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EXPERT REVIEW

Hodgkin lymphoma and imaging in the era of anti-PD-1/PD-L1 therapy

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Abstract

The assessment of treatment response is crucial for patient management since it guides further treatment or surveillance program. For the purpose of response evaluation in Hodgkin Lymphoma patients, contrast-enhanced CT (CECT) and fluorodeoxyglucose (FDG)–positron emission tomography (PET) were demonstrated to be the most reliable imaging modalities. Response criteria based on tumor size variations on CT and/or modification of tumor glycolytic metabolism on FDG PET have been designed for the assessment of response to chemotherapy and targeted molecular agents. The recent introduction of biological agents with immunological activity revealed the need for criteria revision and for novel biomarkers. The treatment response assessment using the standard criteria for defining anatomical or metabolic remission has been shown to be poorly fit for the immune checkpoint inhibitors since they may determine the "tumor flares", a phenomenon that has not the same prognostic implications as progressive disease. Accordingly, the response evaluation criteria have been reviewed introducing as main novelty the concept of "pseudo-progression". Furthermore, PD-1 blockade is not effective in all patients, and delayed or mixed tumor regression can be seen. Therefore, some biomarkers including the detection of PD-L1 on tumor cells, the identification of specific genetic signatures, the longitudinal track of the circulating cell-free DNA, and the imaged-derived parameters have been evaluated to predict response to anti-PD-1/PD-L1 therapy. The present paper reports the available evidence on the role of imaging in patients with HL and future directions for the investigations in the field, with the special focus on the treatment with immune checkpoint inhibitors.

Keywords Hodgkin lymphoma · Nivolumab · Pembrolizumab · Anti-PD-1 · PET/CT · CT · Biomarkers · Response evaluation

Introduction

Hodgkin lymphoma (HL) is a hematological malignancy involving the lymphatic system. The crude incidence of HL in the European Union is 2.3/100,000/year [1]. Most patients are diagnosed between 15 and 30 years of age, followed by another peak in adults aged ≥ 55 years [2, 3]. About 20% of the patients are refractory or relapse after chemotherapy, radiation therapy or their combination. The overall survival for patients with refractory HL remains poor; therefore, the highest chances of survival for those patients are clinical trials and the development of novel therapeutic modalities that could yield durable remissions and improved survival [4]. Based on its histological characteristics (a rather small number of primary tumor-associated CD-30$^+$ Reed Sternberg cells surrounded by a granuloma-like, immune cell-rich environment) HL is an ideal candidate for anti-PD-1 therapy [5]. Therefore, it is not surprising that monoclonal antibodies that block the interaction between PD-1 and PD-L1, by binding to either the ligand or receptor, have shown remarkable activity in HL [6–15]. A growing number of clinical trials evaluating different immune checkpoint inhibitors in classical HL in various treatment settings and in various combinations with other agents is ongoing [16, 17].

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The aim of this paper was to provide an overview, selecting the most relevant papers on the role of imaging in patients with HL treated with immune checkpoint inhibitors.

The present paper is descriptive, with the objective of providing current status and future directions for the investigations in the field; therefore, the recommendations for a systematic review cannot be applied [18].

Checkpoint inhibitors

Programmed-death 1 receptor (PD-1, CD279) is one of the crucial molecules that turn down the activation of the immune response functioning as negative regulator of T cell [19, 20]. The PD-1 receptor binds two ligands the PD-L1 (CD274, B7-H1) and the PD-L2 (CD273, B7-DC) [19]. PD-1 expression typically increases as cells are activated and signaling through PD-1 by its ligands results in cells becoming senescent with an exhausted phenotype. A subset of cells subsequently becomes apoptotic [21]. In the tumor microenvironment, PD-1 expression inhibits numerous immune cell subsets including T cells, B cells, natural killer cells, dendritic cells, and tumor-associated macrophages [22]. The activation of the PD-1/PD-L1 immune checkpoint pathway in cancer represents an adaptive mechanism of resistance used by cancer cells against tumor-infiltrating lymphocytes [5]. Immune checkpoint ligands, PD-L1 and PD-L2, are expressed on the surface of malignant cells in 65–100% of classical HL [7, 23, 24] and in 54% of nodular lymphocyte-predominant HL [24]. Alterations of the PD-L1/PD-L2 locus (present in 97% of cases) have been found to define classical HL and to be associated with patient outcome in a study on 108 newly diagnosed classical HL [23]. The presence of PD-1 ligands, predominantly on the Reed-Sternberg cells, and also on immune cells within the tumor microenvironment, as well as the expression of PD-1 receptors on intratumoral T cells, suggests significant suppression of T-cell function due to PD-1/PD-L1/PD-L2 interactions, providing the rationale for the use of PD-1 blockade to reverse the T-cell inhibition and to allow for a more effective antitumor immune response in HL [21, 23]. Figure 1 summarizes the mechanisms of action of the immuno-therapeutic agents.

Both nivolumab and pembrolizumab are fully humanized IgG4 anti-PD-1 monoclonal antibodies. Nivolumab (Opdivo®, Bristol-Myers Squibb) is approved in both Europe and United States (US) as monotherapy for the treatment of adult patients with relapsed or refractory classical HL after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin. Pembrolizumab (Keytruda®, Merck & Co.) is used in Europe in adult classical HL as monotherapy after brentuximab vedotin and ASCT failure, or when after brentuximab vedotin failure transplant is not possible. In US, it is approved for the treatment of adult and pediatric patients with refractory classical HL, or who have relapsed after three or more prior lines of therapy.

