Current Evidence on PET Response Assessment to Immunotherapy in Lymphomas

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KEYWORDS

• Hodgkin lymphoma • Immunotherapy • Checkpoint inhibitors • CAR-T • PET/CT • FDG PET • Response assessment • LYRIC

KEY POINTS

- Response assessment in malignant lymphoma has progressively grown in the last 20 years.
- Rather than asking how useful PET is in a retrospective view, oncologists and imagers should better cooperate in setting clinical trials right away using the most adequate imaging modality and perform in parallel studies on predictive factors, including imaging biomarkers.
- Ongoing trials and future studies represent another chance for both parties to answer questions on clinical needs and optimize collaboration for the sake of patient benefit.

IMMUNOTHERAPY IN LYMPHOMA

Assignment of the Nobel Prize in Physiology or Medicine in 2018 to Allison and Honjo "for their discovery of cancer therapy by inhibition of negative immune regulation"[1] demonstrates the striking relevance of immunomodulating agents in oncology. However, the use of immunotherapy in cancer treatment has a longer history than actually imaginable and can be dated back to the first time William Coley used his microbial product in 1890.[2] Notwithstanding, its real breakthrough arrived with checkpoint inhibitors in 2010 and the first impressive results obtained with ipilimumab, an anti-CTLA-4 (cytotoxic T lymphocyte antigen-4) antibody, in metastatic melanoma.[3] Subsequently, CTLA-4 and the pathway involving the programmed cell death protein 1 (PD-1) and its ligands (PD-L1 and PD-L2) have revolutionized the oncologic scenario in the last decade leading to the approval by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) of several monoclonal antibodies. Currently, not only ipilimumab but also nivolumab and pembrolizumab (anti-PD-1), atezolizumab, avelumab, or durvalumab (anti-PD-L1) are used as standard of care for multiple solid tumors.[4] Similar outstanding results have been obtained also for hematologic malignancies,[5–7] especially for relapsed or refractory classical Hodgkin lymphoma (HL). The rationale behind the use of checkpoint inhibitors in HL resides in the same characteristics of Reed-Sternberg cells and lymphoma microenvironment, capable of overexpressing PD-L1 in approximately 70% (range 54%–100%) of the cases.[8,9] The activation of the PD-1/PD-L1 pathway limits T-cell response against cancer and promotes Reed-Sternberg cell growth, helping the tumor evade the immune surveillance.[10–13] The blockade of this inhibitory circuit is expected to interrupt the process and promote immune response against cancer cells. In fact, already during the first preliminary data

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with anti-PD-1 therapy in HL, Ansell and colleagues[5] could report response rates of up to 87% in relapsed or refractory cases treated with nivolumab. Therapeutic efficacy was proved later on also with pembrolizumab used in brentuximab vedotin relapsed HL (KEYNOTE-013), providing an overall response rate of 65%.[6] Thanks to these studies and to other confirmatory ones,[11,14] the anti-PD-1 agents nivolumab and pembrolizumab have been approved as standard treatment in relapsed or refractory HL.

The impact of checkpoint inhibitors for the treatment of other lymphoma types has been less striking compared with HL. A lower and more variable rate of PD-1 and PD-L1 expression in other histologies[9,15] has been noted. For instance, in diffuse large B-cell lymphoma (DLBCL), overexpression of PD-L1 ranges between 14% and 31%.[8,9] Also, response rates result markedly below HL, passing from 10.3% to 36%.[15,16] Consequently, no actual approval exists for checkpoint inhibitors in DLBCL. Nevertheless, immunotherapy represents the mainframe for non-Hodgkin lymphoma (NHL) if the standard regimens applying the monoclonal anti-CD20 antibody rituximab are considered,[17] and more recently the chimeric antigen receptor T (CAR-T) cell therapy[18,19] FDA and EMA approved for adults with relapsed or refractory large B-cell lymphomas (**Fig. 1**). CAR-T cells are autologous T lymphocytes that have been engineered to express specific receptors targeting antigens associated with cancer.[15] Axicabtagene ciloleucel and Tisagenlecleucel, the 2 approved therapies,[20–23] target CD19 that is expressed on the B-cell surface in case of malignancy and at all differentiation stages.[24] Overall response rates reached from initially treated cohorts quote up to 82%, with a complete response (CR) rate of 54% and a durable disease responsiveness at follow-up.[19] Possible limitations relate to either side effects or costs, which impact the patients' quality of life and the economic sustainability of national health care systems, respectively.[25]

