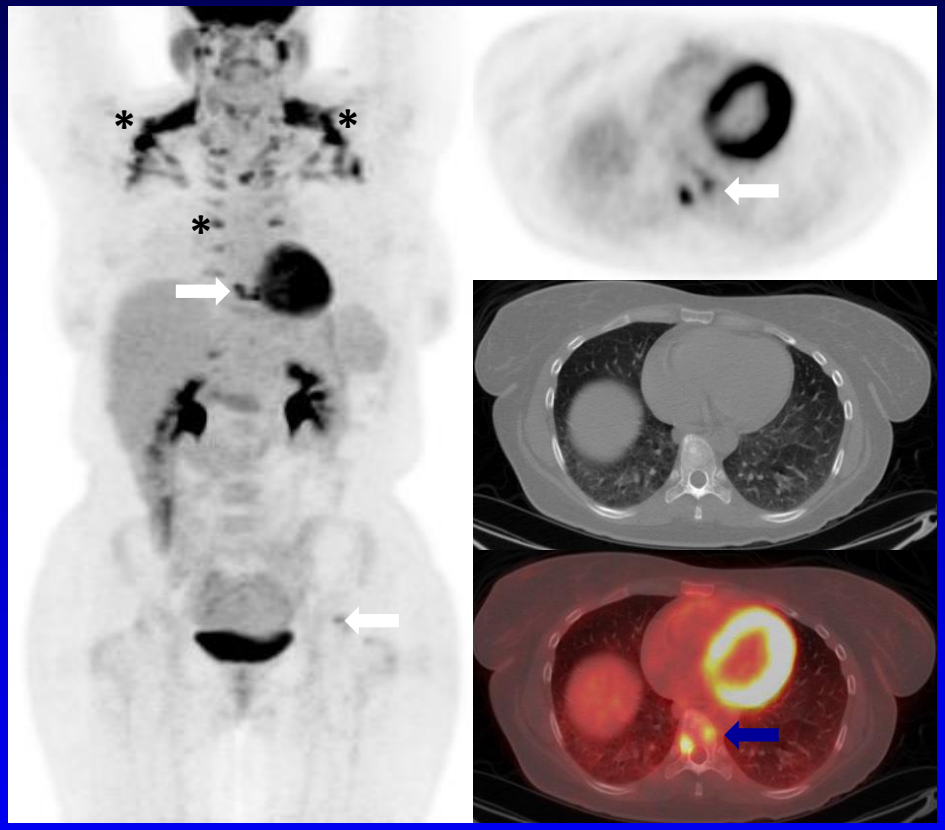
- Not applicable to lymphoma:
  - Rely on RECIST rather than Lugano
  - Timing of response assessment differs
  - Confirmatory studies not required with lymphoma
  - Definition of PD differs
  - Do not include PET-CT
  - Tumors are always abnormal; lymphomas involve nodes which are normally present
    - Normal size despite involvement
    - Enlarged despite non-involvement