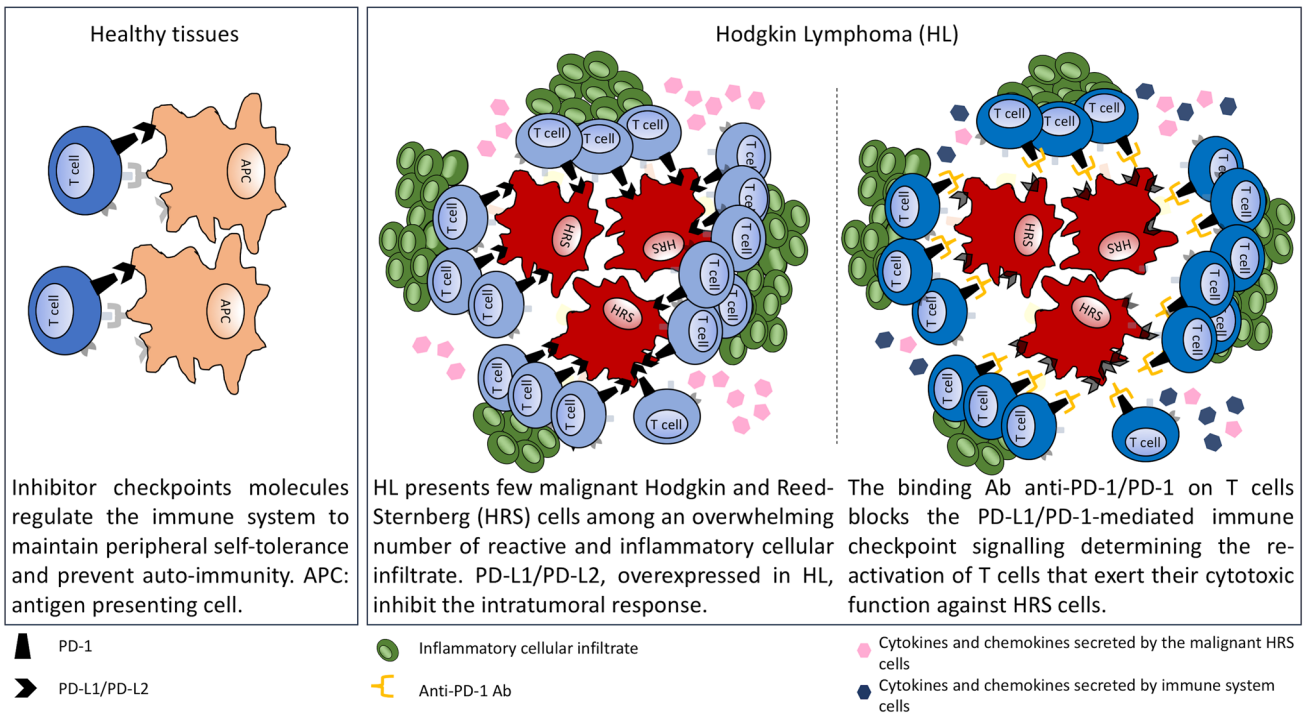

Fig. 1 Mechanisms of action of PD-1 blocking agents

Treatment response criteria in HL

The assessment of response to initial treatment in HL is crucial because the need for additional treatment is based on the treatment response. Many guidelines have been proposed to evaluate treatment response criteria in HL (Fig. 2).

The Cotswold classification, dating back to 1989, first formally defined the complete remission unconfirmed (CRu) to describe cases presenting with a residual mass after treatment that was most probably fibrotic [25].

In 1999, a multidisciplinary panel of experts constituted the International Working Group (IWG) and published guidelines for non-Hodgkin lymphoma (NHL) response assessment and outcomes measurement [26]. The IWG criteria (i.e., Cheson 1999 criteria) included anatomic definitions of response, with normal lymph node size after treatment of 1.5 cm in the longest transverse diameter on computer tomography (CT). A designation of complete response/unconfirmed was adopted to define patients with a greater than 75% reduction in tumor size after therapy but with a residual mass [26]. These recommendations rapidly entered in clinical practice and were used in the approval process for a number of new agents. However, they were subject to misinterpretation and recommended technologies (e.g., gallium scan), which were not the state-of-the-art modalities for lymphoma patients assessment. In 2007, the IWG guidelines were revised. This updated version (i.e., Cheson 2007) included "new" technologies such as immunohistochemistry and 18F-fluorodeoxyglucose–positron emission tomography/CT (FDG PET/CT) to define treatment response [27]. Although these criteria were developed for the end-of-treatment evaluation, they have been used for the interim response assessment as well [2]. However, the 2007 criteria were still subject to misinterpretation, since there was significant potential for ambiguity in the evaluation of the PET scans, which was based on a subjective interpretation of what represented [18F]FDG "background" activity (e.g., blood pool versus adjacent regions) and the degree of significantly discernible uptake, compared to the background [28]. In 2009, the Deauville criteria were introduced to interpret both interim and end-of-treatment FDG PET/CT in HL. These criteria adopted a visual 5-point scale (5-PS) to determine the degree of residual FDG lesion uptake in comparison to that of mediastinum and liver (i.e., reference tissues) [29]. In 2014 an updated version of the Deauville classification (i.e., Lugano 2014 criteria) was published [30]. The goal of the Lugano criteria was to reduce ambiguity and to achieve more consistent therapeutic response assessments for patients enrolled in clinical trials [28]. They were the direct consequence of the need of integration of the Deauville criteria and the input from the investigators at the International Workshop Conferences in 2011 and 2013 [28, 31]. According to the Lugano criteria patients could be classified as complete (Deauville 1–3) or not complete (Deauville 4–5) metabolic responders. The Lugano criteria were based on experience with chemotherapy or chemoimmunotherapy; however, the clinical availability of an increasing number of biologic agents with immune mechanisms required new criteria in image interpretation to account for these agents' biologic or immunomodulatory effects. Therefore, in 2016, the Lugano criteria were refined (i.e., Lymphoma Response to Immunomodulatory Therapy Criteria–LYRIC 2016 criteria) introducing the concept of "indeterminate response" for those cases with "delayed response"

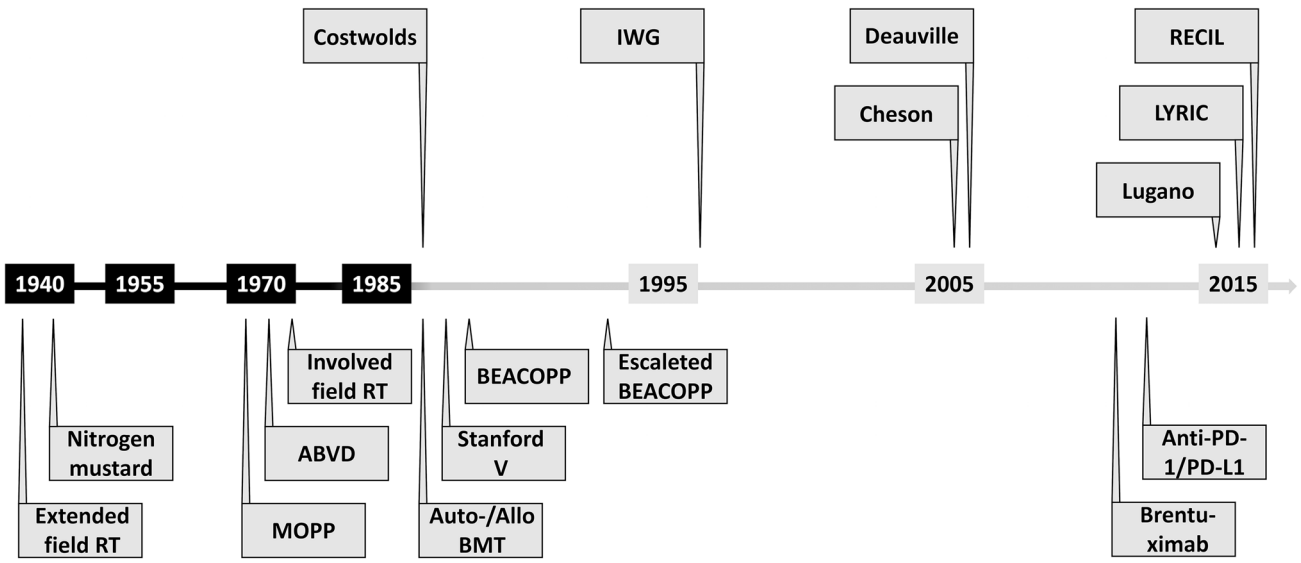

Fig. 2 Timeline depicting the use of treatment agents/modalities and the development of response assessment guidelines in lymphoma

or "pseudo-progression" that may be related to recruitment of immune cells to disease site [32]. In the case of indeterminate response, biopsy or repeat imaging is suggested to re-classify the disease as either true or pseudo-progression. In the same year, aiming at the harmonization of the lymphoma response criteria with response evaluation criteria in solid tumors (RECIST) were proposed and approved the Response Evaluation Criteria in Lymphoma (RECIL 2017). Also the RECIL guidelines include the "pseudo-progression" definition in case of a treatment with immunomodulating agents, new immunotherapies, and cell therapy with chimeric antigen receptor engineered T cells [33].