RESPONSE PATTERNS DURING IMMUNOTHERAPY

Immunotherapy has recently gained the abovementioned remarkable place in cancer treatment not simply as a consequence of the high response rates achieved but also thanks to the durable responses visible after treatment stop or even in case therapy continuation beyond disease progression.[26] This later aspect, reported similarly for solid tumors[27] as well as for hematologic malignancies,[28] introduces additional confusion in response assessment. In fact, one of the peculiarities and potential pitfalls of immunomodulating agents used in cancer concerns response patterns. Besides conventional responses associated with complete or partial regression (**Fig. 2**), stable and progressive disease, immunotherapy with checkpoint inhibitors has promoted pseudoprogression as part of the therapeutic effect. This new pattern of response to treatment, typically observed in solid tumors under immunotherapy and particularly in melanoma, affects 5% to 12% of the cases.[29] The phenomenon is defined as a transient increase in tumor size secondary to an augmented immune infiltrate. Rather than a real progression, pseudoprogression represents a flare phenomenon induced by the massive recruitment of immune cells into the tumor microenvironment. Being a transitory event, pseudoprogression is

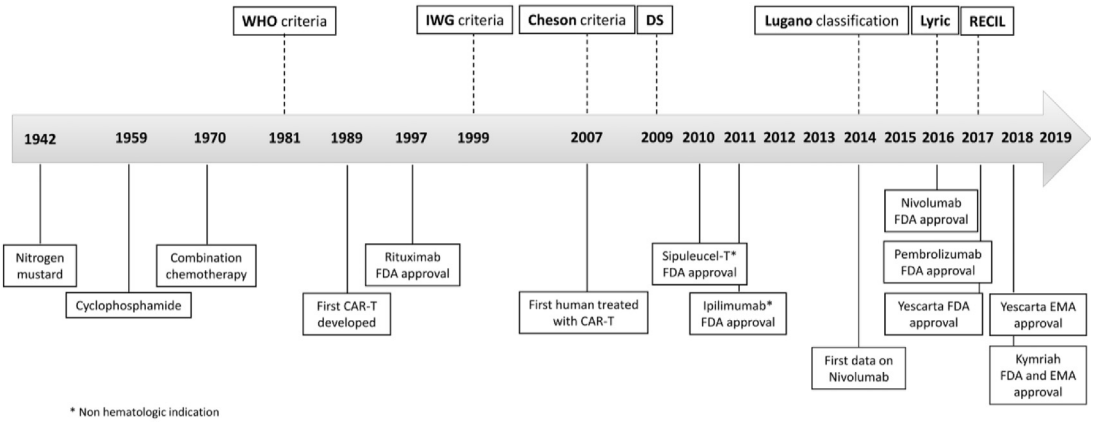

Fig. 1. Timeline of response criteria developed in malignant lymphoma parallel to the evolution of treatment options, focusing primarily on immunotherapy. IWG, international working group; LYRIC, immunomodulatory therapy criteria; WHO, World Health Organization.