* Wolchok et al, Clin Cancer Res 15:7412, 2009

Discordance Between IRC and the Lugano Classification

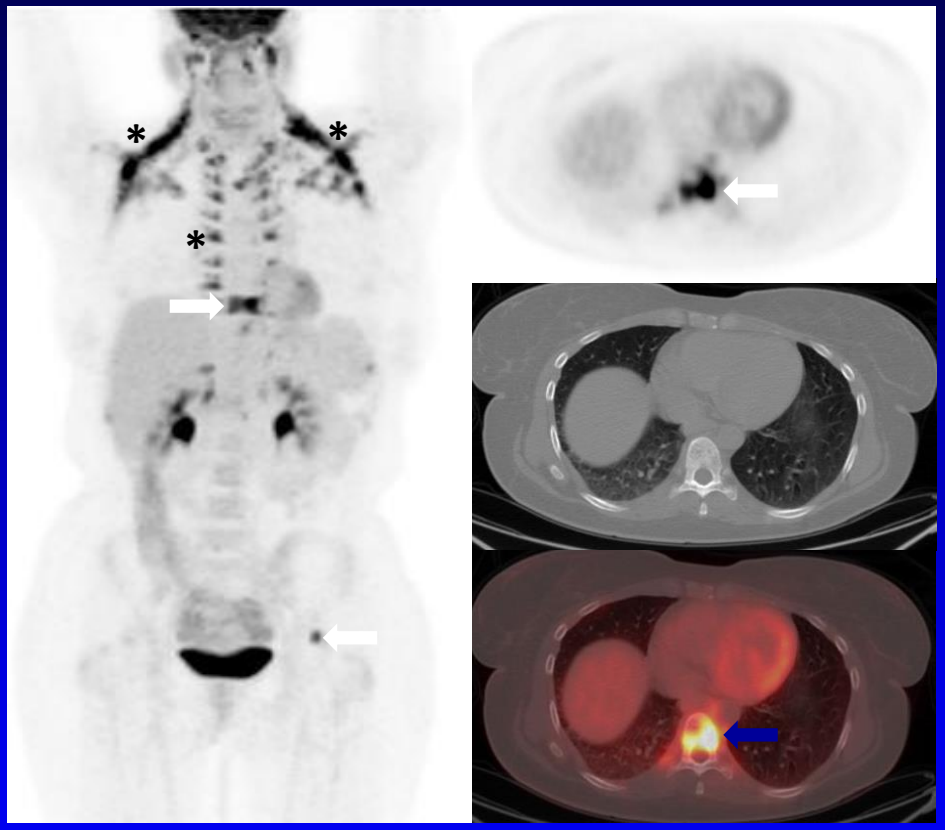
- Lymphomas often have non-measurable disease, imperceptible on CT
  - Bone marrow
  - Soft tissue involvement
- Cannot be integrated into tumor burden

