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General AML, FLT3, IDH1/2

Highlights from ASH 2016: Abstract 102 – Safety and Efficacy of Venetoclax plus LDAC in Treatment-Naïve Patients Aged ≥65 Years with AML

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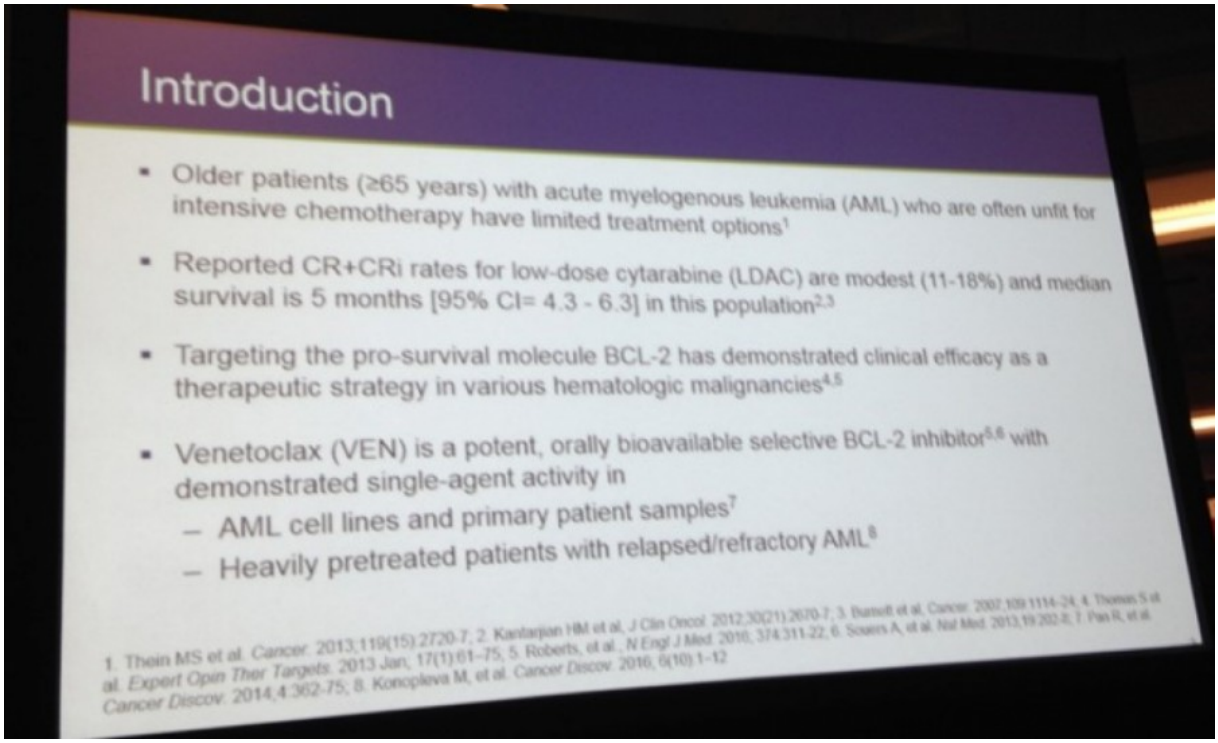