The image-based management of HL during treatment in clinical practice: the ESMO and the NCCN Guidelines

According to the European Society of Medical Oncology (ESMO) Guidelines neck/chest/abdomen contrast-enhanced CT (CECT) and FDG PET/CT should be performed at staging. The interim response evaluation by CECT should be carried out after completion of chemotherapy/before RT in limited and intermediate stages, while in advanced stages it should be performed after four cycles of chemotherapy and before radiation treatment (RT). Interim FDG PET/CT may be useful to identify poor-risk individuals; however, it cannot be considered standard and should be restricted to clinical trials except for the decision of whether patients with advanced HL receiving escalated combination of bleomicin, etoposide, adriamycin, ciclophosphamide, oncovin, procarbazine, and prednisone (BEACOPP) require RT. Final assessment should be carried out after completion of treatment. While CECT is mandatory, FDG PET/CT should be carried out whenever this diagnostic tool is available [34].

According to the National Comprehensive Cancer Network (NCCN) Guidelines neck/chest/abdomen/pelvis CECT scan should be performed at baseline and 6, 12, and 24 months after treatment completion, or as clinically indicated. FDG PET/CT should be performed at baseline. The value of interim FDG PET/CT remains unclear for many clinical scenarios; therefore, all definition of interim-response should be considered in the context of management decisions. The guidelines recommend biopsy for all patients with Deauville score 5 and all patients with a positive biopsy should be managed as described for refractory disease. For those with a negative biopsy, complete response (CR) should be documented, including reversion of PET to "negative" within 3 months after therapy completion. Surveillance FDG PET/CT should not be done routinely due to risk of false positives. Management decisions should not be based on FDG PET/CT scan alone; clinical or pathologic correlation is needed. FDG PET/CT should be performed during the follow-up only if the last scan was scored as a Deauville 4–5. The NCCN Guidelines recommend that the Deauville score, essential to decide how to manage the patient, should be included in all nuclear medicine reports [2].

Neither the ESMO nor the NCCN Guidelines mention that criteria for both CECT and FDG PET/CT treatment response evaluation may not be adequate for anti-PD-1 treatment response assessment.

Treatment response to anti-PD-1 in HL: the role of imaging

Assessing response to treatment in HL is classically based on bi-dimensional measurement of lymph nodes and masses although, as mentioned above, in the past 10 years guidelines have been updated to reflect the value of FDG PET/CT imaging in defining metabolic remission as equivalent to anatomical remission [35]. The added value of FDG PET/CT over conventional morphological imaging is the ability to identify viable tumor in residual lesion(s) [36]. However, the rate of false positive results of FDG PET/CT after treatment is not negligible. Nonetheless, experience in solid tumors has led to the recognition that immunomodulatory therapies, including the immune checkpoint inhibitors, may lead to tumor behaviors not well captured by standard imaging criteria [35, 37]. Specifically, the concern is that some patients receiving immune checkpoint inhibitors demonstrate "tumor flares" that do not have the same prognostic implications as progressive disease (PD). Figures 3 and 4 show examples of two patients with disease classified as indeterminate response. This new "indeterminate response" category, introduced to ensure that patients do not discontinue immune checkpoint inhibitors before receiving maximal benefit, includes patients in whom the tumor grows within the first 12 weeks of therapy without clinical deterioration; a single lesion grows at any time during therapy but overall tumor burden does not increase, or PET/CT imaging shows an increase in FDG uptake without a change in tumor size. Repeat imaging is suggested and, if growth continues, the patient is considered to have PD [32]. However, it is not yet established whether the assessment of "indeterminate response" translates in a different survival outcome than the traditional assessment of PD [35, 38] and the efficacy of the immune checkpoint inhibitors was demonstrated using the Cheson 2007 criteria [27] in almost all the prospective clinical trials (Table 1). More recently, the Lugano criteria have been applied [11, 39, 40].

In the CheckMate-039 clinical trial 23 patients with relapsed/refractory HL were treated with nivolumab. Both the best overall response (i.e., the best response between the date of the first dose and the last efficacy assessment before subsequent therapy) and the objective response rate (i.e., the proportion of the total number of patients whose best overall response was either a partial (PR) or a

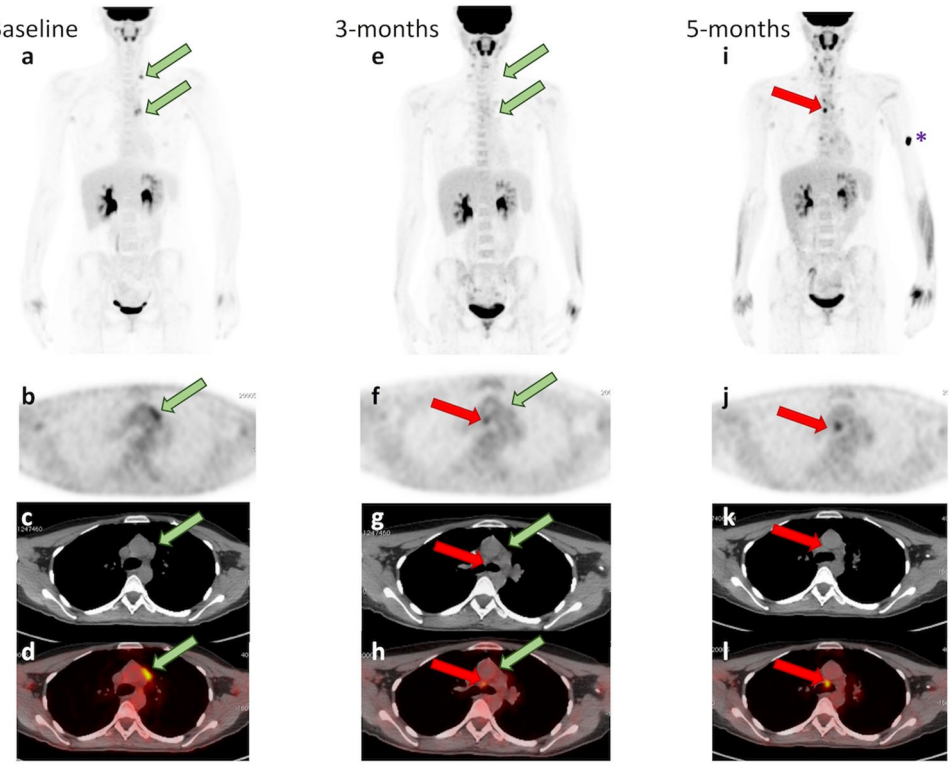

Fig. 3 FDG PET/CT scans (**a, e** and **i**—PET maximum intensity projection; **b, f** and **j**: axial PET; **c, g** and **k**: axial CT; **d, h** and **l**—axial fused PET/CT) performed at baseline (**a, b, c** and **d**), 3 months (**e, f, g** and **h**) and 5 months (**i, j, k** and **l**) from anti-PD-1 (nivolumab) treatment initiation, of a 30-year-old female, affected by classical Hodgkin Lymphoma, stage IIA at diagnosis, refractory to chemotherapy with persistence of disease at mediastinum and left latero-cervical node (green arrows), as shown on baseline FDG PET/CT scan. At 3 months' evaluation the baseline lesions were no more detectable, while a carinal lymph node (red arrows) with FDG uptake (Deauville score 4) was visible and classified as "indeterminate response". At 5 months' evaluation the carinal lymph node was confirmed, with increased FDG uptake (Deauville score 5). *FDG uptake related to an artifact