Discrepancy Between Lugano and Immune Response Criteria



Restaging FDG-PET/CT 1

12 weeks



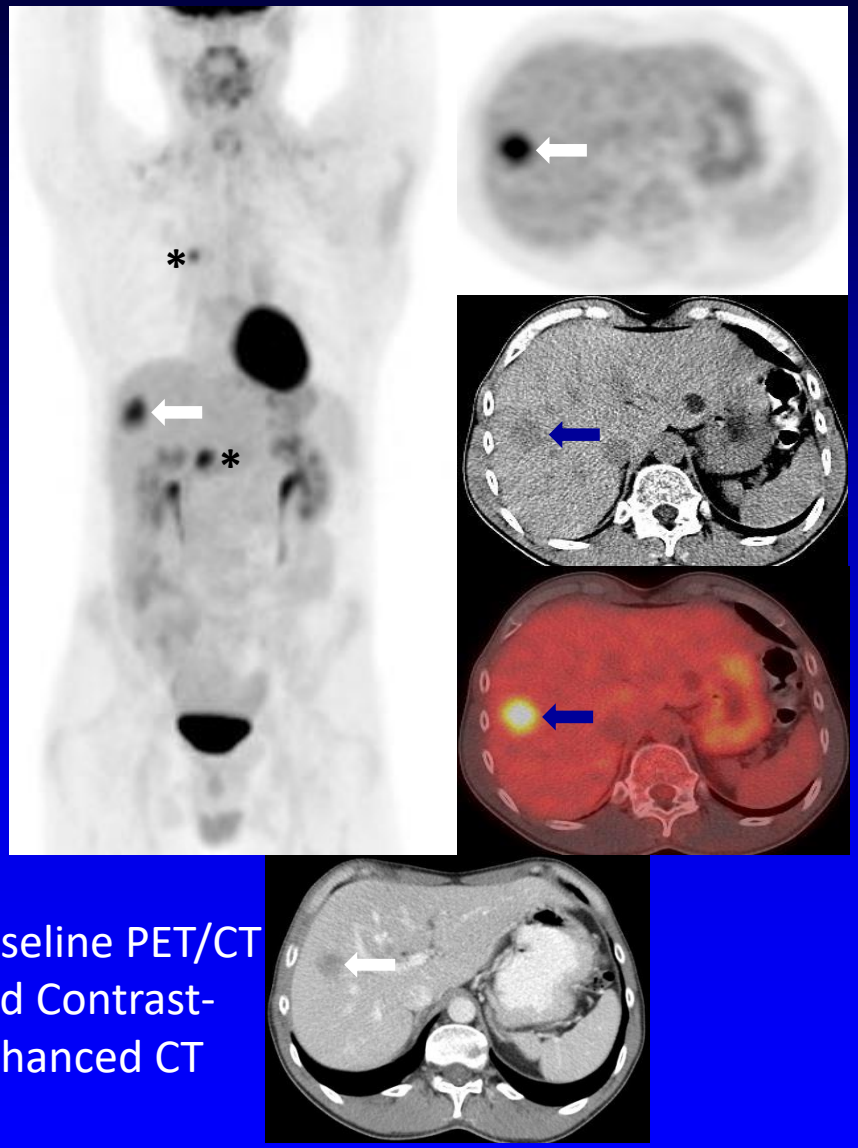
Restaging FDG-PET/CT 2

20 weeks

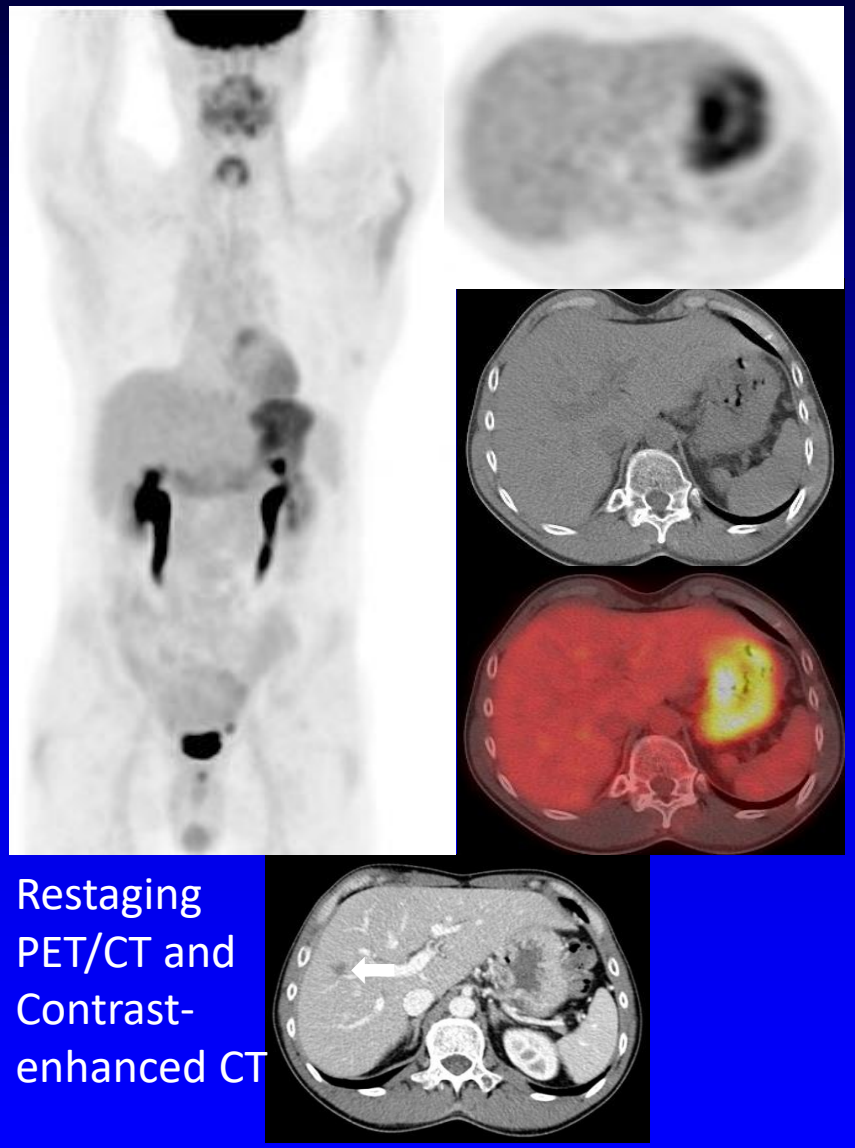
Discordance Between IRC and Lugano

- Restaging PET-CT shows resolution of lesions
- If persistent CT lesions would be considered a PR by IRC
- Considered CR by Lugano if no longer FDG avid

Dicrepancy Between Lugano and IRC



Baseline PET/CT and Contrast-enhanced CT



Restaging PET/CT and Contrast-enhanced CT

LRF Sponsored Workshop 20.11.15: Assessment of Response in Patients On Immunmodulatory Agents

LYMPHOMA RESEARCH FOUNDATION

CANCER RESEARCH INSTITUTE

Response Criteria in Lymphoma Patients Treated with Immunomodulatory Agents Including Immune Checkpoint Inhibitors

Overview:	The *Response Criteria in Lymphoma Patients Treated with Immunomodulatory Agents Workshop* (the workshop) will allow leading clinicians and pharmaceutical researchers to share their experience with immune regulating agents which may induce an immune flare reaction in lymphoma. Lymphoma is one of the major cancer types for which new immune-based cancer treatments are currently in development.
Objective:	The objective of the workshop is to address the unique patient response to this class of drugs and recommend appropriate adaptations of current lymphoma response criteria
Logistics:	One-day program on November 20; the workshop will be held in Washington, DC.

Immune Response Workshop

- Included presentations from investigators and industry representatives on experience with check point inhibitors
- Discussed the relevance of solid tumor IRC to lymphoma
- Determined lymphoma-specific criteria were needed
- Developed Lymphoma Response to Immunomodulatory Therapy Criteria (LyRIC)

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Refinement of the Lugano classification response criteria for lymphoma in the era of immunomodulatory therapy

Bruce D. Cheson, Stephen Ansell, Larry Schwartz, Leo I. Gordon, Ranjana Advani, Heather A. Jacene, Axel Hoos, Sally F. Barrington, Philippe Armand

Blood 2016 :blood-2016-05-718528; doi:10.1182/blood-2016-05-718528

LyRIC: Lymphoma Response to Immunomodulatory Therapy Criteria

LyRIC: Indeterminate Response (IR)

