

Total immunotherapy for Hodgkin lymphoma

Roch Houot, Reid W. Merryman, Franck Morschhauser

▶ **To cite this version:**

Roch Houot, Reid W. Merryman, Franck Morschhauser. Total immunotherapy for Hodgkin lymphoma. Lancet Haematology, 2020, 7 (9), pp.e629-e630. 10.1016/S2352-3026(20)30220-9 . hal-02930371

HAL Id: hal-02930371
https://hal.science/hal-02930371

Submitted on 6 Nov 2020

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Copyright

Total immunotherapy for Hodgkin lymphoma

Roch Houot[1, 2], Reid W. Merryman[2], Franck Morschhauser[3]

[1] Department of Hematology, CHU Rennes, University of Rennes, INSERM U1236, Rennes, France

[2] Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA

[3] Hôpital Claude Huriez, Centre Hospitalier Regional Universitaire, Lille, France

Corresponding Author:

Pr Franck Morschhauser

Univ. Lille, CHU Lille, EA 7365 - GRITA - Groupe de Recherche sur les formes Injectables et les Technologies Associées, F-59000 Lille, France.

Tel: +33 3 20444290

Fax: +33 3 20444708

Email: franck.morschhauser@chru-lille.fr

Text word count: 747

Figures: 0

Tables: 0

Appendix: 1 Table

References: 10

Key words: immunotherapy, brentuximab vedotin, anti-CTLA4, anti-PD1, ipilimumab, nivolumab, Hodgkin

The anti-CD30 antibody-drug conjugate, brentuximab vedotin (BV), and PD-1 monoclonal antibodies (mAbs), nivolumab and pembrolizumab, have dramatically improved outcomes for patients with relapsed or refractory (R/R) classic Hodgkin lymphoma (HL). With the goal of improving the depth and duration of remissions with these agents, combination strategies are underway investigating various combination partners, including conventional chemotherapy and other checkpoint inhibitors. Trials testing the combination of nivolumab and BV in the first and second-line settings showed a significant improvement in complete response (CR) rate compared to treatment with either agent alone, suggesting the potential of this approach.[1]

Dual therapy targeting both the PD-1 and CTLA-4 immune checkpoint receptors has been a successful strategy in several solid tumors. In HL, growing biologic and clinical evidence supports a possible role for the CTLA-4 immune axis in facilitating immune evasion for Hodgkin Reed-Sternberg (HRS) cells. Patel *et al* found that CTLA-4 is the most abundantly expressed immune checkpoint receptor in the HL tumor microenvironment and that CTLA-4-positive T-cells frequently cluster around HRS cells, providing a rationale for targeting CTLA-4 in this disease.[2] Two studies tested the anti-CTLA-4 mAb, ipilimumab, in HL in patients relapsing after allogeneic stem cell transplantation (allo-HCT) and reported 2 CRs out of 14 patients[3] and 2 partial responses (PRs) out of 7 patients[4], respectively. Ipilimumab was also tested in combination with nivolumab (without BV) in the CheckMate-039 study (N=31 HL).[5] The combination was tolerable (although associated with increased toxicity compared to PD-1 monotherapy), but response rates (ORR 74%, CRR 19%) were not noticeably higher than those observed with PD-1 monotherapy.

In the current study, Diefenbach *et al* report the results of a phase 1 trial evaluating 3 combination approaches: BV + ipilimumab (BV+I), BV + nivolumab (BV+N), or the triplet BV+I+N.[6] The primary endpoint was safety, and the authors were able to determine the maximum tolerated dose for all 3 arms. Rates of grade 3-4 adverse events (AEs) were significantly higher for the ipilimumab-containing arms (BV+I 43% and BV+I+N 50% vs BV+N 16%), but severe immune-related AEs were seen in all cohorts, including 1 case of grade 5 pneumonitis in both the BV+N and BV+I+N cohorts. Although this phase 1 trial was not designed to compare efficacy across arms, the nivolumab-containing arms appeared to have superior progression-free survival (PFS) compared to BV+I, and the authors selected these two regimens (BV+N and BV+I+N) for an ongoing randomized phase 2 trial. A summary table is in the appendix.

It's possible that the triplet regimen may augment depth and duration of response, but the expected extra toxicity of this regimen may be challenging to stomach, particularly in earlier lines of therapy.