complete response) were assessed by CT scan (FDG PET/CT was used to confirm a CR). The objective response rate was 87% (4 CR and 16 PR) [6]. In the Checkmate-205 clinical trial recently updated, 243 patients were treated with nivolumab. The primary outcome of the study was to evaluate the proportion of patients achieving an objective response, defined as the percentage of treated patients with a best overall response of complete or partial remission (assessed by an independent radiological review committee). Patients were assessed for tumor responses by CT (preferred) or MRI and FDG PET/CT. For patients with bone marrow involvement at screening, a bone marrow biopsy was required to confirm complete remission [7]. After a median follow-up of 18 months, 40% of patients continued to receive treatment. An objective response was observed in 168 patients (40 CR and 128 PR) with a median duration of response of 16.6 months, and a median progression-free survival of 14.7 months [15]. A higher percentage of objective response (4 CR and 9 PR with a median time to response of 8 weeks) was observed in 17 patients treated within the Japanese nivolumab phase II study. The objective response ratio (primary study endpoint) was assessed by a central review committee using CT (preferred) or MRI and FDG PET/CT [8]. In the KEYNOTE-013 study were enrolled 31 HL patients with the aim of assessing the CR rate at any time after treatment with pembrolizumab. An objective response was observed in 20 patients (5 CR and 15 PR) [9]. The KEYNOTE-087 study enrolled and treated 210 patients to evaluate the overall response rate to pembrolizumab in three different cohorts of patients with refractory/relapsed HL (i.e., disease progression after autologous stem cell transplant (ASCT) with/without brentuximab vedotin and salvage chemotherapy plus brentuximab vedotin). Response was assessed by CT scan by an independent radiological review committee. FDG PET/CT was performed to confirm CR or PD and as clinically indicated. The overall response rate was higher than that observed in the KEYNOTE-013 study with 145/210 responders (47 CR and 98 PR) [10, 41].

The efficacy of low-dose pembrolizumab was evaluated in 5 HL patients with excellent results. Treatment response was evaluated by FDG PET/CT applying the 5-PS according to

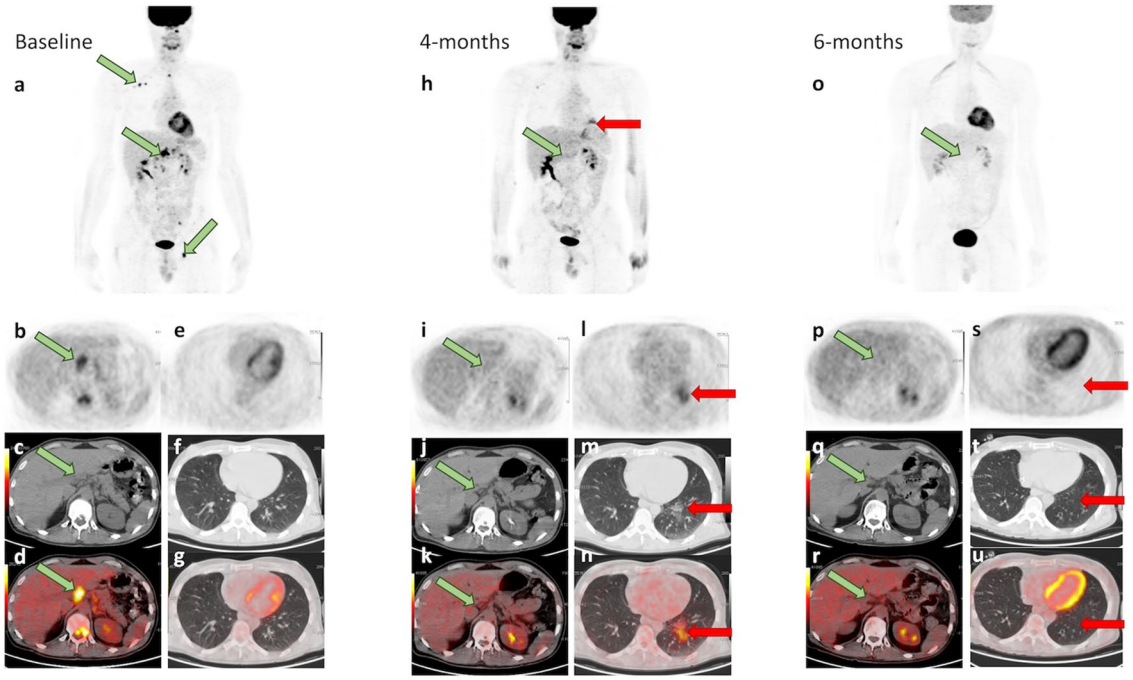

Fig. 4 FDG PET/CT scans (**a, h** and **o**—PET maximum intensity projection; **b, e, i, l, p** and **s**: axial PET; **c, f, j, m, q** and **t**: axial CT; **d, g, k, n, r** and **u**: axial fused PET/CT) performed at baseline (**a, b, c, d, e, f** and **g**), 4 months (**h, i, j, k, l, m** and **n**) and 6 months (**o, p, q, r, s, t** and **u**) from anti PD-1 (nivolumab) treatment initiation, of a 37-year-old male, affected by classical Hodgkin Lymphoma, stage IIA at diagnosis, refractory to chemotherapy with persistence of disease at nodal supra and sub diaphragmatic level (green arrows), as shown on baseline FDG PET/CT scan. At 4 months' evaluation the baseline lesions were no more detectable, while a pulmonary lesion (red arrows) with FDG uptake (Deauville score 4) was visible and classified as "indeterminate response". At 6 months' evaluation the pulmonary finding was no longer present on both PET and CT images

the Lugano 2014 criteria. All treated patients had an objective response (4 CR and 1 PR) [11].

Anti-PD1/PD-L1 in HL: the search for valuable biomarkers

Since the 2000s, the assessment of lymphoma has been essentially based on clinical examination, imaging, and bone marrow biopsy [36]. The advent of immunotherapies has opened different scenarios and has given rise to new needs. With innovative expensive targeted therapies for lymphomas, the need for accurate staging systems and standardized criteria for response is even more critical [36]. Therefore, biomarkers to selectively identify best candidates are necessary [42, 43].