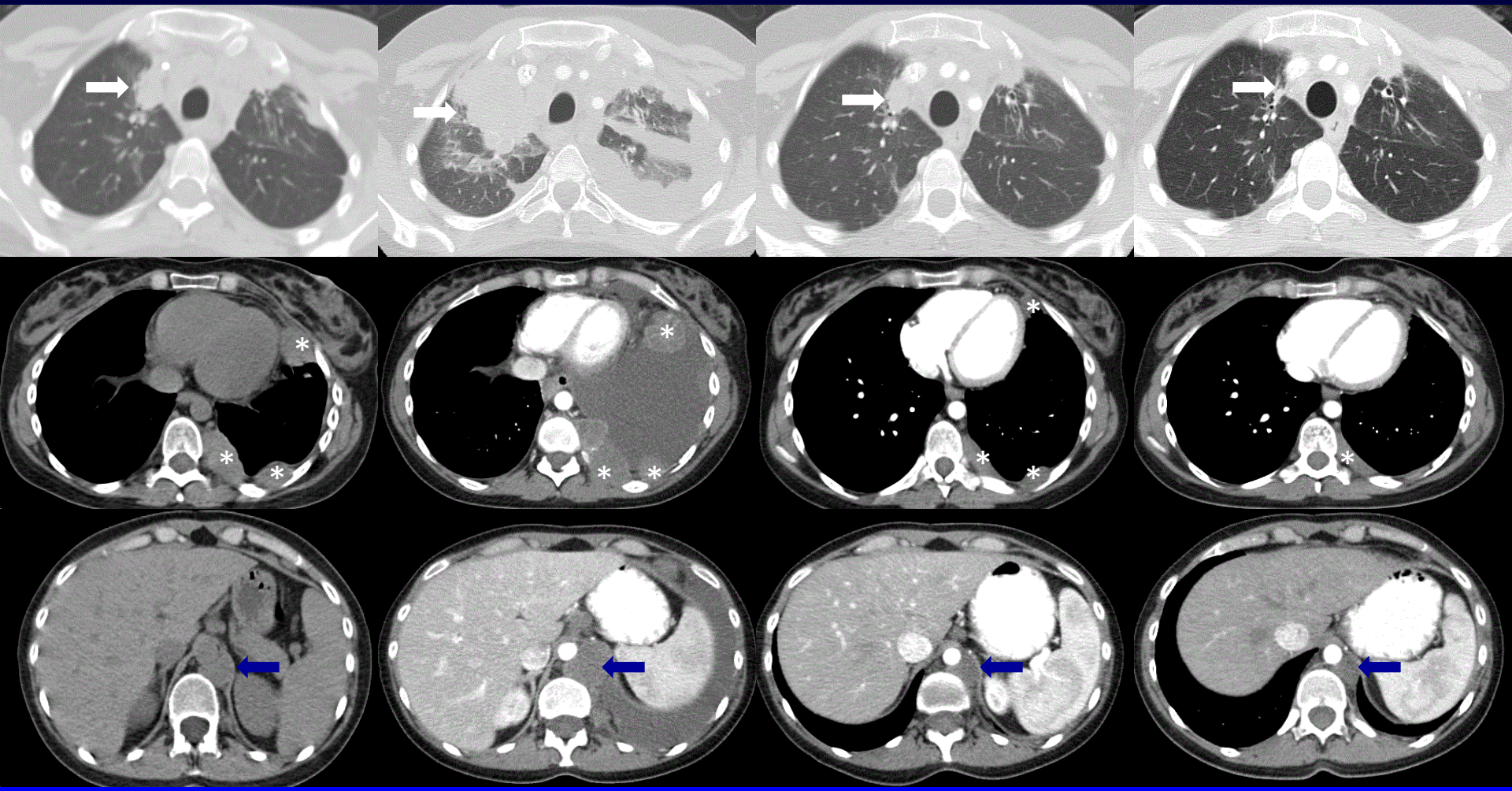
- Provisional term
- To identify lesions that may be flare vs PD
- Does not make direct reference to underlying mechanism
- Allows appropriate patients to remain on treatment
  - until reassessment to confirm or refute PD
  - or biopsy proven disease

Definitions of Types of IR

IR1: Increase in overall tumor burden (by SPD) of ≥50% of up to 6 measurable lesions in the first 12 weeks of therapy, without clinical deterioration

