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IMMUNOTHERAPY IN HODGKIN LYMPHOMA: CURRENT AND EVOLVING ROLES

Introduction
Classical Hodgkin lymphoma (cHL) is a very curable form of cancer for the majority of patients that receive standard primary therapy.[1] Many patients will have a second opportunity for cure at the time of first progression using approaches that incorporate high dose chemotherapy and autologous stem cell transplant (ASCT). In the non-curative setting, a group of patients (including patients with advanced age and comorbidities precluding standard therapy approaches and those with lymphoma that persists despite these treatments) will be treated with palliative intent. While these patients have had limited options in the past,[2,3] novel therapies have rapidly become the standard of care in this setting. Antibodies targeting CD30 (the antibody drug conjugate brentuximab vedotin [BV]) and the immune checkpoint through PD1 (nivolumab and pembrolizumab) have now become standard approved treatments for patients beyond second-line treatment. The biology of PD1 appears particularly relevant in cHL, providing a strong clinical rationale for evaluating these agents in this malignancy.[4] Clinicians in Canada now have several choices when making treatment decisions in patients with relapsed or refractory cHL (RR-cHL). Prospective trials are now determining the role of anti-PD1 antibodies in the curative setting.

Current role of Immunotherapy in cHL: Relapsed or Refractory Disease
Both nivolumab and pembrolizumab are currently approved by Health Canada for the treatment of RR-cHL and funding is broadly available across the country for this indication. Both agents were initially evaluated in phase I studies that demonstrated excellent efficacy and a favourable toxicity profile.[5,6] These initial trials were followed by phase 2 studies that included several different patient cohorts.

The CheckMate-205 study evaluated nivolumab in three cohorts of patients post-ASCT, representing a total of 243 patients.[7-10] The cohorts included HL patients that were BV-naïve, patients post-ASCT and subsequently treated with BV, and patients post-BV at any time during their disease course. Protocol-mandated therapy was nivolumab 3 mg/kg intravenously every 2 weeks until disease progression or toxicity. Patients in one cohort (BV before and/or after ASCT) could discontinue treatment after 1 year in persistent complete response (CR) and could resume treatment if they relapsed within 2 years of the last dose. The overall response rate (ORR) was 69% (95% CI, 63-75) and ranged between 65-73% in each cohort while the CR rate was 16%. The median progression-free survival (PFS)

Patients' Characteristics and Key Outcome and Toxicity Measures	Nivolumab	Pembrolizumab
Trial Name/Code	CheckMate 205	KEYNOTE-087
Location	Europe, North America	Europe, North America, Israel,
Dose/Schedule	3 mg/kg every 2 weeks	200 mg every 3 weeks
Duration of treatment	Until PD or unacceptable toxicity §	Until PD or unacceptable toxicity or investigator decision or max of 24 months ¶
Treatment beyond progression	Accepted per early protocol amendment (see text)	Permitted for clinically stable patients if agreed on by investigator and sponsor
Inclusion criteria	3 different clinical scenarios (arms A, B, C) always after autoSCT and after BV in Arms B and, partly, C	3 different clinical scenarios (cohorts 1, 2, 3) after autoSCT (cohorts 1, 3) and after BV (cohorts 1, 2, and partly 3)
Primary endpoint	ORR by IRC	ORR by IRC and safety
Patients (#)	243	210
Age (median [Range])	34 (26–46) †	35 (18–76)
Age ≥ 65 years (%)	6 §§	8.6
ECOG PS 0–1 (%)	100	100
Previous lines of Tx (median [Range])	4 (3–5) †	4 (1–12)
≥ 3 lines of previous Tx (%)	85	87
Ineligible for autoSCT (%)	0	39
Previous ASCT (%)	100	61
Previous BV (%)	74	83
Median follow-up (months)	33.0	27.6
ORR per IRC (%)	71	72
CR rate per IRC (%)	21	28
Progression free survival (PFS)	15 mo (median)	13.7 mo (median)
Duration of response	18 mo (median) ††	16.5 mo (median) ††
Overall survival	~87–88% at 2 yrs	90.9% at 2 yrs
Discontinuation (patient number [%])	26 (11%) ¶	14 (6.7%) ¶
Toxicity		
TRAEs in ≥ 10% of patients	Rash, fatigue, diarrhea, pruritus, nausea, IRRs	Rash, fatigue, hypothyroidism, pyrexia
TRAEs gr. 3/4 in ≥ 2% of patients	lipase elevations, neutropenia, ALT elevations	neutropenia
TRAEs of special interest	hypothyroidism/thyroiditis (12%), pneumonitis (4%), hyperthyroidism (2%) but none gr. 3/4, rash 9%, hepatitis 5% (4% gr. 3/4)	hypothyroidism (16%), pneumonitis (5%), hyperthyroidism (4%) but none gr. 3/4

Table 1 Comparison of patients' characteristics and overall results for nivolumab, pembrolizumab, phase II trials for rr-cHL.