Blood and tissue biomarkers

It is clear from the clinical results obtained to date that PD-1 blockade by itself is not effective in all patients with responsive tumors and even in those with response, delayed or mixed tumor regression can be seen. This is related to the dynamic nature of the immune system and the number of elements involved in the complex immune response against cancer [44]. The high response rate to anti-PD-1/PD-L1 therapy in HL could not be directly dependent on high ligand expression but on the effect that this high ligand expression may have on the microenvironment [22, 43]. Therefore, developing biomarkers for immuno-therapeutics is more challenging than developing biomarkers for targeted-therapy [45]. Immunohistochemical detection of PD-L1 on tumor cells is so far the most common biomarker for patient selection and prediction of response to anti-PD-1/PD-L1 therapy in clinical practice [46]. In fact, PD-L1 overexpression is expected to predict a better response to checkpoint inhibition and improve patient selection [45]. However, there are some challenges associated with the cell detection of PD-L1. First, there is no a standard definition of the cut-off to be considered overexpression and the use of different assays prevents the direct comparison of the results [45, 47]. Additionally, the PD-L1 expression on tumor and immune cells is a dynamic process that can also be regulated by intrinsic oncogenic pathways, and may not be reflected by a single time point evaluation [20, 45, 48].

The identification of the genetic signatures (e.g., 9p24.1 gene translocations or amplifications) by DNA sequencing techniques has been proposed to identify patients who have higher chances to respond to checkpoint inhibition [45, 49].

Table 1 Summary of prospective clinical trials' results that proved the efficacy of the immune checkpoint inhibitors in Hodgkin Lymphoma

Study	Drug	Patients, *n*	Imaging	Overall response rate (%)	Response evaluation criteria	Reference(s)
CheckMate-039 (phase I)	Nivolumab	23	CT Baseline and at weeks 4, 8, 16, and 24 and every 16 weeks thereafter FDG PET/CT Baseline and for confirmation of a complete response	87	Cheson 2007	[6]
Checkmate-205 (phase II)	Nivolumab	243	CT (preferred) or MRI Baseline and at weeks 9, 17, 25, 37, and 49 during the 1st year of treatment, then every 16 weeks until week 97, continuing every 26 weeks beyond week 97 until documented PD or until the patient initiated a preparative regimen for cell transplantation FDG PET/CT Baseline and at weeks 17 and 25. At week 49 only for patients who did not have two consecutive negative scans before this timepoint	69	Cheson 2007[a]	[15]
Japanese (phase II)	Nivolumab	17	CT (preferred) or MRI Baseline and at cycles 4, 8, 12, 18, 24, 32, 40, 48 and 61, and every 13 cycles thereafter FDG PET/CT Baseline and on day 15 in cycles 8, 12 and 24	76	Cheson 2007[a]	[8]
KEYNOTE-013 (phase Ib)	Pembrolizumab	31	CT Baseline and after 12 weeks of treatment and every 8 weeks thereafter FDG PET/CT Baseline and after 12 weeks of treatment and every 8 weeks thereafter	64	Cheson 2007	[9]
KEYNOTE-087 (phase II)	Pembrolizumab	210	CT Baseline and every 12 weeks of treatment and every 8 weeks thereafter FDG PET/CT Baseline and at weeks 12 and 24 to confirm CR/PD and as clinically indicated	69	Cheson 2007[a]	[10, 41]
Not reported	Pembrolizumab, low dose	5	FDG PET/CT Not reported	100	Lugano 2014	[11]

[a]Response assessment performed by an independent radiologic review committee

As mentioned above, the tumor microenvironment could predict response to checkpoint inhibitors, and tumor-infiltrating immune cells may be examined by immunohistochemistry or flow cytometry [43, 45].

Profile of the circulating cell-free DNA has been described in a proof-of-concept study to vary rapidly at treatment initiation suggesting a potential role for response monitoring [50]. Recently, longitudinal ctDNA profiling has

been demonstrated to identify treatment-dependent patterns of clonal evolution in 80 newly diagnosed and 32 refractory HL patients relapsing after chemotherapy and in those maintained in PR under immunotherapy. Moreover, the authors affirmed that quantification of ctDNA complemented interim PET/CT in response assessment [51].

In some cancer types, virtually each tumor is virus-associated, while in other cancers including HL, only a subset of cases is virus-associated. Therefore, the presence or absence of the causative virus (i.e., Epstein-Barr virus in HL) could represent a predictive biomarker for response to immune checkpoint blockade. Alternatively, measures of endogenous immune responses to these viruses in patients bearing virus-positive tumors could serve as a predictive biomarker [49].

Imaging biomarkers

The need to find reliable biomarkers is also based on the need for sustainable healthcare costs since an antibody-based treatment is expensive (e.g., a single course of nivolumab costs between $100,000 and $150,000) [52]. Therefore, biomarkers derived from conventional imaging, antibody-based imaging or other imaging-based approaches could be valuable to select patients suitable for checkpoint inhibitors treatment. Recently, Dercle et al. [53] showed that 3 month-FDG PET/CT was able to detect all HL patients responding to immune-checkpoint blockade by anti-PD1 treatment (responders experienced a significant shrinkage in tumor volume—ΔMTV, ΔTLG—, a decrease in tumor glucose metabolism and an increase in spleen metabolism) [53]. These results appear to be in line with the immunohistochemical finding of the association between glucose transporter 1 (GLUT1) and PD-L1/PD-L2 expression [54]. Nonetheless, even though the role of functional imaging parameters appears promising it should be validated in larger series. Figures 5 and 6 show two cases of patients with CR and PR, respectively, on interim FDG PET/CT. However, as mentioned above, tumor behaviors related to immunomodulatory therapies may not be well-captured by standard criteria applied to conventional imaging. The main issue of applying standard imaging criteria to immune checkpoint molecules treatment assessment is related to the fact that the mechanism of these new drugs is a complex and dynamic process, only partly understood and different among tumor types.

In this regard, PET/MR modality adding functional information derived from MR technologies, especially diffusion weighted imaging (DWI), can provide additional information about tumor cellularity improving the characterization of the tumor phenotype [36].

Molecular imaging has been at the forefront of non-invasive assessment "in vivo" of the tumor phenotype during the past decade and allows to image tumors using designable imaging agents [52]. The improvements in radiochemistry and isotope development, nanomedicine and nanotechnologies, made possible to design PET imaging agents suited for a specific target. Therefore, the possibility to image patients by immunoPET with PD1/