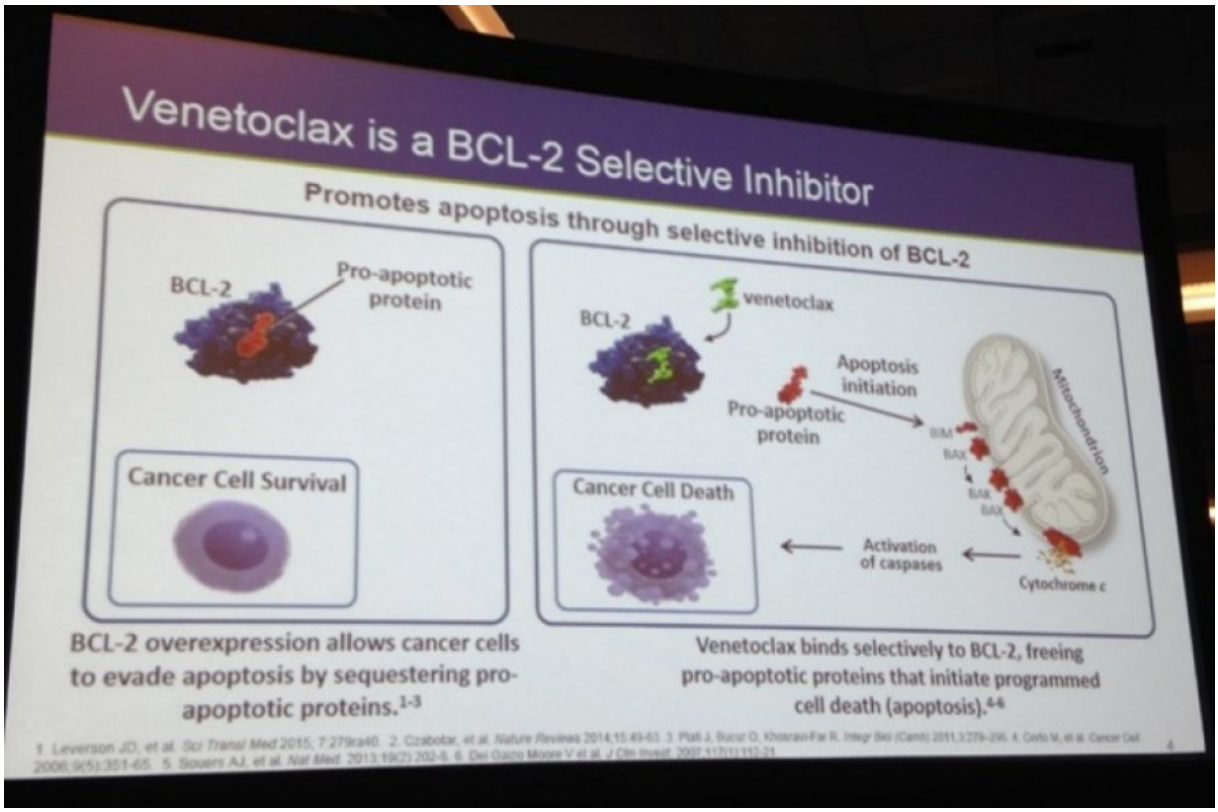
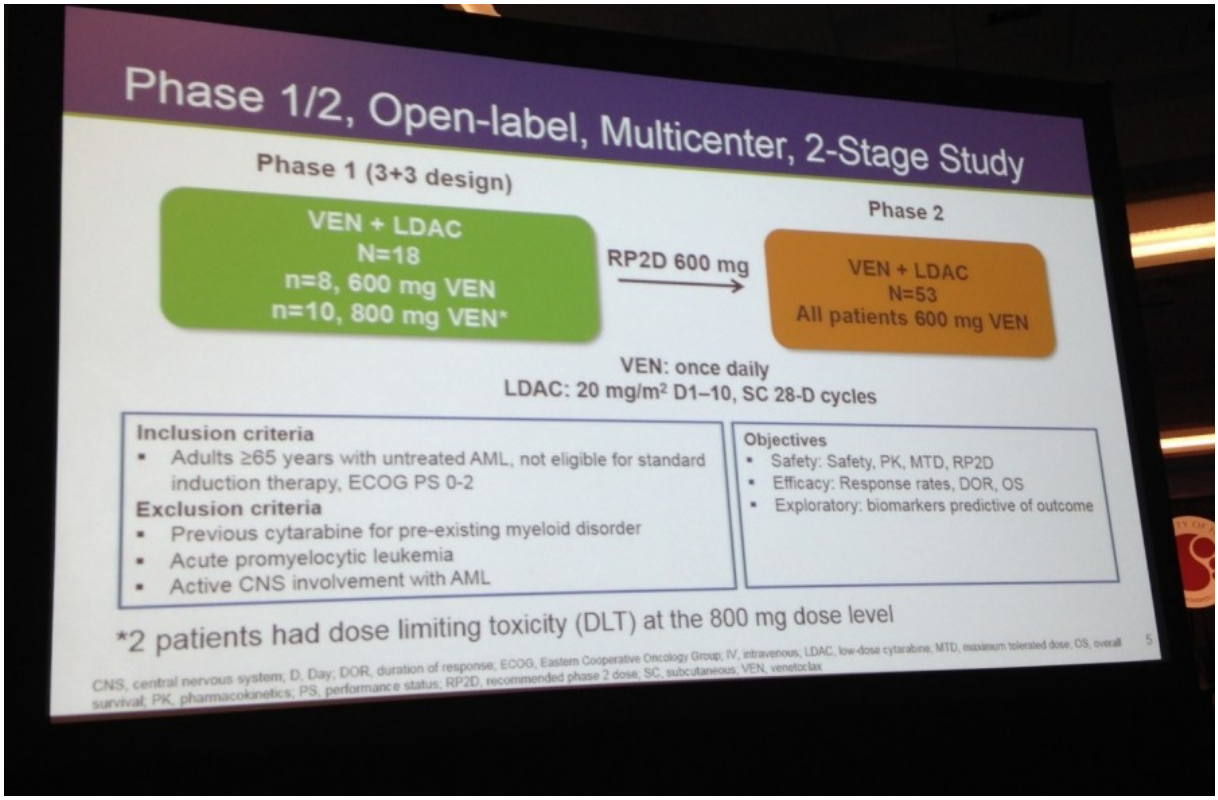
On Saturday 3rd December, at the 58th Annual Meeting & Exposition of the American Society of Hematology (ASH) in San Diego, CA, there was an engrossing session focusing on "Acute Myeloid Leukemia: Novel Therapy, excluding Transplantation."