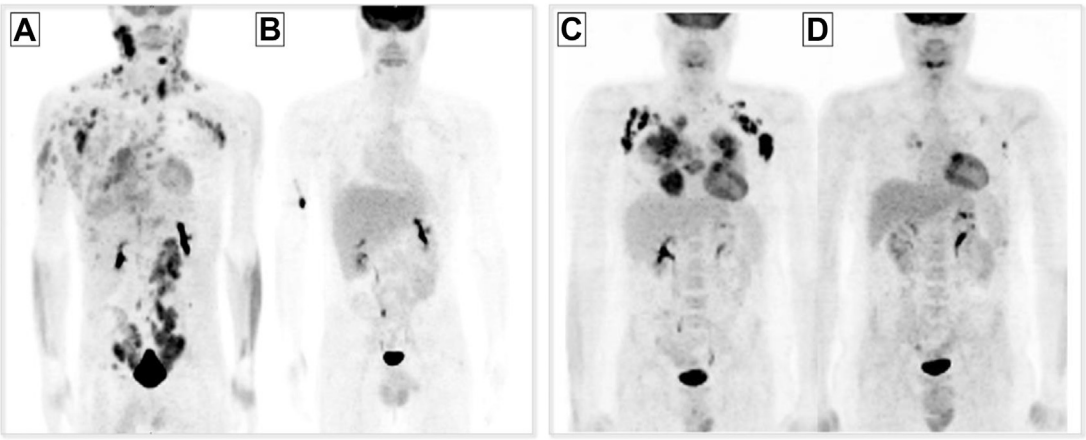

Fig. 2. Pictorial example of 2 patients with HL undergoing immunotherapy with Nivolumab investigated at baseline (*A*, *C*) and after 17 weeks of treatment (*B*, *D*). These 2 cases display different patterns of response: the first patient on the left (*A*, *B*) shows a CMR, despite the extensive tumor burden at baseline; the second patient (*C*, *D*) results in a partial responder having some residual metabolically active disease (DS 4) in the left axilla and right pulmonary hilum.

confirmed as such only during subsequent scanning (or in the case of biopsy), demonstrating indeed tumor regression and treatment benefit.[30,31]

Another specific pattern of response first described for immunotherapy is hyperprogression. Hyperprogression affects 4% to 29% of patients and involves in particular the elderly population (age >65 years).[32–34] The key element to define the phenomenon, as initially described by Champiat and colleagues,[32] relies on the tumor growth rate, which in the case of hyperprogression increases at minimum 2-fold between baseline and after therapy initiation. Later on, the timing for assessing hyperprogression could be restricted to 2 months after treatments start.[35] Contrary to pseudoprogression, hyperprogression does not represent a problem for image interpretation, given the usual dramatic tumor growth and clinical worsening, leading in general to a very poor prognosis.[36]

Last, anecdotal reports describe a possible abscopal effect in the course of immunotherapy.[37,38] Being by definition immune mediated, the abscopal effect can determine tumor shrinkage at distant sites of disease following locoregional treatments, typically radiation therapy.

PROPOSED RESPONSE CRITERIA IN LYMPHOMA

Several criteria have been proposed to face the problems of the so-called pseudoprogression (see **Fig. 1**). The Lymphoma response to immunomodulatory therapy criteria (LYRIC) published in 2016[31] have tried to integrate to the Lugano classification dedicated to lymphoma the Immune response criteria previously proposed for solid tumors.[30] They were mainly dedicated to the evaluation of the response to checkpoint inhibitors in HL. Because of the small number of observations, it was considered difficult to identify the different relevant pathophysiologic imaging patterns observed under therapy, which could be of help to eliminate the diagnosis of progression. Therefore, LYRIC classified all of these patterns under the category of indeterminate response (IR), with 3 subcategories: IR1, increase in overall tumor burden (as assessed by sum of product diameters [SPD]) of $\geq$50% of up to 6 measurable lesions in the first 12 weeks of therapy, without clinical deterioration; IR2, appearance of new lesions, or growth of 1 or more existing lesions $\geq$50% at any time during treatment occurring in the context of lack of overall progression (<50% increase of overall tumor burden, as measured by SPD of up to 6 lesions); IR3, increase in fludeoxyglucose (FDG) uptake of 1 or more lesions without a concomitant increase in lesion size or number. Importantly, it was also proposed to consider that an increase of FDG avidity of 1 or more lesions suggestive of lymphoma without a concomitant increase in size of those lesions meeting progressive disease (PD) criteria does not constitute PD. These categories were opened to changes using the experience drawn from the clinical observations made under immunomodulatory treatments. LYRIC encouraged biopsy for IR1 and IR2 and advised to evaluate

these intermediate features by following up in all cases after 12 weeks by a new scanning in order to judge progression on a basis of an increase of size of greater than 10% for IR1, a new lesion leading to a tumor burden greater than 50% for IR2, or an increase of the lesion size or new lesion for IR3. There is no change between LYRIC and Lugano criteria regarding complete metabolic response (CMR) and partial metabolic response (PMR).