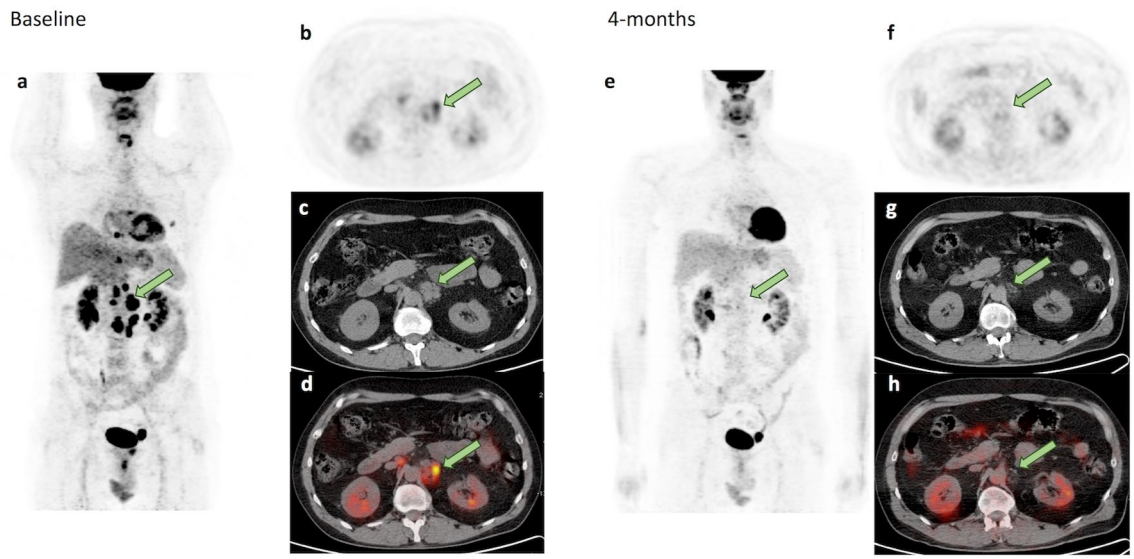

Fig. 5 FDG PET/CT scans (**a** and **e**: PET maximum intensity projection; **b** and **f**: axial PET; **c** and **g**: axial CT; **d** and **h**: axial fused PET/CT) performed at baseline (**a, b, c** and **d**), and 4 months (**e, f, g** and **h**) from anti PD-1 (nivolumab) treatment initiation, of a 45 year-old male, affected by classical Hodgkin Lymphoma, stage IIIXB at diagnosis, refractory to chemotherapy with persistence of disease at node supra and sub diaphragmatic level (green arrows), as shown on baseline FDG PET/CT scan. At 4 months evaluation the baseline lesions were no more detectable (Deauville score 1). Therefore, the patient was classified in "complete response"

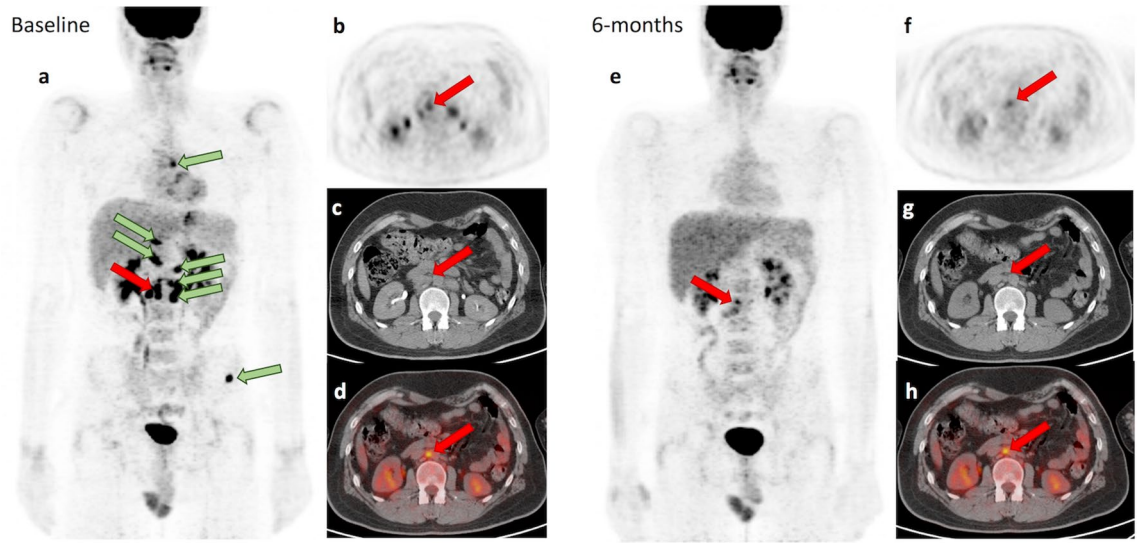

Fig. 6 FDG PET/CT scans (**a** and **e**: PET maximum intensity projection; **b** and **f**: axial PET; **c** and **g**: axial CT; **d** and **h**: axial fused PET/CT) performed at baseline (**a, b, c** and **d**), and 6 months (**e, f, g** and **h**) from anti PD-1 (nivolumab) treatment initiation, of a 28 year-old male, affected by classical Hodgkin Lymphoma, stage IVB at diagnosis, refractory to chemotherapy with persistence of disease at node supra and sub diaphragmatic level and at the iliac left bone (green arrows), as shown on baseline FDG PET/CT scan. At 6 months' evaluation the baseline most of lesions were no more detectable (Deauville score 1) while some inter-cavo-aortic lymph nodes displaying FDG uptake were still present (Deauville 4). Therefore, the patient was classified in "partial response"

PD-L1-radiopharmaceuticals to visualize "in vivo" the PD-L1 expression and its variation over time might be realistic in the next future.

Recently, a renewed interest has been shown in radiomics. It is based on the concept that biomedical images contain more information than that provided by qualitative analysis and that this information, reflecting the underlying pathophysiology, can be revealed via quantitative image analyses [55]. In fact, up to hundreds of image-derived parameters can be calculated from CT, PET/CT and MR, to be tested for correlations with biological features. As described above, current conventional imaging practice is generally qualitative or, when quantitative, measurements are commonly limited to one or bi-dimensional assessment of tumor size. However, these measures do not reflect the complexity of tumor heterogeneity or behavior, nor, in many cases, are changes in these measures predictive of therapeutic benefit [55], especially in the immunotherapies era. The modern re-birth of radiomics aims to convert images into mineable data, with high fidelity and high throughput [55]. Literature data on radiomics in HL focused on chemotherapy response prediction using either CECT [56] or PET/CT imaging [57] are promising, but still not definitive. However, initial experiences in solid tumors suggest that radiomics may predict early failure to nivolumab and may help in the selection of patients who may benefit from PD-1/PD-L1 treatment [58, 59].

Conclusions

The emergence of modern more individualized therapeutic approaches in HL needs to be accompanied by robust predictive models and reliable response assessment biomarkers and criteria. Immune checkpoint inhibitors represent a major advance in the treatment of relapsed/refractory HL patients. Initial attempts to face the uncertainties related to the assessment of treatment response have been made, but further investigations for the evaluation of the role of both immuno-histochemical and imaging biomarkers are needed. Novel blood, tissue, and image-derived parameters have shown promising potential. These, even in combination with conventional risk factors, should be validated. To provide robust data for response definition, concomitantly with new drug approval, a multi-biomarker monitoring should be incorporated into clinical trials. This strategy should allow to precisely and timely define biomarkers cumulative accuracy in assessing the disease status of HL patients, and at long term, to improve outcome and optimize resources use.

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Author contributions MK and MS: Literature search and review, manuscript writing; AC: Manuscript writing and editing.

Compliance with ethical standards

Conflict of interest A. Chiti received speaker honoraria from General Electric, Blue Earth Diagnostics and Sirtex Medical System, acted as scientific advisor for Blue Earth Diagnostics and Advanced Accelerator Applications, and benefited from an unconditional grant from Sanofi to Humanitas University. All honoraria and grants are outside the scope of the submitted work. All other authors have no conflicts of interest.

Research involving human participants Not applicable.