IRC = independent review committee; IRRs = infusion-related reactions; NR = not reported; TRAEs = treatment-related adverse events. NOTE: Comparisons are not meaningful between nivo/pembro because of highly different eligibility criteria and follow-up times. Even toxicities are difficult to compare due to the very different follow-up times.

§ In arm C only, patients were to discontinue nivolumab after one year in persistent CR and treatment could be resumed if relapse occurred within two years from the last dose; ¶ Patients attaining CR could stop treatment after a minimum of six months and 2 doses after CR; †numbers in parentheses are interquartile range (IQR); §§ 60 years; †† median duration of response for CRs versus PRs: for nivolumab 32 versus 13 months and for pembrolizumab not reached versus 10.9 months; ¶ most frequent causes; Nivolumab: IMRAEs including pneumonitis (2%) and autoimmune hepatitis (1%); Pembrolizumab: pneumonitis (3%), IRRs (1%)

in all patients was 14.7 months (95% CI 11.3-18.5 months). The most common serious drug-related adverse events (AEs) included infusion-related reactions (2%); pneumonitis (1%), pneumonia (1%), pleural effusion (1%) and fever (1%). The most common immune-mediated AEs included hypothyroidism/thyroiditis (12%; all grade 1-2), and rash (9% with 4 classified as grade 3 events) while pneumonitis was only 4% (with no grade 3-4 events).

The KEYNOTE-087 was a single-arm phase II study that examined the efficacy of pembrolizumab in a multi-cohort that included patients with relapse post ASCT (with or without BV exposure) or with chemoresistant disease.[11] Pembrolizumab was administered with a fixed dose of 200 mg IV every 3 weeks and for a fixed duration of up to 2 years. The ORR was 71.9% (95% CI: 65.3-77.9%) and the CR rate was 27.6%. The median PFS was 13.7 months (95% CI: 11.1-17.0).[12] The most common grade 3 treatment-related AEs were neutropenia and diarrhea. The most common immune-mediated AEs were hypothyroidism (15.7%), pneumonitis (4.8%; none grade 3 or greater) and hyperthyroidism (3.8%). Infusion-related reactions occurred in 5.2% of patients. Quality of life and patient reported outcomes were also studied. Patients reported an improvement in QLQ-C30 functional and symptom scores at 12 and 24 weeks into therapy across all cohorts.[13]

The CheckMate and KEYNOTE trials in RR-cHL both demonstrate consistent patient benefit with favourable efficacy and toxicity although it is important to highlight a few key differences in the trials **(Table 1).** KEYNOTE-087 enrolled a cohort of patients that did undergo ASCT while the CheckMate cohorts only included patients post-ASCT failure. The CheckMate studies generally continued treatment until progression (with one cohort allowed discontinuation of treatment if patients remained in CR for at least one year) while the KEYNOTE studies limited treatment to two years. Treatment administration was every two weeks with nivolumab in the CheckMate study while it was every three weeks for pembrolizumab in the KEYNOTE study. Additional studies in malignancy have demonstrated dosing can be extended to once every 4 weeks with nivolumab (480 mg per dose) and every 6 weeks for pembrolizumab (400 mg per dose). Clinicians should consider these dosing interval differences when selecting a specific antibody for an individual patient.