The second group of criteria is the Response evaluation criteria in Lymphoma (RECIL), defined by an international working group in 2017.[39] Contrary to the LYRIC, the objective of RECIL criteria was to homogenize response criteria in trials testing the efficacy of new drugs and including lymphoma and solid tumors. RECIL changed the way to measure the lesions, relying only on unidimensional measurement of the long diameter of 3 selected targets. Contrasting with LYRIC and Lugano criteria, RECIL criteria modified the complete and partial response (PR) categories, decreasing the role of PET. The proposal was based on the observation that some immunomodulatory drugs can alter glucose metabolism, suppressing the existing relationship between the drug efficacy and the FDG uptake observed under chemotherapy. Consequently, the concept of CMR defined in Lugano classification is replaced by CR requiring not only Deauville scoring (DS) 1 to 3 but also at least a 30% reduction of the lesions by computed tomography (CT). PR replaces PMR and implies a 30% reduction of the sum of the longest diameter associated with a positive DS 4 to 5. The objective is to minimize the risk of classifying some of these patients falling in the IR2 category of the LYRIC as PD. To evaluate the effect of agents not fulfilling the criteria for a PR, a third category, named minor response, has been identified with at least a 10% reduction of the tumor burden whatever the PET results. The progression implies a greater than 20% increase of tumor burden or the presence of a new lesion (to put in perspective with the >50% of IR1), whatever the DS. For relapse from CR, at least 1 lesion should measure 2 cm in the long axis. By contrast with LYRIC, RECIL classification does not give recommendation for follow-up of the lesions.

EVIDENCE FROM THE LITERATURE

The first preliminary results on anti-PD-1 therapy in HL were published in December 2014.[5] To assess response to treatment, the investigators used therein a combination of morphologic (CT) and metabolic (FDG PET) data, with the later ones used mainly to confirm CR. Later on, Armand and colleagues[6] reported data on pembrolizumab during the KEYNOTE-013 trial by applying as criteria for response the International Harmonization Project in lymphoma or Cheson 2007 criteria.[40] The same criteria, or their subsequent development,[41] have been variably used also for other immunotherapy trials in HL.[14,28,42–44] Noteworthy, the first dedicated reports on PET response evaluation in lymphoma treated with checkpoint inhibitors were all derived from retrospective analyses. As summarized in **Table 1**, all cases applied Cheson 2014 (or Lugano) criteria for response assessment and compared in parallel (or partially) the results with the proposed LYRIC criteria.[45–47]

The group from Gustave Roussy was the first to describe the kinetics[48] and the patterns of response to immunotherapy.[45] Initially, the investigators analyzed the cohort of 16 patients to assess timing and depth of response to immunotherapy.[48] The investigators report 12.7 months as median time to nadir (range 3–23 months). Within 6 months of treatment, 4 CMR were reported. In 3 cases, CMR was detectable already at 3 months (early evaluation), whereas the fourth converted from PMR to CMR after early evaluation. No other CMR occurred after 6 months of treatment. Of note, 78% of responsive patients at 3 months (3 CMR and 4 PMR) remained in tumor control at 1 year.[48] The same cohort was subsequently analyzed with regards to imaging.[45] In particular, by adopting the DS on a lesion basis (n = 290), response assessment at 3 and 6 months showed a positive predictive value of 88% and 97%, and a negative predictive value of 92% and 97%, respectively. In the study, moreover, all semiquantitative and quantitative variations of PET parameters at 3 months resulted in predictive of the best overall response.