Cheson et al, Blood, e-pub online, Sept 2016

IR1



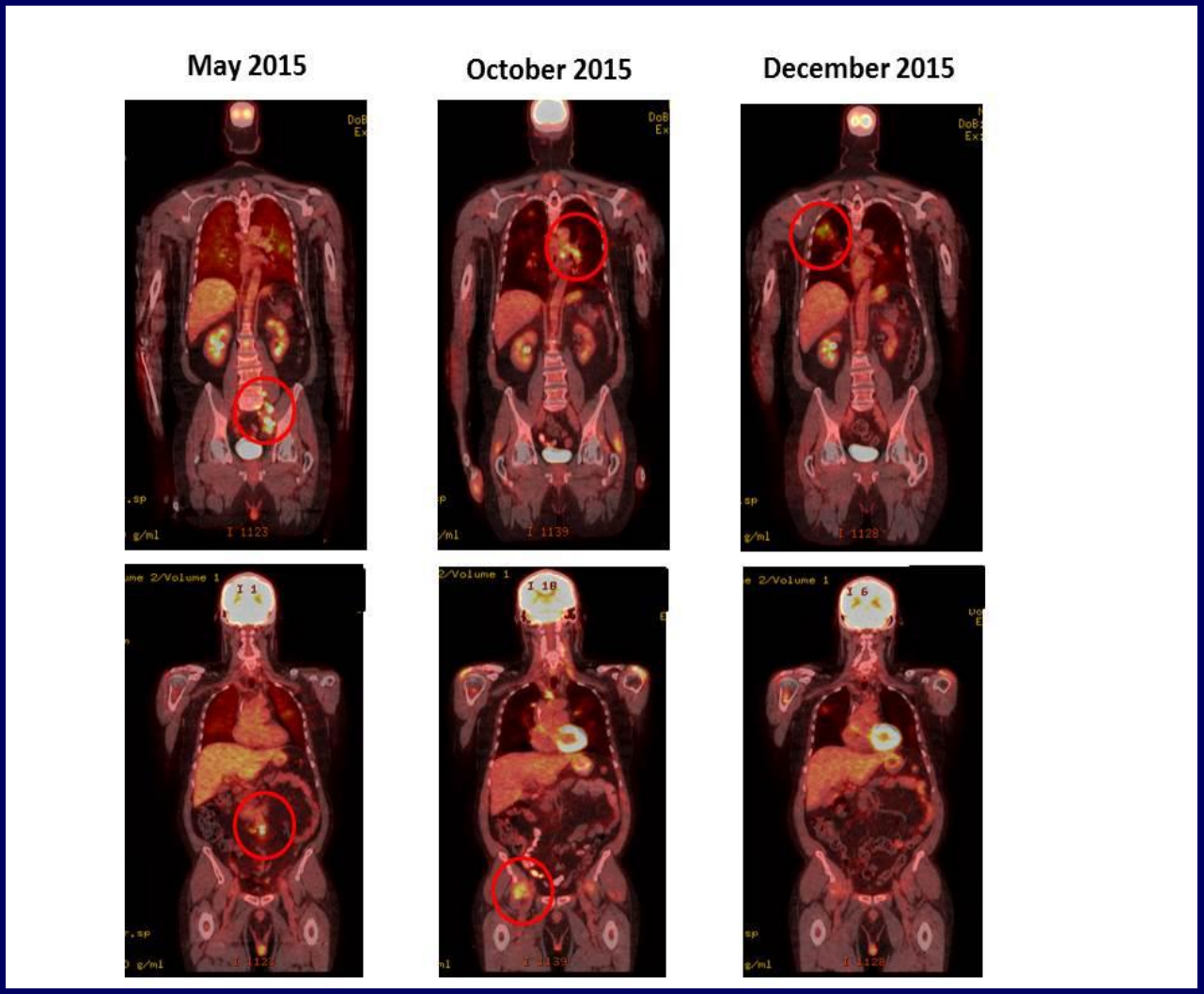
Baseline CT | Restaging CT 1- 3 wks | Restaging CT 2- 7 wks | Restaging CT 3-13 wks

Courtesy H. Jacene

Definitions of Types of IR

IR2: Appearance of new lesions; or growth of one or more existing lesion(s) ≥50%; at any time during treatment; occurring in the context of lack of overall progression (<50% increase) of overall tumor burden, by SPD of up to 6 lesions at any time during the treatment.