Andrew Wei, MD, The Australian Centre for Blood Diseases, Alfred Hospital and Monash University, Melbourne, Australia, presented data from a study on the efficacy and safety of venetoclax combined with Low-Dose Cytarabine (LDAC). Since treatment options for older patients with Acute Myeloid Leukemia (AML) who are unfit for intensive chemotherapy are limited, this study is of importance in improving outcomes in older AML patients.



Venetoclax (ABT-199) is a selective BCL-2 inhibitor that has demonstrated a synergistic effect with cytarabine in AML cell lines and primary samples (Lin TL, *et al.).* Thus, AML patients with a median age of 75 were enrolled in this study.

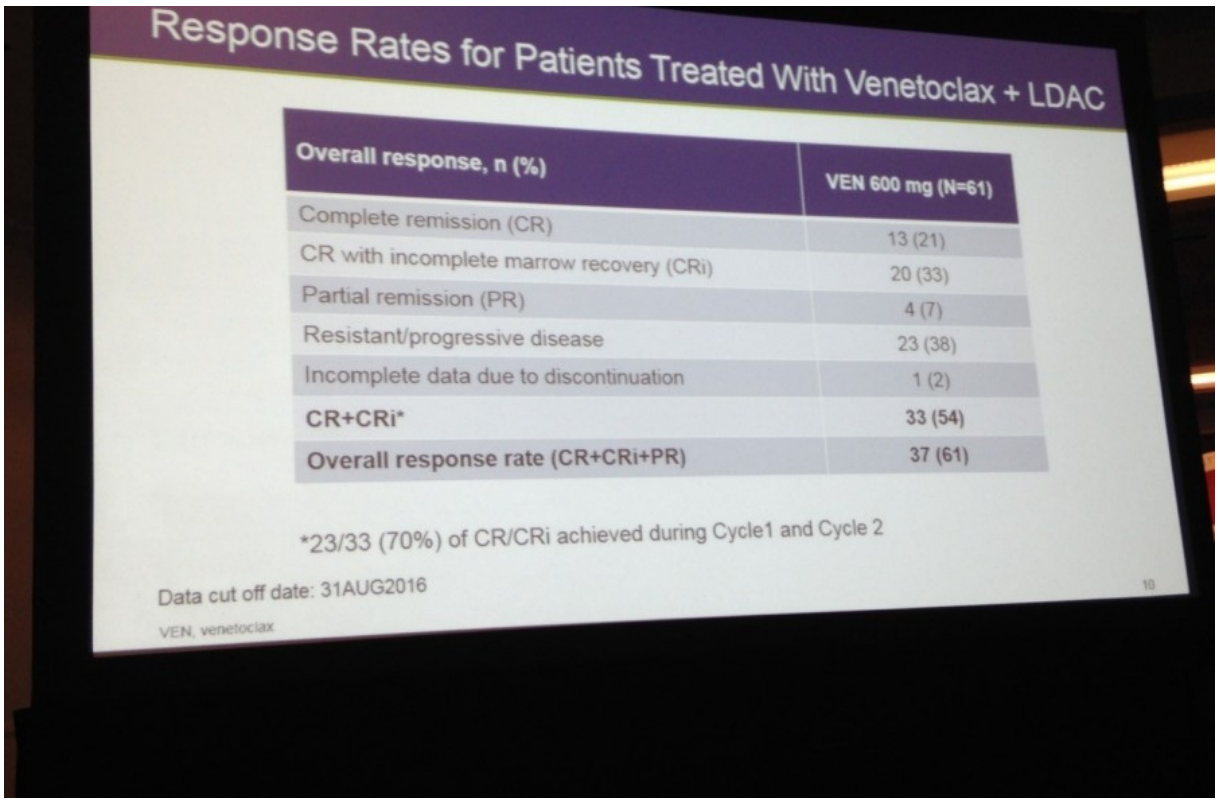


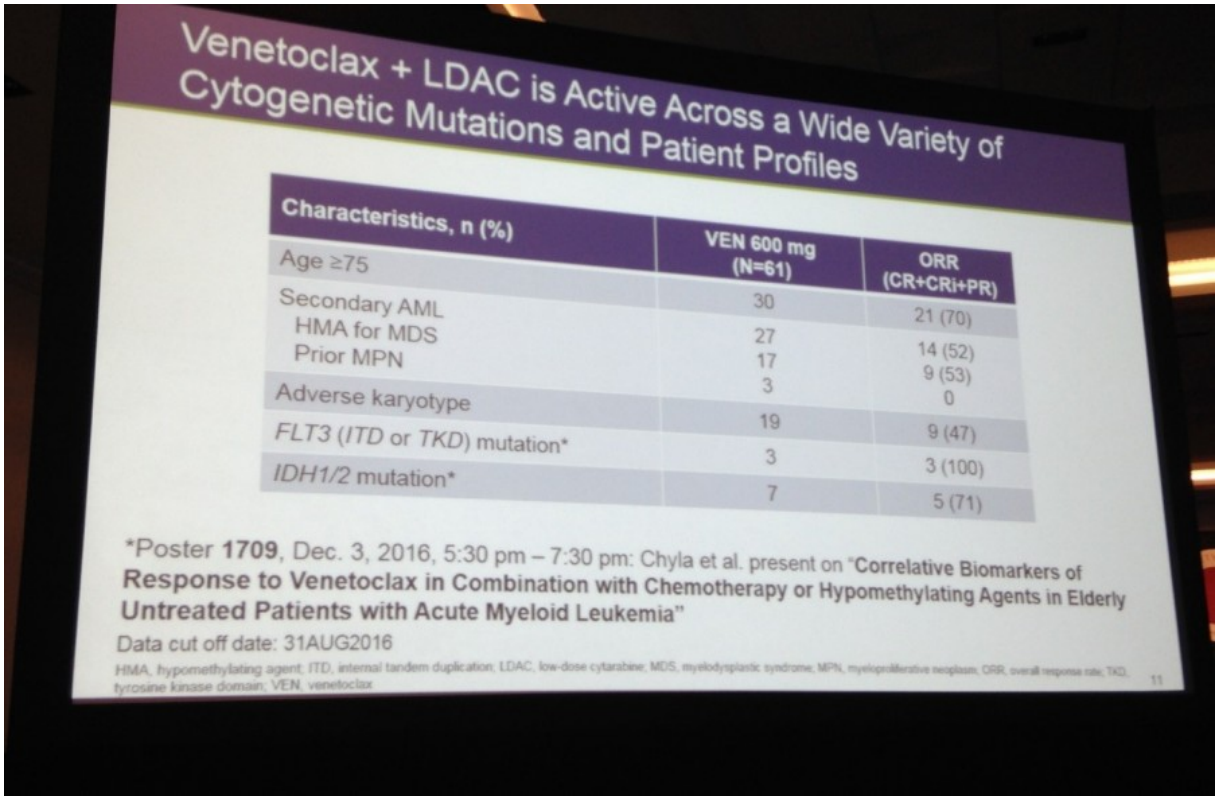


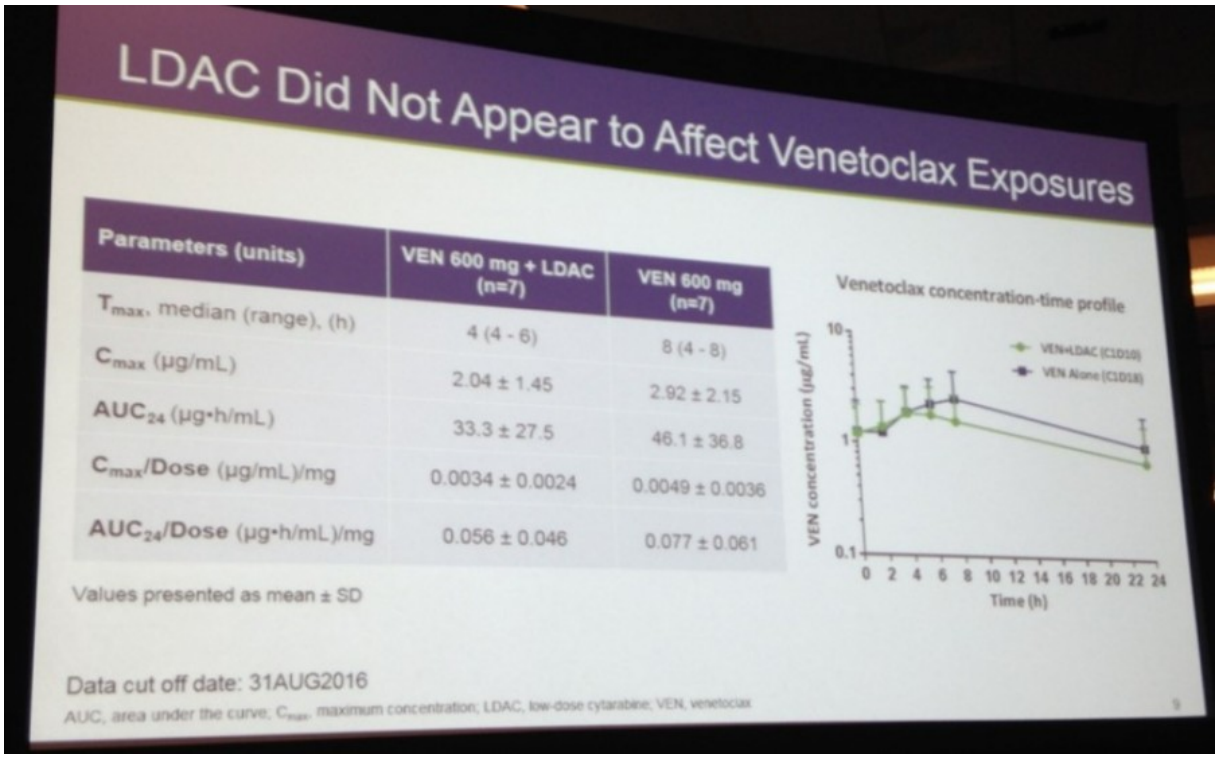
The key findings were:

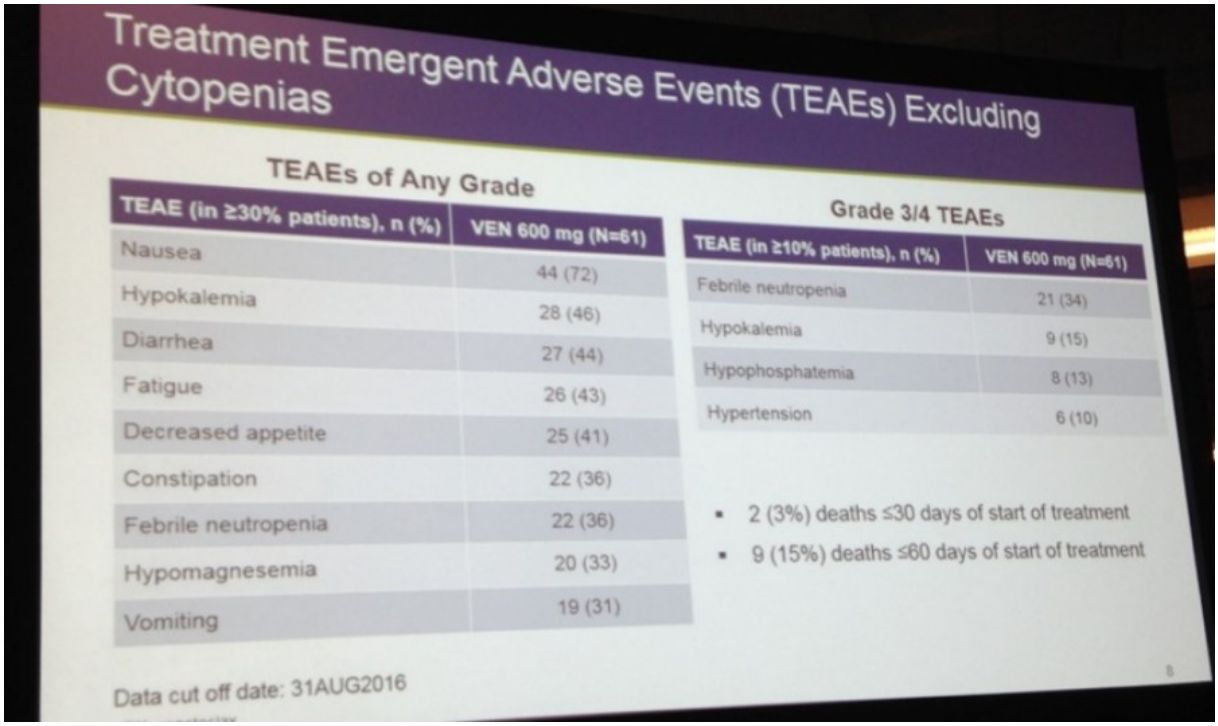
- 37/61 (61%) patients achieved an objective response (CR+CRi+PR)