The 5-point scale criteria were considered also in the article from Castello and colleagues.[47] Therein, 43 HL patients treated with anti-PD-1 therapy were enrolled and assessed at 8 weeks (early) and 17 weeks (interim) after treatment start. At early evaluation, performed in 22 patients, visual analysis with DS significantly differentiated responders from nonresponders ($P = .003$).[41] Also, at 17-week evaluation (n = 40), DS was confirmed as significantly different among groups ($P = .008$). By classifying patients at interim evaluation into responders (CR + PR) and nonresponders (stable disease [SD] + PD), the investigators observed a significantly lower risk of progression or death for the first group (hazard ratio 0.13; $P = .01$).

These findings seem to suggest for metabolic response in general, and DS in particular, a predictive role also for immunotherapy with checkpoint inhibitors.[49]

Table 1
Summary of available articles on fludeoxyglucose PET/computed tomographic response evaluation in lymphoma treated with immunotherapy

Authors, Reference	Patients	Study Type	Histology	Treatment	Response Criteria	Results
Dercle et al,[45] 2018	16	Retrospective[a]	HL	Nivolumab (n = 1); Pembrolizumab (n = 15)	Lugano/ LYRIC	Best responses on PET: 6 CR, 4 PR, 2 SD, 4 PD. LYRIC IR were observed in 7 patients, 5 were confirmed PD Responders had increased spleen metabolism at 3 mo
Dercle et al,[48] 2018	16	Retrospective[a]	HL	Nivolumab (n = 1); Pembrolizumab (n = 15)	Lugano/ LYRIC	78% of patients classified as responders at 3 mo remained in tumor control at 1 y. CMR occurred within 6 mo
Rossi et al,[46] 2018	30	Retrospective	HL	Nivolumab (n = 26); Pembrolizumab (n = 4)	Lugano/ LYRIC	Best response: 5 CR, 17 PR, 2 SD, and 6 PD DS 4 and 5 by Lugano (n = 15) were reclassified by LYRIC as PR (n = 4), IR1 (n = 2), IR2 (n = 8), and IR3 (n = 1)
Castello et al,[47] 2019	43	Retrospective	HL	Nivolumab (n = 42); Pembrolizumab (n = 1)	Lugano/ LYRIC	Best clinical responses: 26 CR, 5 PR, 8 SD, and 4 PD. LYRIC reclassified 3 IR1, whereas the last PD case was confirmed. At interim, DS well-differentiated responders from nonresponders
Shah et al,[50] 2018	7	Prospective	3 DLBCL, 4 FL	CAR-T (CTL019)	DS/ Lugano	Responses at 1 mo: 3 CR, 2 PR, and 2 PD
Wang et al,[51] 2019	19	Retrospective	14 DLBCL, 3 FL	CD19-targeting CAR-T	PERCIST	Best overall responses: 7 CR, 8 PR. Possible pseudoprogression in 3. CRS (grade 0–2) had significantly lower MTV and TLG than those with severe CRS (grade 3–4)

Abbreviations: LYRIC, immunomodulatory therapy criteria; PD, 0 progressive disease.
[a] Same study population analyzed with two different ways.

When comparing Lugano criteria with LYRIC, Dercle and colleagues[45] outlined 7 patients with IR, of which 5 cases (71%) were confirmed as PD, whereas only 2 turned out to be pseudoprogression.[45] In the study from Lysa centers,[46] instead, only tangentially comparing the 2 response criteria, the DS 4 and 5 assessed with Lugano criteria (15/30 patients) were reclassified by LYRIC as PR (27%) or IR: IR1 (13%), IR2 (53%), and IR3 (7%). More consistent data were obtained by contrast from Castello and colleagues.[47] In particular, no significant differences were detected between the 2 response criteria, although 3 out of 4 PD patients were reclassified as IR1 according to LYRIC. Given the retrospective nature of all these studies, the clinical utility for new LYRIC criteria appears plausible but not thoroughly proved yet.

