Ibrutinib and nivolumab combination in R/R NHL and CLL/SLL patients

Sylvia Agathou  |  Feb 8, 2019

On 1 February 2019, Anas Younes from Memorial Sloan Kettering Cancer Center, New York, NY, USA and colleagues, published in The Lancet Haematology a phase 1-2a study investigating the safety of ibrutinib in combination with nivolumab in relapsed or refractory (R/R) non-Hodgkin lymphoma (NHL) or chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) patients.

In this two-part, multicenter, open label, phase 1-2a study the appropriate dose (phase 1), as well as the safety and activity (phase 2a) of ibrutinib in combination with nivolumab were assessed in the following patient populations: R/R CLL/SLL with del17p or del11q (high-risk), follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), or Richter's transformation (RT). The primary aim of the phase 1 part of the study was to establish the appropriate treatment dose. The primary endpoint of the phase 2a part was to measure the preliminary efficacy of ibrutinib and nivolumab in the aforementioned patient populations, by assessing the proportion of patients achieving an overall response.

Study design & baseline characteristics

- N = 141 R/R NHL or CLL/SLL patients included in the analysis:
  - CLL: n = 30 (del17p, n = 19; del11q, n = 17)
  - SLL: n = 6
  - DLBCL: n = 45 (including nine patients with transformed DLBCL)
  - FL: n = 40
• RT: n = 20

• Median patient age (range): 65 (54–71) years

• Median number of previous lines (range): 3 (2–3)

Phase 1 (n = 14)
• N = 14 R/R patients with FL, DLBCL or CLL/SLL

• Dosing (14-day cycles):
  • Dose escalation of ibrutinib not nivolumab
  • Ibrutinib: 420 mg (n = 7; CLL/SLL, FL, DLBCL) or 560 mg (n = 7; FL, DLBCL) orally every day
  • Nivolumab: 3 mg/kg intravenous infusion (1 hour) every two weeks
  • Combination treatment was administered until disease progression (PD) or unacceptable toxicity
  • Ibrutinib dose reduction to 280 mg was allowed
  • Nivolumab dose reductions were not permitted

Phase 2a (n = 127)
• N = 127 R/R patients with FL, DLBCL or CLL/SLL

• Dosing:
  • Ibrutinib: 420 mg (n = 35; CLL/SLL) or 560 mg (n = 92; FL, DLBCL, FT) orally every day
  • Nivolumab: 3 mg/kg intravenous infusion (1 hour) every two weeks

Key findings

Phase 1 (n = 14)
• At the 420 mg ibrutinib dose:
- One Grade 3 dose-limiting toxicity occurred (hyperbilirubinemia in a DLBCL patient), which resolved after five days

- No dose-limiting toxicities occurred at the 560 mg dose

- The recommended phase 2 doses were 420 mg ibrutinib plus 3 mg/kg nivolumab for CLL/SLL patients 560 mg ibrutinib plus 3 mg/kg nivolumab for FL, DLBCL or RT patients

**Phase 2 (n = 127)**
- Overall response rates:
  - CLL/SLL: 61% (n = 22/36)
  - FL: 33% (n = 13/40)
  - DLBCL: 36% (n = 16/45)
  - RT: 65% (n = 13/20)

- Median duration of stable disease or better (range):
  - CLL/SLL: 19.7 (17.0–20.5) months
  - FL: 15.9 (14.1–20.0) months
  - DLBCL: 18.4 (15.6–19.4) months
  - RT: 13.0 (12.1–13.8) months

- Median duration of response (range):
  - CLL/SLL: 19.2 (9.4–19.4) months
  - FL: 10.2 (6.7–14.2) months
  - DLBCL: not estimable (NE)
  - RT: 6.9 (1.4–NE) months

- Median progression-free survival (PFS):
  - CLL/SLL: NE due to small sample size
• FL: 9.1 months (95% CI, 3.1−14.0) [median follow-up: 19.6 months]
• DLBCL: 2.6 months (95% CI, 1.9−7.6) [median follow-up: 18.4 months]
• RT: 5.0 months (95% CI, 2.4−NE) [median follow-up: 8.7 months]
• Median overall survival (OS):
  • CLL/SLL: not reached (NR) [median follow-up: 21.5 months]
  • FL: NR [median follow-up: 19.2 months]
  • DLBCL: 13.5 months (95% CI, 6.5−NE) [median follow-up: 19.6 months]
  • RT: 10.3 months (95% CI, 4.8−NE) [median follow-up: 8.9 months]

**Phase 1 & 2a**
• At data cut-off:
  • Median treatment duration with ibrutinib was:
    • CLL/SLL group: 14.4 (4.5−21.7) months
    • FL: 5.0 (2.3−14.8) months
    • DLBCL: 3.2 (1.4−13.0) months
    • RT: 3.6 (1.3−8.0) months
  • Treatment discontinuation occurred in 75% (n = 106/141) of all patients:
    • CLL/SLL group: n = 23/36 (64%)
    • FL: n = 33/40 (83%)
    • DLBCL: n = 36/45 (80%)
    • RT: n = 14/20 (70%)
  • Main reasons for treatment discontinuation were:
    • PD or relapse: 39%
    • Adverse events (AEs): 28%
- Of which, 20% were treatment related
  - Physicians decision: 2%
  - Other: 1%
- Treatment discontinuation due to AEs:
  - CLL/SLL group: n = 11/36 (31%)
  - FL: n = 11/40 (28%)
  - DLBCL: n = 8/45 (18%)
  - RT: n = 9/20 (45%)
- Three deaths occurred during the study:
  - n = 2 (DLBCL patients, one respiratory arrest and one gastric bleeding)
  - n = 1 (SLL patient, unknown cause)
- In both parts of the study, the most common any grade AEs were:
  - Dairrhea: 33%
  - Neutropenia: 31%
  - Fatigue: 26%
- Grade 3–5 AEs were reported in 82% of patients
- Grade 3–4 treatment-emergent AEs (TEAEs) occurred in 58% of patients
- No Grade 5 TEAEs were reported
- Most common haematological Grade 3–4 AEs were:
  - Neutropenia: 28%
  - Anemia: 23%
- Serious AEs occurred in seventy-seven patients, with the most common being:
  - Anemia
- Pneumonia
- Febrile neutropenia
- Atrial fibrillation
- Bacterial pneumonia
- Cardiac failure
- Dyspnoea
- Gastroenteritis
- Hematuria
- Neutropenia
- *Pneumocystis jirovecii* pneumonia

- Treatment-related serious AEs were reported in 21% of patients, with the most common being:
  - Febrile neutropenia: 2%
  - Anemia: 2%
  - Bacterial pneumonia: 1%
  - Neutropenia: 1%
  - Cardiac failure: 1%
  - Pneumonitis: 1%

- At data cut-off, n = 51 deaths occurred:
  - PD: n = 29
  - AEs: n = 16 (all unrelated to the drug)
  - Unknown: n = 1
  - Other causes: n = 5
Conclusions

- Ibrutinib and nivolumab combination had manageable toxicity profiles in R/R NHL or CLL/SLL patients

- The clinical outcomes of ibrutinib and nivolumab combination were similar to the ones previously reported in the field with ibrutinib monotherapy in CLL/SLL, FL or DLBCL patients

- The best overall response to ibrutinib and nivolumab combination was observed in the RT patient cohort with a 65% overall response. A very promising result that needs further validation, especially in RT patients who were unresponsive to previous ibrutinib monotherapy

References: