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Alisertib monotherapy for PTCL patients: Results from a phase III trial

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On 1 February 2019, Owen O'Connor from Columbia University Medical Centre, New York, NY, USA and colleagues, published in the *Journal of Clinical Oncology* a phase III study (LUMIERE) investigating the efficacy of alisertib in relapsed or refractory (R/R) peripheral T-cell lymphoma (PTCL) patients.

Alisertib is an investigational Aurora A kinase inhibitor. Aurora A kinase is involved in cell mitosis and accumulating evidence indicates its pathological upregulation in PTCL. From phase I-II studies the recommended dose and treatment pattern of alisertib monotherapy have been established, together with its promising activity in various lymphomas, including R/R B-cell and T-cell lymphomas. The aim of this randomized, multicenter, two-arm, open-label, phase III trial (NCT01482962) was to investigate the efficacy of alisertib monotherapy *versus* investigator's choice treatment in R/R PTCL patients. The primary endpoints of this study were overall response rate (ORR), and progression-free survival (PFS). Secondary endpoints included, overall survival (OS), safety, complete response (CR) rate, time-to-progression (TTP), time-to-partial response (TTR), and duration of response (DoR).

Study design & baseline characteristics

- N = 271 R/R PTCL patients after ≥ 1 prior system therapy, aged ≥ 18 were enrolled
- PTCL subtypes included:
  - PTCL-not otherwise specified (NOS)
  - Anaplastic large-cell lymphoma
  - Angioimmunoblastic T-cell lymphoma
  - Enteropathy associated T-cell lymphoma
  - Hepatosplenic T-cell lymphoma
  - Subcutaneous panniculitis-like T-cell lymphoma
  - Transformed mycosis fungoides
  - Extranodal natural killer/T-cell lymphoma nasal type
- Patients were stratified according to:
  - Extranodal disease
  - International Prognostic Index (IPI) score:
    - low/intermediate *versus* intermediate/high
  - Region:
    - North America and European Union *versus* the rest of the world

- Patients were randomized in two arms:
  - Alisertib (Arm A; n = 138): orally, 50 mg twice daily on Days 1–7 (21-day cycles)
  - Investigator's choice monotherapy (Arm B; n = 133), intravenously either of the following:
    - Gemcitabine (n = 30): 1000 mg/m^2 over 30 min, on Days 1, 8, and 15 (28-day cycles)
    - Pralatrexate (n = 80): 30 mg/m^2 over 3–5 min once weekly for six weeks (7-week cycles)
      - These patients also received vitamin B_{12} (1 mg every 8–10 weeks) and oral folic acid (1.0–25 mg daily)
    - Romidepsin (n = 23; USA only): 14 mg/m^2 over 4 h on Days 1, 8, and 15 (28-day cycles)
  - Alisertib dose reductions with minimum 10 mg decrements per cycle and a maximum of two dose reductions were allowed in case of toxicity
  - Baseline characteristics were well-balanced between the arms
  - Median number or prior lines: 2
  - Data cut-off: 30 June 2015

Key findings

- In the alisertib arm:
  - Median number of treatment cycles (range) = 4 (0–50) cycles
  - Mean treatment duration (range) = 20.8 (1–148) weeks
  - Mean relative dose intensity = 92.9%
- In the comparator arm:
  - Median number of treatment cycles (range) = 2 (0–17) cycles
  - Mean treatment duration (range) = 16.6 (1–115) weeks
  - Mean relative dose intensity = 66.1%
- ORR:
  - Alisertib: 33% (n = 34/102 patients)
  - Comparator arm: 45% (n = 41/92 patients)
  - Comparison: odds ratio = 0.60 (95% CI, 0.33–1.08)
  - Gemcitabine: 35% (n = 8/23)
  - Pralatrexate: 43% (n = 22/51)
  - Romidepsin: 61% (n = 11/18)
- CR rate:
  - Alisertib: 18%
  - Comparator arm: 27%

- Although the number of patients in the alisertib and comparator arms were balanced across regions, there was a greater difference in ORR between treatment arms in North America (29% alisertib *versus* 59% comparator) than in other regions (Western Europe: 33% *versus* 36%; rest of world: 36% *versus* 41%, respectively)
- Progressive disease (PD) was the most common reason for a PFS event in both arms
- Median PFS:
    - Alisertib: 115 days
    - Comparators: 104 days
        - Gemcitabine: 57 days
        - Pralatrexate: 101 days
        - Romidepsin: 242 days
    - Comparison: HR = 0.87, (95% CI, 0.644–1.162)
- Median follow-up duration for OS:
    - Alisertib: 519 days
    - Comparators: 586 days
- Median OS:
    - Alisertib: 415 days
    - Comparators: 367 days
    - Comparison: HR = 0.98, (95% CI, 0.707–1.369)
- Twelve-month survival:
    - Alisertib: 53.7%
    - Comparators: 51.5%
- Twenty-four-month survival:
    - Alisertib: 35%
    - Comparators: 35%
- Median DoR:
    - Alisertib: 225 days
    - Comparators: 172 days
        - Gemcitabine: 134 days
        - Pralatrexate: 162 days
        - Romidepsin: 473 days
    - Median TTR:
        - Alisertib: 62 days
        - Comparators: 64 days

        - Gemcitabine: 90 days
        - Pralatrexate: 67 days
        - Romidepsin: 61 days
    - Median TTP:
        - Alisertib: 162 days
        - Comparators: 116 days
        - Comparison: HR = 0.95, (95% CI, 0.679–1.329)
    - At 24 months, patients who had not experienced PD:
        - Alisertib: 12.8%
        - Comparators: 14.3%
    - Median time to subsequent antineoplactic therapy:
        - Alisertib: 336 days
        - Comparators: 233 days
            - Gemcitabine: 144 days
            - Pralatrexate: 233 days
            - Romidepsin: not estimable
        - Comparison: HR = 0.98, (95% CI, 0.692–1.385)

Safety

- Most common any cause Grade ≥ 3 adverse events (AEs; alisertib *versus* comparators):
    - Neutropenia: 43% *versus* 25%
    - Thrombocytopenia: 29% *versus* 27%
    - Anemia: 33% *versus* 11%
- Most common treatment-emergent AEs (TEAEs; alisertib *versus* comparators):
    - Neutropenia: 45% *versus* 30%
    - Thrombocytopenia: 34% *versus* 38%
    - Anemia: 43% *versus* 24%
    - Diarrhea: 32% *versus* 19%
    - Stomatitis: 31% *versus* 42%
- Serious AEs occurred in:
    - Alisertib: 55%
    - Comparators: 54%
- Overall, 26 study deaths occurred (alisertib, 11 [8%]; comparators, 15 [12%])

- Of these, n = 3 in the alisertib and n = 1 in the comparator arm were drug-related

Conclusions

- Alisertib did not lead to superior outcomes (PFS, ORR) *versus* comparator drugs (gemcitabine, pralatrexate or romidepsin) when administered to R/R PTCL patients

References

1. O'Connor O.A. *et al.* Randomized Phase III Study of Alisertib or Investigator's Choice (Selected Single Agent) in Patients With Relapsed or Refractory Peripheral T-Cell Lymphoma. *J Clin Oncol.* 2019 Feb 1:JCO1800899. DOI: 10.1200/JCO.18.00899 [Epub ahead of print].