More embryonal data exist for CAR-T cell therapy and metabolic response (see **Table 1**). Two separate articles analyze the imaging predictive role by focusing on either early response assessment[50] or side effects.[51] In the first case, Shah and colleagues[50] prospectively analyzed early PET/CT in patients with DLBCL and follicular lymphoma (FL) undergoing CTL019 CAR-T cells. Imaging was obtained 1 month after therapy and response assessment based on DS (Lugano criteria). Their preliminary data published as a correspondence letter on the first 7 patients document 3 CR, 2 PR, and 2 PD at early stage. All complete responders (DS 1 + 2) remained in remission for more than 2 years after the end of therapy, whereas the others progressed. The second article on CAR-T, instead, retrospectively analyzed 17 NHL (14 DLBCL and 3 FL) aiming to define useful semiquantitative and quantitative parameters for prediction of adverse events.[51] Response to therapy was once again assessed at 1 month, but differently from all previously reported articles, it was based on PERCIST (PET Response Criteria in Solid Tumors).[52] Along with CR and PR, the investigators observed 3 cases of pseudoprogression related to local inflammation following the CAR-T effect. Interestingly, high metabolic burden at baseline, that is, metabolic tumor volume (MTV) and total lesion glycolysis (TLG) could predict severe CRS (grade 3 + 4). In particular, median MTV was 49.3 cm^3 versus 1137.7 cm^3 (P = .012), and median TLG was 379.1 versus 9384 (P = .012), respectively, for mild/moderate CRS versus severe CRS. Larger cohorts are welcome (**Table 2**) to confirm the promising results reported from these articles, it is hoped, for better harmonizing response criteria also for CAR-T therapy.

IMMUNE-RELATED ADVERSE EVENTS

Adverse events are crucial aspects to be taken into account for all oncologic regimens. In accordance with the type of drug administered, the dose, and the duration of therapy, the related adverse events can vary significantly and impact the performance and the quality of patient's life at different grades. With the latest revolution brought forward by immunotherapy in oncology, immune-related adverse events (IAEs) have consequently emerged even more prepotently and are considered major limitations to therapeutic prosecution and a handicap for response assessment (**Fig. 3**). Therefore, it is mandatory for both imagers and clinicians to be aware of their manifestations, timing, and potential differential diagnoses. Notwithstanding, when considering numbers, IAEs are less debilitating and better tolerated compared with toxic side effects secondary to conventional therapies.[53] In fact, in a pooled metaanalysis in advanced solid tumors, by comparing 3450 patients from 7 randomized clinical trials (RCTs), Nishijima and colleagues[53] documented a significantly lower risk of any all-grade and high-grade (grade III–IV) adverse event during PD-1/PD-L1 inhibitors compared with chemotherapy. The overall corresponding incidences were 67.6% versus 82.9% (any all grade), and 11.4% versus 35.7% (high grade), respectively. By contrast, the investigators report a higher risk for rash, pruritus, colitis, aminotransferase elevations, thyroid disease, and pneumonitis during checkpoint inhibitors, typically representing side effects related to the immune modulation. In the case of hematologic malignancies, IAEs seem to occur in most patients treated with nivolumab or pembrolizumab,[5,54] although high-grade IAEs interest 10% to 11% of the patients, with grade 3 to 4 events being represented by pancreatitis, hepatitis, and diarrhea. Thanks to the metabolic assessment with FDG PET/CT, most abovementioned events can be easily depicted and should be promptly reported, because they can be visible before any clinical manifestation.

Although potentially occurring at any time during treatment, IAEs tend to be more frequent after the first 2 to 3 months of therapy. This aspect is a direct consequence of immune system activation. Therefore, IAEs can be considered the undesirable proof that immunotherapy is actually doing what is expected.[55] In this regard, a predictive and prognostic role for IAEs during checkpoint inhibitors and a direct association to therapeutic benefit have been reported.[45,56,57] First, Haratani and colleagues[56] revealed that in patients with non–small cell lung cancer treated

Table 2
Clinical trials[a] evaluating fludeoxyglucose PET/computed tomography in lymphoma treated with immunotherapy