- The 12-month OS estimate for all patients was 74.7%
- 2 patients whom had achieved CR/CRi died (disease progression [n=1])

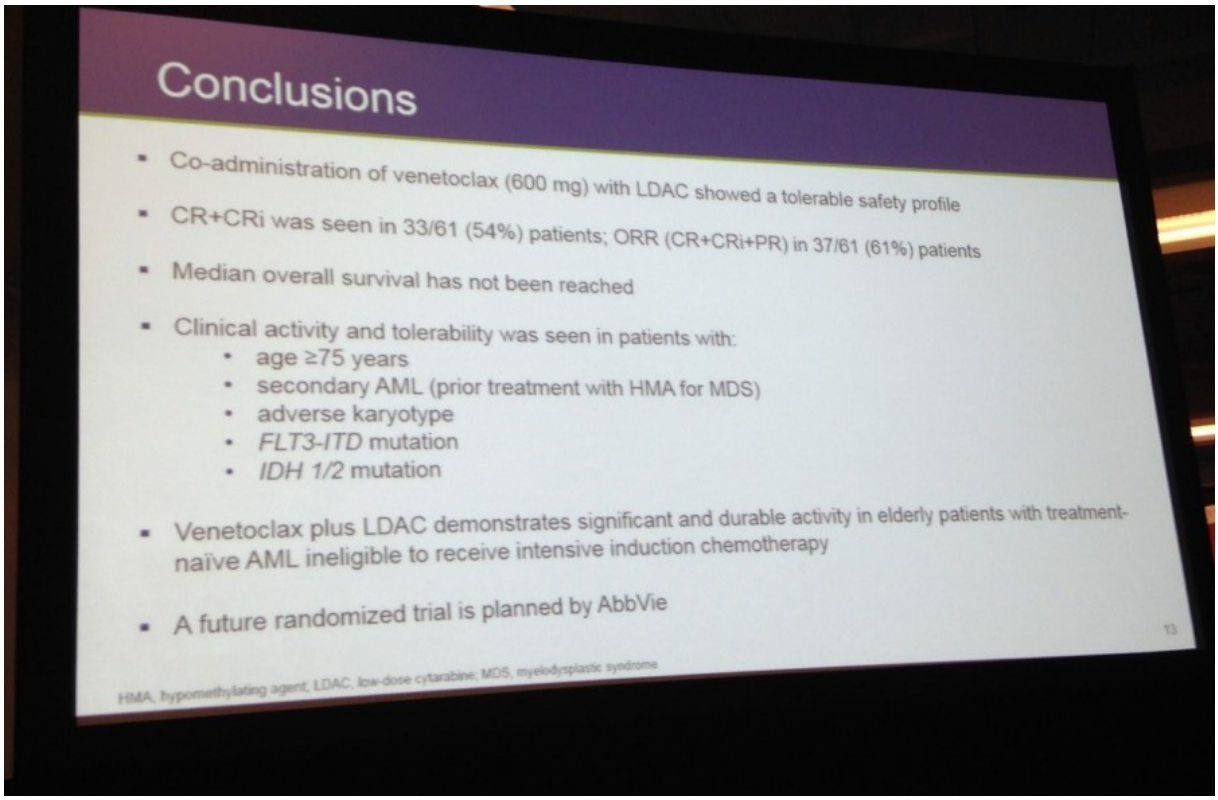








The authors concluded that venetoclax (600mg RP2D) plus LDAC demonstrated an acceptable safety and pharmacokinetic profile in patients aged ≥65 years with treatment-naïve AML. There was a durable response observed.



Abstract 102

Background: Multiple studies have demonstrated the modest efficacy of low-dose cytarabine (LDAC) in older patients (≥65 years) with Acute Myeloid Leukemia (AML) who are unlikely to benefit from an anthracycline and cytarabine intensive induction [CR/CRi rates of 10 – 26%; (CRi = complete remission with incomplete marrow recovery)]. Venetoclax, a selective BCL-2 inhibitor has demonstrated single-agent activity in patients with relapsed and refractory AML [Konopleva et al., ASH 2014]. When administered with LDAC, the recommended phase 2 dose (RP2D) of venetoclax was 600 mg daily [Lin et al., ASCO 2016 (abstract 7007)]. Here we present the safety and efficacy data at RP2D of venetoclax from the dose escalation and expansion phases of the study (NCT02287233).

Methods: Patients enrolled as of 15DEC2015 are included in this analysis with a data cut-off date of 31MAR2016. Patients were eligible if considered unfit for intensive chemotherapy, had an ECOG performance status of 0-2 and adequate renal and liver function. Patients treated with cytarabine for a pre-existing myeloid disorder, or those with acute promyelocytic leukemia or active CNS involvement with AML were excluded from the study.