Unlike many patients with solid tumors who are receiving combination immune checkpoint regimens, patients with R/R HL are fortunate to have a number of other treatment options, including curative ones. First, anti-PD1 therapy (alone or in combination with BV) offers long-term remissions (and potentially a cure in a subset of patients) with limited toxicity. Second, among patients who fail single agent or doublet BV+N therapy, many can be rescued with salvage therapies; in fact, anti-PD1 therapy may "re-sensitize" the tumor to chemotherapy and thus offer a new chance of remission with conventional chemotherapy.[7,8] Furthermore, other novel therapies have demonstrated encouraging preliminary results, including CD25 ADCs, and cellular therapies, like CD30 chimeric antigen receptor T cells and Epstein-Barr virus (EBV)-directed cytotoxic T cells. Finally, autologous stem cell transplantation (auto-SCT) looks to be very effective after anti-PD1 therapy[9] and allo-HCT, which was initially reported to be very toxic after PD1 blockade, appears to be safer with the use of post-transplant cyclophosphamide.[10]

The ongoing phase II trial should offer more clues about how best to utilize these novel therapies. Since the triplet regimen may increase the risk of severe, life-threatening toxicities (like pneumonitis and myocarditis), it would need to be significantly more effective than doublet therapy with higher response rates, but more importantly, improved DOR and survival. Ideally, this trial and other ongoing studies can identify predictive biomarkers to select patients who are more likely to benefit from the addition of ipilimumab and/or less likely to develop severe toxicity. If such biomarkers could identify patients who can achieve long-term remissions with doublet or triplet therapy without the need for consolidative SCT, more upfront toxicity would be easier to accept. With so many novel agents, the optimal strategy for patients with R/R disease is not yet clear. While much work remains, combination approaches, if safely wielded, may offer improved outcomes for patients with HL.

References

1 Herrera AF, Moskowitz AJ, Bartlett NL, *et al.* Interim results of brentuximab vedotin in combination with nivolumab in patients with relapsed or refractory Hodgkin lymphoma. *Blood* 2018; **131**: 1183–94.

2 Patel SS, Weirather JL, Lipschitz M, *et al.* The microenvironmental niche in classic Hodgkin lymphoma is enriched for CTLA-4–positive T cells that are PD-1–negative. *Blood* 2019; **134**: 2059–69.

3 Bashey A, Medina B, Corringham S, *et al.* CTLA4 blockade with ipilimumab to treat relapse of malignancy after allogeneic hematopoietic cell transplantation. *Blood* 2009; **113**: 1581–8.

4 Davids MS, Kim HT, Bachireddy P, *et al.* Ipilimumab for patients with relapse after allogeneic transplantation. *N Engl J Med* 2016; **375**: 143–53.

5 Ansell S, Gutierrez ME, Shipp MA, *et al.* A Phase 1 Study of Nivolumab in Combination with Ipilimumab for Relapsed or Refractory Hematologic Malignancies (CheckMate 039). *Blood* 2016; **128**: 183–183.

6 Diefenbach CS. Ipilimumab, Nivolumab and Brentuximab Vedotin in Patients with Relapsed Hodgkin Lymphoma: Phase 1 Results of a Multicenter Phase 1/2 Clinical Trial. *Lancet Haematol* 2020.

7 Rossi C, Gilhodes J, Maerevoet M, *et al.* 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* 2018; **93**: 1042–9.

8 Carreau NA, Armand P, Merryman RW, *et al.* Checkpoint blockade treatment sensitises relapsed/refractory non-Hodgkin lymphoma to subsequent therapy. *Br J Haematol* 2020; : 1–8.

9 Merryman RW, Redd RA, Nieto Y, *et al.* Outcome of Autologous Stem Cell Transplantation Following PD-(L)1 Based Salvage Therapy for Multiply Relapsed Patients with Classic Hodgkin Lymphoma. *Blood* 2019; **134**: 4571–4571.

10 Merryman RW, Castagna L, Corradini P, *et al.* Safety and Efficacy of Allogeneic Hematopoietic Stem Cell Transplant after Programmed Cell Death 1 (PD-1) / Programmed Cell Death Ligand 1 (PD-L1) Blockade for Classical Hodgkin Lymphoma: Analysis of a Large International Cohort. *Blood* 2019; **134**: 775–775.