Abstract 7535: Checkmate 205: Nivolumab (nivo) in classical Hodgkin lymphoma (cHL) after autologous stem cell transplant (ASCT) and brentuximab vedotin (BV)—A phase 2 study

Amplification of 9p24.1 resulting in overexpression of PD-1 ligands is a characteristic of Classical Hodgkin Lymphoma (cHL); therefore, PD-1 blockade presents as a potential therapeutic strategy. Nivolumab is an anti-PD-1 IgG4 monoclonal antibody which has achieved promising results in R/R cHL patients in a phase Ib study (NCT02181738; Ansell et al 2015).

The data presented in this abstract is from the phase II Checkmate 2015 study (NCT02181738), which in its second cohort (B) aimed to assess the efficacy and safety of nivolumab in cHL patients who had been administered brentuximab vedotin after failed Autologous Stem-Cell Transplant (ASCT). Patients with cHL who relapse after ASCT or progress after brentuximab vedotin have a very poor outcomes.

- 80 treated cHL pts; median age = 37 years; median number of prior regimens = 4 (range, 3–15)
- 90% of pts had drug-related AEs: 25% Grade 3–4, 1% G5 (multi-organ failure)
- The most frequent drug-related AEs were fatigue (25%), infusion reaction (20%), and rash (16%)
- The most common SAEs were pyrexia, tumor progression, arrhythmia, infusion reaction, septic meningitis, and pneumonia (<4% each)
- Select immune-related AEs, all Grade 1–2, occurred in 26%
- At database lock (October 2015), median follow-up = 8.9 months (range, 1.9–11.7)
- 64% of pts remain on therapy; main reason for discontinuation was progressive disease (16%)
- Independent Radiologic Review Committee (IRRC) ORR = 66% (95% CI, 54.8–76.4); CR rate = 8.8% (95% CI, 3.6–17.2); PR rate = 57.5% (95% CI, 45.9–68.5)
- Investigator (Inv) ORR = 73% (95% CI, 61.4–81.9); CR rate = 27.5% (95% CI, 18.1–38.6); PR rate = 45.0% (95% CI, 33.8–56.5)
62% (33/53) of IRRC responders remain in response at database lock

6 pts chose to discontinue nivolumab and undergo SCT, all of these pts were alive at data cut-off

IRRC 6-month PFS = 77%; OS = 99%

In 43 pts who had no prior brentuximab vedotin response, nivolumab treatment resulted in an IRRC ORR of 72% (31/43)

The conclusion of this abstract is that nivolumab achieved a high responses and was well tolerated in patients with cHL post-ASCT and brentuximab vedotin, including patients with no prior responses to brentuximab vedotin. The PFS and OS are encouraging in this heavily pretreated population.

Abstract 7555: Pembrolizumab for relapsed/refractory classical Hodgkin lymphoma (R/R cHL): phase 2 KEYNOTE-087 study

Pembrolizumab is another humanized monoclonal IgG4 antibody which targets PD-1 abrogating its binding to PD-L1 and PD-L2. Pembrolizumab has been shown to have efficient antitumor activity (ORR = 65%) in the phase Ib KEYNOTE-013 study of heavily pretreated cHL patients (NCT01953692). To confirm the clinical activity of pembrolizumab, the phase II KEYNOTE-087 (NCT02453594) multicohort study was initiated. The study contained 3 cohorts:

- **Cohort 1:** R/R cHL after ASCT and subsequent BV therapy
- **Cohort 2:** ineligible for ASCT due to chemo-resistance (no response to salvage chemotherapy) and BV therapy failure
- **Cohort 3:** R/R cHL after ASCT but not treated with BV after ASCT

Pembrolizumab was administered at a 200mg IV Q 3w fixed dose. As of 1st February 2016 (data cut-off), 60 patients from cohorts 1 and 2 were evaluable:

- Median age: cohort 1 = 36 years (range, 19–64); cohort 2 = 33 years (range, 20–71)
- Received 4 or more previous therapies = 67%; failed previous brentuximab vedotin = 100%
- Best response cohort 1 (n=30): ORR = 70% (95% CI, 51–85); CR = 20% (6 pts); PR = 50% (15 pts); SD = 20% (6 pts)
- Best response cohort 2 (n=30): ORR = 80% (95% CI, 61–92); CR = 27% (8 pts); PR = 53% (16 pts); SD = 13% (4 pts)
- Median treatment cycles administered = 6
- The most frequent treatment-related AEs in the combined cohorts are pyrexia (13%), diarrhea (8%), as well as fatigue, back pain, platelet count decrease, dry skin, and cough (7% each)

The conclusion of this abstract was that pembrolizumab demonstrated early responses in heavily pretreated cHL patients; in particular an unprecedented high ORR (80%) in patients who were not eligible for ASCT and who failed brentuximab vedotin.
Poster discussion

Nancy Bartlett began by outlining the different phase II treatment regimens:

- **Nivolumab 3mg/kg IV Q 2 weeks**
  - Same dose/schedule as dose expansion study
- **Pembrolizumab 200mg flat dose IV Q 3 weeks**
  - Dose expansion/schedule 10mg/kg Q 2 weeks
  - Flat exposure-response relationship for efficacy and safety in the 2mg/kg – 10mg/kg range across clinical studies (200mg "in range" if you weigh <100kg)
  - Continue until PD or unacceptable toxicity
  - Patients allowed to continue treatment past PD if clinical benefit

Time to response and durability with nivolumab was then discussed.

- Median time to response = 2.1 months (range, 1.6–5.7)
- Median DoR = 7.8 months
- Median PFS = 10 months

The presentation then focused on whether standard PET criteria are adequate for response assessment. Possible false positive PETs occur due to PD-1 blockade activating T-cells at tumor site, this may explain lower CR rates and differences in investigator determined CR vs IRRC (28% vs. 9%).

It was then discussed if nivolumab could act as a bridge to allo-SCT. However, a "warning and precaution" has been issued by the FDA for complications of allo-SCT post-nivolumab. In a phase I/dose expansion study using nivolumab as a bridge to allo-SCT, 4/5 patients died of transplant complications (Ansell ASH, 2015, Blood, 126:583). It is of utmost important to follow patients closely for hyperacute and severe acute GVHD, VOD, and other immune-mediated reactions. In a phase II Nivolumab study, 6 patients went on to allo-SCT (all alive at data cut-off).

A possible treatment option in the post-transplant relapsed setting is immunotherapy combinations, for example:

- **Nivolumab plus brentuximab vedotin (plus ipilimumab)** (E4412, NCT01896999)
  - Theoretical concern for nivolumab/brentuximab vedotin antagonism
  - Activated T-cells express CD30
- **Nivolumab plus ipilimumab/lirilumab (anti-KIR monoclonal antibody)** (NCT01592370)
- **Pembrolizumab plus antiCD30/CD16A bispecific antibody (AFM13)** (NCT02665650)
• Pembrolizumab plus lenalidomide (in development)

• Anti-PD1 plus antiCD137 or IL-15 agonist?

Nancy Bartlett concluded the talk by highlighting that pembrolizumab and nivolumab as single-agents achieve high response rates in patients with cHL who are multiply R/R; with ORRs between 66–83% and CR rates between 9–28%. However, longer follow-up is required in order to determine the durability of responses. These agents are well tolerated, but Bartlett cautioned that close attention is needed to detect any immune-mediated adverse reactions early. Lastly, these agents could be used in exciting potential combinations to treat post-transplant failures and as well for earlier lines of therapy.

References