Identifier	Phase	Official Title	Histology	Treatment	Estimated Participants	Imaging Timing	Sponsor	Status
NCT02476734	Early phase 1	A Pilot Study Using FDG-PET/CT Imaging as an Early Predictor of Disease Response in Lymphoma Subjects Receiving Redirected Autologous CART-19 T-cell Immunotherapy	DLBCL, FL	CART-19 autologous T cells	8	6 wk and 1 mo after infusion	University of Pennsylvania	Completed
NCT03086954	Phase 1	Open, Single Arm, Multicenter Phase 2 Clinical Study to Evaluating the Efficacy and Safety of the Chimeric Antigen Receptor T Cell Immunotherapy (CAR-T) for CD19 Positive Lymphoma	CD19-positive NHL	CAR-T	24	90 d after CAR-T	Sinobioway Cell Therapy Co, Ltd	Not yet recruiting
NCT03703050	Phase 2	Phase II Trial of Nivolumab for Pediatric and Adult Relapsing/Refractory ALK + Anaplastic Large Cell Lymphoma, for Evaluation of Response in Patients With Progressive Disease (Cohort 1) or as Consolidative Immunotherapy in Patients in Complete Remission After Relapse (Cohort 2)	ALK + anaplastic large cell lymphoma	Nivolumab	38	24 wk of induction	Gustave Roussy, Cancer Campus, Grand Paris	Recruiting

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Table 2
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Identifier	Phase	Official Title	Histology	Treatment	Estimated Participants	Imaging Timing	Sponsor	Status
NCT03038672	Phase 2–RCT	A Randomized Phase 2 Study of CDX-1127 (Varlilumab) in Combination With Nivolumab in Patients With Relapsed or Refractory Aggressive B-Cell Lymphomas	Relapsed or refractory aggressive B-cell lymphomas	Nivolumab with or without varlilumab	106	Up to 2 y	National Cancer Institute	Recruiting
NCT03498612	Phase 2	Phase II Window Study of Pembrolizumab in Untreated B-Cell Non-Hodgkin Lymphoproliferative Diseases	B-cell NHL; FL; indolent HNL; marginal zone lymphoma	Pembrolizumab	33	After 6 cycles	University of Washington	Recruiting

[a] Trials not considering PET imaging for immunotherapy with checkpoint inhibitors or CAR-T cells have been removed from the list.
Data from https://clinicaltrials.gov/; keywords: PET, immunotherapy | lymphoma.