IR2



Courtesy H. Jacene

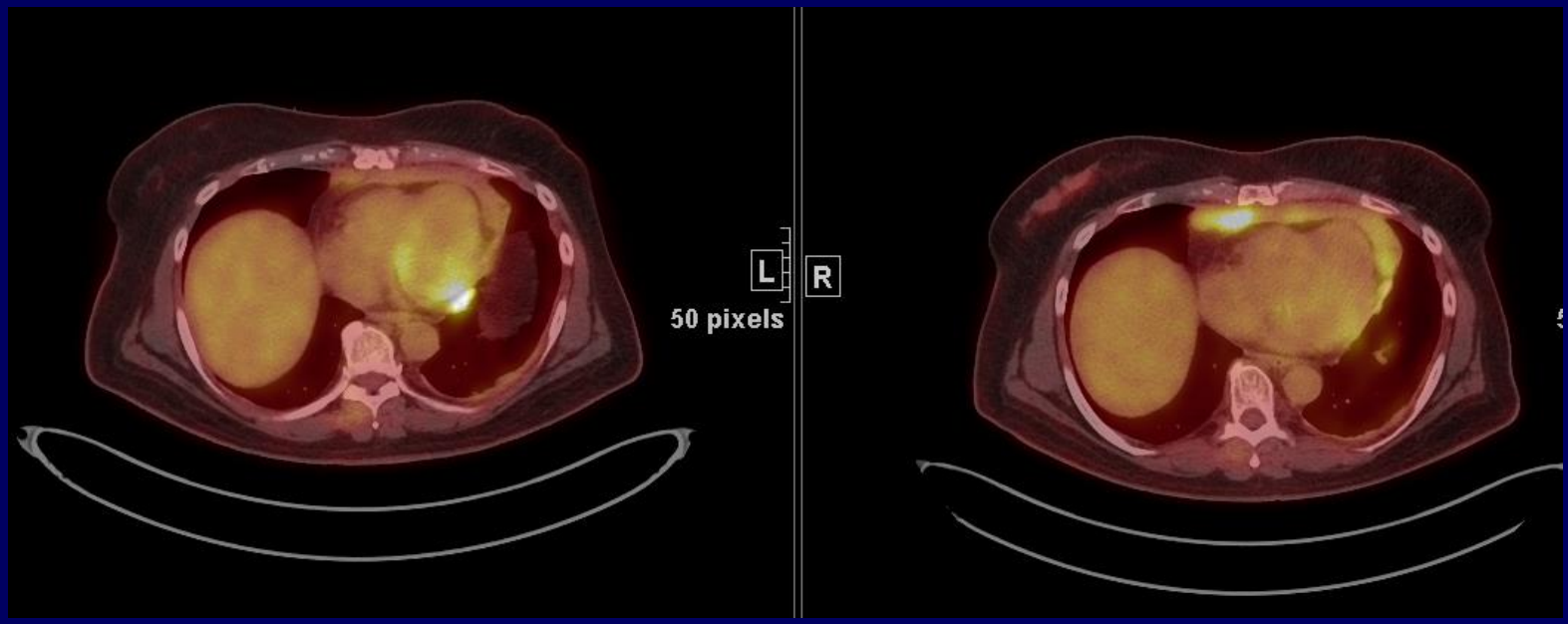
Definitions of Types of IR

IR3: Increase in FDG uptake of one or more lesion(s) without a concomitant increase in lesion size or number

IR(3) an increase in FDG uptake of one or more lesions suggestive of lymphoma without a concomitant increase in size of those lesions meeting PD

July 2, 2014

Sept 3, 2014



Courtesy L. Schwartz

Follow-up of IR

- Repeat scan in ~12 wks (earlier if indicated)
- PD if:
  - IR1 – further increase ≥ 10% in SPD
    - ≥ 5 mm in 1 dimension for lesions ≤ 2 cm
    - ≥ 10 mm for lesions > 2 cm
  - IR2 – new lesion added to SPD (unless benign) and, if ≥50% increase – PD
  - IR3 – PD if increase in size or new lesions

Use of the IR Category

- Incorporated as a secondary endpoint of future clinical trials of immunomodulatory agents
- Allow for treatment past “PD” if clinically indicated
- Collect data to determine appropriateness of this approach

Conclusions

- PET-CT is standard for restaging FDG-avid lymphomas
- Use of immunotherapies may result in false-positive/flare reactions
- LyRIC criteria provide guidance as to how to assess such responses
- Incorporation of other methodologies may increase specificity
- Reduce number of patients removed from potentially effective therapies