Informed consent Not applicable.

References

1. Eichenauer DA, Aleman BMP, André M et al (2018) Hodgkin lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. https://doi.org/10.1093/annonc/mdy080/4999396
2. Hoppe RT, Advani RH, Ai WZ et al (2017) Hodgkin lymphoma Version 1.2017: clinical practice guidelines in oncology. JNCCN J Natl Compr Cancer Netw 15:608–638
3. Siegel RL, Miller KD, Jemal A (2017) Cancer statistics, 2017. CA Cancer J Clin 67:7–30. https://doi.org/10.3322/caac.21387
4. Galanina N, Kline J, Bishop MR (2017) Emerging role of checkpoint blockade therapy in lymphoma. Ther Adv Hematol 8:81–90. https://doi.org/10.1177/2040620716673787
5. Ilcus C, Bagacean C, Tempescul A et al (2017) Immune checkpoint blockade: the role of PD-1-PD-L axis in lymphoid malignancies. Oncol Targets Ther 10:2349–2363. https://doi.org/10.2147/OTT.S133385
6. Ansell S, Lesokhin AM, Borrello I et al (2015) PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. N Engl J Med 372:311–319. https://doi.org/10.1056/NEJMoa1411087.PD-1
7. Younes A, Santoro A, Shipp M et al (2016) Nivolumab for classical Hodgkin's lymphoma after failure of both autologous stem-cell transplantation and brentuximab vedotin: a multicentre, multicohort, single-arm phase II trial. Lancet Oncol 17:1283–1294. https://doi.org/10.1016/S1470-2045(16)30167-X
8. Maruyama D, Hatake K, Kinoshita T et al (2017) Multicenter phase II study of nivolumab in Japanese patients with relapsed or refractory classical Hodgkin lymphoma. Cancer Sci 108:1007–1012. https://doi.org/10.1111/cas.13230
9. Armand P, Shipp MA, Ribrag V et al (2016) Programmed death-1 blockade with pembrolizumab in patients with classical Hodgkin lymphoma after brentuximab vedotin failure. J Clin Oncol 34:3733–3739. https://doi.org/10.1200/JCO.2016.67.3467
10. Moskowitz CH, Zinzani PL, Fanale MA et al (2016) Pembrolizumab in relapsed/refractory classical Hodgkin lymphoma: primary end point analysis of the phase II keynote-087 study. Blood 128:1107
11. Chan TSY, Luk TH, Lau JSM et al (2017) Low-dose pembrolizumab for relapsed/refractory Hodgkin lymphoma: high efficacy with minimal toxicity. Ann Hematol 96:647–651. https://doi.org/10.1007/s00277-017-2931-z
12. Onizuka M, Kojima M, Matsui K et al (2017) Successful treatment with low-dose nivolumab in refractory Hodgkin lymphoma after allogeneic stem cell transplantation. Int J Hematol 106:141–145. https://doi.org/10.1007/s12185-017-2181-9
13. Foran AE, Nadel HR, Lee AF et al (2016) Nivolumab in the treatment of refractory pediatric Hodgkin lymphoma. J Pediatr Hematol Oncol 39:1. https://doi.org/10.1097/MPH.0000000000000703
14. Benjamini O, Lavie D, Dann EJ et al (2016) Real-life experience of nivolumab in heavily pretreated relapsed and refractory classical Hodgkin lymphoma. Blood 128:3008
15. Armand P, Engert A, Younes A et al (2018) Nivolumab for relapsed/refractory classic Hodgkin lymphoma after failure of autologous hematopoietic cell transplantation: extended follow-up of the multicohort single-arm phase II checkmate 205 trial. J Clin Oncol 36:1428–1439. https://doi.org/10.1200/JCO.2017.76.0793
16. Clinicaltrials.gov. https://clinicaltrials.gov/ct2/results?cond=Lymphoma+AND+%22Hodgkin+Lymphoma%22&intr=Nivolumab&recrs=a&recrs=f&recrs=d&age_v=&gndr=&type=&rslt=&Search=Apply. Accessed 1 Aug 2018
17. Borchmann S, von Tresckow B (2017) Novel agents in classical Hodgkin lymphoma. Leuk Lymphoma 8194:1–12. https://doi.org/10.1080/10428194.2017.1300898
18. Sadeghi R, Treglia G (2017) Systematic reviews and meta-analyses of diagnostic studies: a practical guideline. Clin Transl Imaging 5:83–87. https://doi.org/10.1007/s40336-016-0219-2
19. Jelinek T, Mihalyova J, Kascak M et al (2017) PD-1/PD-L1 inhibitors in haematological malignancies: update 2017. Immunology 152:357–371. https://doi.org/10.1111/imm.12788
20. Zou W, Wolchok JD, Chen L (2016) PD-L1 (B7-H1) and PD-1 pathway blockade for cancer therapy: mechanisms, response biomarkers, and combinations. Sci Transl Med 8:328rv4. https://doi.org/10.1126/scitranslmed.aad7118
21. Ansell SM (2017) Nivolumab in the treatment of Hodgkin lymphoma. Clin Cancer Res 23:1623–1626. https://doi.org/10.1158/1078-0432.CCR-16-1387
22. Gordon SR, Maute RL, Dulken BW et al (2017) PD-1 expression by tumour-associated macrophages inhibits phagocytosis and tumour immunity. Nat 545:495–499. https://doi.org/10.1038/nature22396
23. Roemer MGM, Advani RH, Ligon AH et al (2016) PD-L1 and PD-L2 genetic alterations define classical Hodgkin lymphoma and predict outcome. J Clin Oncol 34:2690–2697. https://doi.org/10.1200/JCO.2016.66.4482
24. Menter T, Bodmer-Haecki A, Dirnhofer S, Tzankov A (2016) Evaluation of the diagnostic and prognostic value of PDL1 expression in Hodgkin and B-cell lymphomas. Hum Pathol 54:17–24. https://doi.org/10.1016/j.humpath.2016.03.005
25. Lister TA, Crowther D, Sutcliffe SB et al (1989) Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: cotswolds meeting. J Clin Oncol 7:1630–1636. https://doi.org/10.1200/JCO.1989.7.11.1630
26. Cheson BD, Horning SJ, Coiffier B et al (1999) Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. J Clin Oncol 17:1244. https://doi.org/10.1200/JCO.1999.17.4.1244
27. Cheson BD, Pfistner B, Juweid ME et al (2007) Revised response criteria for malignant lymphoma. J Clin Oncol 25:579–586. https://doi.org/10.1200/JCO.2006.09.2403
28. Van Heertum RL, Scarimbolo R, Wolodzko JG et al (2017) Lugano 2014 criteria for assessing FDG PET/CT in lymphoma: an operational approach for clinical trials. Drug Des Devel Ther 11:1719–1728. https://doi.org/10.2147/DDDT.S136988
29. Meignan M, Gallamini A, Meignan M et al (2009) Report on the first international workshop on interim-PET-scan in lymphoma. Leuk Lymphoma 50:1257–1260. https://doi.org/10.1080/10428190903040048
30. Cheson BD, Fisher RI, Barrington SF et al (2014) Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 32:3059–3068. https://doi.org/10.1200/JCO.2013.54.8800

