INTERVIEW

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Track 3 Activity and ongoing investigations of immune checkpoint inhibitors in HL

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DR LOVE: Would you discuss the efficacy of immune checkpoint inhibitors and ongoing investigation of these agents for patients with Hodgkin lymphoma (HL)?

DR YOUNES: Immune checkpoint inhibitors for HL are generating a lot of excitement because as single agents the anti-PD-1 antibodies nivolumab and pembrolizumab elicit response rates exceeding 60% in the relapsed/refractory setting (Younes 2016; [1.1]). These are patients for whom autologous transplant and brentuximab vedotin have failed. Because these agents are highly active in the relapsed/refractory setting, they are now being investigated as first- and second-line therapy.

1.1

Efficacy and Safety of Nivolumab for Relapsed/Refractory Classical Hodgkin Lymphoma

Efficacy	Phase I CA209-039 study[1] (n = 23)	Phase II CheckMate 205 study[2] (n = 80)
Objective response rate	87%	66%
Complete response	22%	9%
Partial response	65%	58%
Median PFS	Not reached	10 mo
Overall survival rate	83% (1.5 y)	99% (6 mo)
Select adverse events (any grade)	n = 23	n = 80
Fatigue	NR	25%
Skin related	22%	41%
Gastrointestinal	17%	26%
Hepatic	9%	10%
Pulmonary	4%	1%
Endocrine disorders	17%	18%
Hypersensitivity/infusion reactions	9%	21%

PFS = progression-free survival; NR = not reported

[1] Ansell S et al. *Proc ASH* 2015;**Abstract 583**; [2] Younes A et al. *Proc ASCO* 2016;**Abstract 7535**.

Ongoing trials are combining anti-PD-1 antibodies with brentuximab vedotin in the first-line (NCT02758717) and second-line (NCT02572167, NCT01896999) settings. Clinical trials have also been designed to evaluate immune checkpoint inhibitors after treatment with doxorubicin/bleomycin/vinblastine/dacarbazine (ABVD) and concurrently with ABVD or AVD (doxorubicin/vinblastine/dacarbazine).

DR LOVE: What do we know about the biology of HL and why patients with this disease respond so well to immune checkpoint inhibitors?

DR YOUNES: We're learning from the solid tumor experience in terms of what predicts response to anti-PD-1 antibodies. The higher the expression of PD-L1 on tumor cells, the more robust the response to these agents. Also, the higher the number of T cells in the tumor microenvironment, especially those that express PD-1, the better the response to anti-PD-1 antibodies.

Both these phenomena are observed in HL. Reed-Sternberg cells overexpress PD-L1 and PD-L2 because of amplification of chromosome 9p24.1. This amplification also involves the JAK2 locus, which increases both activity of the JAK/STAT pathway and PD-L1 expression. Furthermore, the HL tumor environment harbors a large number of T cells. These T cells can be reprogrammed with checkpoint inhibitors to mediate killing of the malignant cells.

Editor's note: Subsequent to this interview, on May 17, 2016, the FDA granted accelerated approval to nivolumab for the treatment of classical HL that has relapsed or progressed after autologous hematopoietic stem cell transplant and post-transplant brentuximab vedotin therapy.

Tracks 4-5, 7, 11

DR LOVE: The Phase III ECHELON-1 trial that you chair is evaluating ABVD versus brentuximab vedotin/AVD as front-line therapy for advanced classical HL (NCT01712490). What is the current status of that trial?

DR YOUNES: This trial has completed accrual with more than 1,000 patients enrolled. In about 2 years we should have interim data. The Phase I trial of brentuximab vedotin in combination with AVD for newly diagnosed, advanced HL demonstrated a progression-free survival (PFS) rate of 92% after a 3-year follow-up, which is remarkable (Connors 2014). If the results of the randomized ECHELON-1 trial are positive, it will be practice changing for patients with HL.

DR LOVE: What is known about predictors of response and durability of response to brentuximab vedotin in HL?

DR YOUNES: Unfortunately we have no prognostic model to predict who will achieve a complete response (CR) to treatment with brentuximab vedotin. Most patients experience their best response after 4 to 5 cycles of therapy, so we assess response at that time. Patients who achieve a partial remission can maintain that response with continued dosing but are unlikely to achieve a CR. However, patients who achieve a CR could potentially be cured. Because the response is durable for many of the patients who achieve a CR, we don't rush to consider a hematopoietic stem cell transplant. We simply observe these patients, keeping in mind that they may require transplant in the future.

DR LOVE: What are the key tolerability issues with brentuximab vedotin?