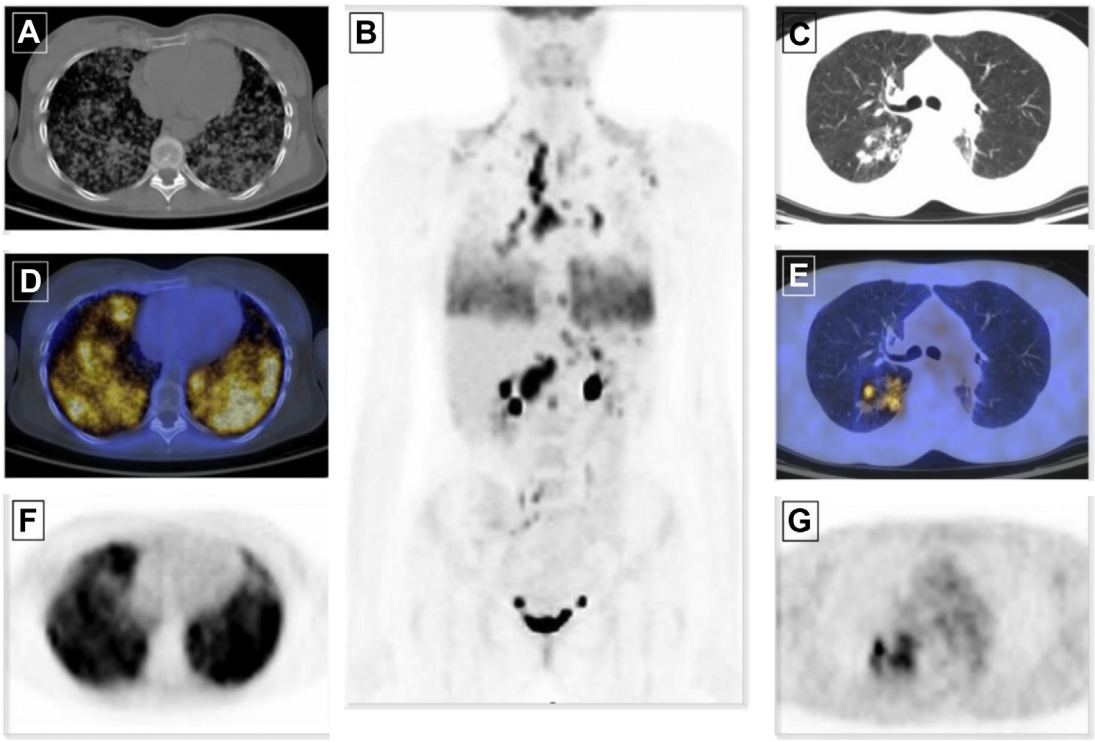

Fig. 3. Different lung involvement in patients with HL undergoing immunotherapy. On the left panels (*A*, *B*, *D*, *F*), a massive parenchymal carcinomatosis is shown, along with multiple nodal involvement in the supradiaphragmatic and infradiaphragmatic regions. On the right side (*C*, *E*, *G*), axial views show the appearance of immune-related pneumonitis after 3 months of Nivolumab; the parenchymal consolidation regressed subsequently, and when biopsied, proved to be inflammatory infiltrate.

with Nivolumab (n = 134), the overall response rate was significantly higher in patients with IAEs than in those without (52.3% vs 27.9%, respectively). When using a 6-week landmark analysis, the investigators also showed that IAEs were significantly associated with increased progression-free survival and overall survival. In HL patients treated with anti-PD-1 regimen (n = 16), the reported sign of immune system activation related to response resulted in being the splenic metabolism.[45] In particular, an increase in healthy splenic maximum standardized uptake value (SUV_{max}) at 3 months could predict the best overall response. More recently, in another mixed group analysis, comprising melanoma (n = 21), lymphoma (n = 11), and renal cell carcinoma (n = 8), Nobashi and colleagues[57] showed that early occurrence of thyroiditis could anticipate early response to immunotherapy. Differently from Dercle and colleagues,[45] the later article of the group from Stanford[57] reported any decrease of SUV_{max} in the spleen to be associated with clinical benefit. Herein, 82% of the patients developing IAEs had a CR to treatment and, in 7 out of 11 cases, the presence of IAEs could be revealed only by means of FDG PET scan.[57]

For CAR-T cell therapy in B-cell lymphoma, the situation is somehow different. At first, this therapeutic regimen is associated with other adverse effects, such as cytokine release syndrome (CRS), CAR-T cell-related neurologic toxicities, and B-cell aplasia, not commonly detectable with FDG PET.[51,58–60] Second, concurrent local inflammation is more frequently seen compared with the IAEs mentioned earlier for HL. Last, but not least, adverse events occur quite early after CAR-T therapy administration, that is, hours or days after the first infusion, whereas late side effects are not properly documented.[60] In literature, simple case reports and more recently a retrospective case series[51,60,61] have so far described the appearance of delayed adverse events, also by means of FDG PET/CT.[51,60]

SUMMARY

In a recent expert opinion report,[13] one of the "burning" questions pointed out by the investigator consisted of the effective utility of PET

scans in HL undergoing immunotherapy. The answer provided was that PET is less accurate in this context compared with what was expected during chemotherapy[49] and that should not be used outside of clinical trials.[13] The observation is somehow correct, although, considering the small amount of publications available and the lack of coherence in applying response criteria, it should be better to say that there are no sufficient data to make any conclusion. The principle applies to any other imaging modality used to assess response in the case of new treatments types. In fact, CT has not demonstrated to be foolproof in solid tumors treated with immunotherapy,[30,62] and one should not expect it to be better than PET, especially for HL, given the well-known superiority of metabolic imaging over morphology in this malignancy.[40,41] Maybe, rather than asking how useful PET is in a retrospective view, oncologists and imagers should better cooperate in setting clinical trials right away using the most adequate imaging modality and performing in parallel studies on predictive factors, including imaging biomarkers. The ongoing trials (see **Table 2**) and future studies represent another chance for both parties to answer questions on clinical needs and optimize collaboration for the sake of patient benefit.

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