31. Barrington SF, Mikhaeel NG, Kostakoglu L et al (2014) Role of imaging in the staging and response assessment of lymphoma: consensus of the international conference on malignant lymphomas imaging working group. J Clin Oncol 32:3048–3058. https://doi.org/10.1200/jco.2013.53.5229
32. Cheson BD, Ansell S, Schwartz L et al (2016) Refinement of the lugano Classification lymphoma response criteria in the era of immunomodulatory therapy. Blood 128:2489–2496. https://doi.org/10.1182/blood-2016-05-718528
33. Younes A, Hilden P, Coiffier B et al (2017) International working group consensus response evaluation criteria in lymphoma (RECIL 2017). Ann Oncol 28:1436–1447. https://doi.org/10.1093/annonc/mdx097
34. Eichenauer DA, Engert A, Andre M et al (2014) Hodgkin's lymphoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 25:iii70–iii75. https://doi.org/10.1093/annonc/mdu181
35. Jain MD, Kuruvilla J (2017) Anti-PD-1 antibodies as a therapeutic strategy in classical Hodgkin lymphoma. Drugs 77:1645–1655. https://doi.org/10.1007/s40265-017-0796-z
36. Kalimuthu S, Jeong JH, Oh JM, Ahn B-C (2017) Drug discovery by molecular imaging and monitoring therapy response in lymphoma. Int J Mol Sci 18:1639. https://doi.org/10.3390/ijms18081639
37. Seymour L, Bogaerts J, Perrone A et al (2017) iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol 18:e143–e152. https://doi.org/10.1016/S1470-2045(17)30074-8
38. Cheson BD, Ansell S, Schwartz L et al (2016) Perspectives refinement of the lugano classification lymphoma response criteria in the era of immunomodulatory therapy. Blood 128:2489–2497. https://doi.org/10.1182/blood-2016-05-718528.BLOOD
39. Rossi C, Gilhodes J, Maerevoet M et al (2018) Efficacy of chemotherapy or chemo-anti-PD-1 combination after failed anti-PD-1 therapy for relapsed and refractory Hodgkin lymphoma: a series from lysa centers. Am J Hematol. https://doi.org/10.1002/ajh.25154
40. Herrera AF, Moskowitz AJ, Bartlett NL et al (2018) Interim results of brentuximab vedotin in combination with nivolumab in patients with relapsed or refractory Hodgkin lymphoma. Blood 131:1183–1194. https://doi.org/10.1182/blood-2017-10-811224
41. Chen R, Zinzani PL, Fanale MA et al (2017) Phase II study of the efficacy and safety of pembrolizumab for relapsed/refractory classic Hodgkin lymphoma. J Clin Oncol 35:2125–2132. https://doi.org/10.1200/JCO.2016.72.1316
42. Ok CY, Young KH (2017) Checkpoint inhibitors in hematological malignancies. J Hematol Oncol 10:1–16. https://doi.org/10.1186/s13045-017-0474-3
43. Armand P (2015) Checkpoint blockade in lymphoma. Hematol Am Soc Hematol Educ Progr 2015:69–73. https://doi.org/10.1182/asheducation-2015.1.69
44. Topalian SL, Hodi FS, Brahmer JR et al (2012) Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 366:2443–2454. https://doi.org/10.1056/NEJMoa1200690
45. Vareki SM, Garrigós C, Duran I (2017) Biomarkers of response to PD-1/PD-L1 inhibition. Crit Rev Oncol Hematol 116:116–124. https://doi.org/10.1016/j.critrevonc.2017.06.001
46. Patel SP, Kurzrock R (2015) PD-L1 expression as a predictive biomarker in cancer immunotherapy. Mol Cancer Ther 14:847–856
47. Hansen AR, Siu LL, T M (2016) PD-L1 testing in cancer. JAMA Oncol 2:15. https://doi.org/10.1001/jamaoncol.2015.4685
48. Mukherji D, Jabbour MN, Saroufim M et al (2016) Programmed death-ligand 1 expression in muscle-invasive bladder cancer cystectomy specimens and lymph node metastasis: a reliable treatment selection biomarker? Clin Genitourin Cancer 14:183–187. https://doi.org/10.1016/j.clgc.2015.12.002
49. Topalian SL, Taube JM, Anders RA, Pardoll DM (2016) Mechanism-driven biomarkers to guide immune checkpoint blockade in cancer therapy. Nat Rev Cancer 16:275–287. https://doi.org/10.1038/nrc.2016.36
50. Vandenberghe P, Wlodarska I, Tousseyn T et al (2015) Non-invasive detection of genomic imbalances in hodgkin/reed-sternberg cells in early and advanced stage Hodgkin's lymphoma by sequencing of circulating cell-free DNA: a technical proof-of-principle study. Lancet Haematol 2:e55–e65. https://doi.org/10.1016/S2352-3026(14)00039-8
51. Spina V, Bruscaggin A, Cuccaro A et al (2018) Circulating tumor DNA reveals genetics, clonal evolution and residual disease in classical Hodgkin lymphoma. Blood 131:2413–2425. https://doi.org/10.1182/blood-2017-11-812073
52. England CG, Rui L, Cai W (2017) Lymphoma: current status of clinical and preclinical imaging with radiolabeled antibodies. Eur J Nucl Med Mol Imaging 44:517–532. https://doi.org/10.1007/s00259-016-3560-9
53. Dercle L, Seban R-D, Lazarovici J et al (2018) 18F-FDG PET and CT scans detect new imaging patterns of response and progression in patients with Hodgkin lymphoma treated by anti-programmed death 1 immune checkpoint inhibitor. J Nucl Med 59:15–24. https://doi.org/10.2967/jnumed.117.193011
54. Koh YW, Han J-H, Park SY et al (2017) GLUT1 as a prognostic factor for classical Hodgkin's lymphoma: correlation with PD-L1 and PD-L2 expression. J Pathol Transl Med 51:152–158. https://doi.org/10.4132/jptm.2016.11.03
55. Kumar V, Gu Y, Basu S et al (2012) Radiomics: the process and the challenges. Magn Reson Imaging 30:1234–1248. https://doi.org/10.1016/j.mri.2012.06.010
56. Ganeshan B, Miles KA, Babikir S et al (2017) CT-based texture analysis potentially provides prognostic information complementary to interim FDG PET for patients with Hodgkin's and aggressive non-Hodgkin's lymphomas. Eur Radiol 27:1012–1020. https://doi.org/10.1007/s00330-016-4470-8
57. Ben Bouallègue F, Al Tabaa Y, Kafrouni M et al (2017) Association between textural and morphological tumor indices on baseline PET-CT and early metabolic response on interim PET-CT in bulky malignant lymphomas. Med Phys 44:4608–4619. https://doi.org/10.1002/mp.12349
58. Nardone V, Tini P, Aldi E et al (2017) Predictive value of CT texture analysis in lung cancer patients undergoing nivolumab | OncologyPRO. Ann Oncol 28:ii24–ii27
59. Xie Y, Khunger M, Thawani R et al (2017) Evolution of radiomic features on serial CT scans as an imaging based biomarker for evaluating respo. J Clin Oncol 35:e14534