DR YOUNES: This agent is fairly well tolerated. Neuropathy is one of the most common side effects, but it is usually only Grade 2 in severity. Once patients start experiencing severe neuropathy the dose can be reduced or interrupted to prevent any increase in severity.

DR LOVE: The Phase III AETHERA trial evaluating brentuximab vedotin as consolidation therapy for patients at high risk of relapse after autologous stem cell transplant (ASCT) produced promising results (Moskowitz 2015a). What are your thoughts about using brentuximab vedotin as post-transplant maintenance?

DR YOUNES: The AETHERA trial stipulated specific indications for the use of brentuximab vedotin. Eligible patients were those at high risk of relapse or disease progression after ASCT. These patients had extranodal disease before ASCT, or they had primary refractory disease and did not achieve a CR after transplant. I would consider maintenance brentuximab vedotin for such patients in my practice. However, some patients want a break from therapy and prefer to hold off until their disease progresses.

DR LOVE: At ASH 2015 a study investigating another antibody-drug conjugate, denintuzumab mafodotin, for relapsed/refractory B-lineage non-Hodgkin lymphoma (NHL) reported promising results (Moskowitz 2015b). What was observed in that study?

DR YOUNES: Denintuzumab mafodotin (SGN-CD19A) is an anti-CD19 monoclonal antibody conjugated to monomethyl auristatin F, a microtubule-disrupting agent. This antibody-drug conjugate was found to be active and elicited a 30% to 40% response rate

for patients with relapsed/refractory NHL. An unusual toxicity of the cornea occurs in some patients, typically after the second cycle. This side effect is generally reversible.

Track 10

DR LOVE: At ASH 2015 a study was reported evaluating ibrutinib as part of a novel regimen called DA-TEDDI-R (dose-adjusted temozolomide, etoposide, doxorubicin, dexamethasone, ibrutinib and rituximab) for patients with untreated and relapsed/refractory disease (Dunleavy 2015; [1.2]). What are your thoughts about that study?

DR YOUNES: Primary CNS diffuse large B-cell lymphoma (DLBCL) has a predominantly activated B-cell phenotype, and ibrutinib is active in patients with relapsed/refractory DLBCL of this phenotype. This provided a rationale for investigating ibrutinib for primary CNS lymphoma.

This important trial first evaluated whether ibrutinib could penetrate the CNS. It also assessed single-agent activity and whether ibrutinib could be combined with chemotherapy. Surprisingly, most of the patients with relapsed/refractory primary CNS lymphoma responded to single-agent ibrutinib. This is promising for patients with this disease. ■

1.2

Phase I Study of Dose-Adjusted TEDDI-R with Ibrutinib for Patients with Untreated or Relapsed/Refractory (R/R) Primary CNS Lymphoma

- N = 14 patients with untreated or R/R primary CNS lymphoma.
- Ibrutinib and its active metabolite achieved meaningful cerebrospinal fluid concentrations of >IC_{50} for 2 to 10 hours.
- Of 11 evaluable patients, 10 achieved partial response to ibrutinib alone before cycle 1.
- Of 14 patients, 9 achieved complete response by month 3:
  - 3 of 6 patients with R/R disease maintained the complete response for >8 months and 1 for >15 months.
  - 1 of 3 patients with previously untreated disease experienced relapse at 6 months.

Dunleavy K et al. *Proc ASH* 2015;**Abstract 472**.

SELECT PUBLICATIONS

Ansell S et al. **Nivolumab in patients (pts) with relapsed or refractory classical Hodgkin lymphoma (R/R cHL): Clinical outcomes from extended follow-up of a phase 1 study (CA209-039).** *Proc ASH* 2015;**Abstract 583**.

Connors JM et al. **Brentuximab vedotin combined with ABVD or AVD for patients with newly diagnosed advanced stage Hodgkin lymphoma: Long-term outcomes.** *Proc ASH* 2014;**Abstract 292**.

Dunleavy K et al. **Phase I study of dose-adjusted-TEDDI-R with ibrutinib in untreated and relapsed/refractory primary CNS lymphoma.** *Proc ASH* 2015;**Abstract 472**.

Moskowitz CH et al. **Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): A randomised, double-blind, placebo-controlled, phase 3 trial.** *Lancet* 2015a;385(9980):1853-62.

Moskowitz CH et al. **A phase 1 study of denintuzumab mafodotin (SGN-CD19A) in relapsed/refractory B-lineage non-Hodgkin lymphoma.** *Proc ASH* 2015b;**Abstract 182**.

Younes A et al. **CheckMate 205: Nivolumab (nivo) in classical Hodgkin lymphoma (cHL) after autologous stem cell transplant (ASCT) and brentuximab vedotin (BV) — A phase 2 study.** *Proc ASCO* 2016;**Abstract 7535**.