Confirmatory phase III trials were performed for both antibodies. Unfortunately, CheckMate-812 (NCT03138499) which evaluated nivolumab in combination with brentuximab vedotin versus a control of BV monotherapy was terminated prematurely due to insufficient enrolment. In contrast, KEYNOTE-204 evaluated pembrolizumab in patients with RR-cHL who had relapsed post-ASCT or were ineligible for ASCT. Patients received either pembrolizumab (200 mg IV) or BV (1.8 mg/kg IV) every 3 weeks for 35 cycles or until progression or unacceptable toxicity. Efficacy results have been reported and show that pembrolizumab demonstrated an improvement in PFS over BV (HR 0.65, CI 0.48-0.88, p=0.0027; median PFS 13.2 versus 8.3 months). The overall survival analysis is event driven and results are forthcoming. The overall response rate (ORR) for pembrolizumab was 65.6% (CR 25%) and was 54.2% (CR 24%) for BV but did not reach the pre-defined statistical threshold for superiority. Quality of life was also prospectively evaluated and reported.[14] EORTC QLQ-C30 and EuroQoL EQ5D scales were utilized and demonstrated improved quality of life scores with pembrolizumab compared to worsening scores with BV.

The results from the KEYNOTE-204 study portend a potential new standard of care for patients with RR-cHL that have relapsed post-ASCT or are ineligible for transplantation. Pembrolizumab has shown both favourable efficacy and quality of life when compared to BV in this patient population and supports the use of anti-PD1 antibody therapy as the preferred choice. The potential for the combination of BV and anti-PD1 antibodies is of significant clinical interest which remains, to date, unanswered due to enrolment challenges associated with CheckMate-812. Accepting that patients in Canada are increasingly likely to receive BV earlier in the disease course (either with primary treatment based on the results of the ECHELON-1 study or as maintenance treatment post-ASCT based on the results of the AETHERA study),[15,16] the use of checkpoint antibodies in RR-cHL is a well-established gold standard. Clinicians now have a positive randomized controlled trial and two large phase II trials to guide practice in Canada.

Evolving Role of Immunotherapy in cHL: Curative Disease

The clinical trials that will shed light on the role of both nivolumab and pembrolizumab in the curative setting are currently ongoing. Phase I and II studies have evaluated both antibodies in combination in the frontline and second-line curative setting. Published studies using these therapeutic agents have largely focused on younger patients and patients undergoing salvage therapy with a goal of ASCT.

Salvage therapy studies with nivolumab have been published evaluating combinations with BV and ICE (ifosfamide, carboplatin and etoposide given sequentially after nivolumab monotherapy and in combination with nivolumab) chemotherapy.[17,18] These trials highlight favourable ORR (85-95%) and CR rates (65-90%) and appear to compare favourably with traditional chemotherapy ORR and CR rates.[19] Clinicians should be aware that historical results with regimens such as the

GDP (gemcitabine, dexamethasone, cisplatin) phase II experience in Canada used older outcome measures and CT (not FDG PET) imaging.[20] Similar studies are being performed with pembrolizumab with a published single-arm study describing the combination with GVD (gemcitabine, vinorelbine and liposomal doxorubicin). An impressive CR rate of 92% was noted for patients in the two-cycle cohort.[21] Interpretation of these studies is challenging given the lack of a randomized control arm. The Canadian Cancer Trials Group (CCTG) is currently recruiting for a randomized phase II trial of pembrolizumab and brentuximab vedotin versus GDP, followed by high dose chemotherapy and ASCT for RR-cHL.

In the frontline setting, combinations of anti-PD1 antibodies have been evaluated in combination with AVD (doxorubicin, vinblastine, dacarbazine). Nivolumab has been evaluated in the localized early unfavourable setting by the German Hodgkin Study Group (GHSG) and in an industry-sponsored study in advanced disease.[22,23] Both studies demonstrated the feasibility of nivolumab-AVD in these settings. Currently, a study from the North American Intergroup is currently evaluating nivolumab-AVD versus BV-AVD in a large phase III trial (NCT03907488). Pembrolizumab has also been explored in a single arm feasibility phase II trial with 3 cycles of pembrolizumab followed by sequential AVD in early unfavourable or advanced stage cHL.[24] The combination of pembrolizumab and AVD in untreated cHL is currently being studied in a larger single-arm phase II trial (NCT03331341). It is important to note the cautionary experience of nivolumab in combination with BV in the primary treatment setting for patients that were ineligible for traditional chemotherapy as this study did not meet its primary efficacy endpoint.[25]

Conclusions

Immunotherapy with nivolumab and pembrolizumab has been a major advance in the treatment of RR-cHL based on well conducted clinical trials. Current studies are evaluating these agents in combination with standard therapy for primary treatment and in the second-line curative setting. Frontline trials will require long-term follow-up and consideration of efficacy and late effects to better integrate these agents into this setting.

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