Venetoclax 600 mg was administered orally once daily on days 2 – 28 of Cycle 1 and days 1 - 28 of subsequent cycles. A 5-day dose ramp-up schedule was followed to reach the 600 mg dose. LDAC 20 mg/m^2 was administered s.c. daily on days 1-10 in 28-day cycles. To mitigate the potential risk of tumor lysis syndrome (TLS), all patients were hospitalized and received prophylaxis commencing 48 hours prior to venetoclax during Cycle 1. Adverse events (AEs) were graded by NCI CTCAE Version 4.0.

Results: Twenty patients were enrolled in the study (escalation, n=8; expansion, n=12). The median age was 74 years (range: 66 – 87). 8/20 (40%) patients had an antecedent hematologic disorder. Median time on venetoclax was 147.5 days (range: 8 - 455). Grade 3/4 AEs (≥10% patients) excluding cytopenias were febrile neutropenia (35%), hypertension (20%), hypophosphatemia (20%), decreased appetite, increased blood bilirubin, hyponatremia, hypoxia, hypotension, pneumonia, sepsis, syncope, urinary tract infection, and vomiting (10% each). No events of TLS occurred.

Venetoclax exposures on Cycle 1 Day 10 (with LDAC) vs. Cycle 1 Day 18 (venetoclax alone) were comparable. The mean ± SD of maximum observed concentration (C_{max}, µg/mL/mg) were 2.04 ± 1.45 vs. 2.92 ± 2.15, respectively. The mean ± SD of area under the curve (AUC_{24}, µg*hr/mL) were 33.3 ± 27.5 vs. 46.1 ± 36.8, respectively. Similarly, coadministration of venetoclax did not markedly affect LDAC exposures. The mean ± SD of C_{max} (ng/mL) of LDAC on Cycle 1 Day 1 (LDAC alone) vs. Cycle 1 Day 10 (with venetoclax) were 158.89 ± 79.08 vs 166.49 ± 32.06, respectively. Similarly, the mean ± SD of AUC_{inf} (ng*hr/mL) were 170.64 ± 102.86 vs 246.51 ± 93.41, respectively.

15/20 (75%) patients achieved an objective response (CR+CRi+PR). Of them, 14/20 (70%) patients had a CR+CRi; all 14 patients belonged to a subset of 18 patients with no prior myeloproliferative neoplasm (MPN). 16/19 (84%) patients with available data had their bone marrow blast percentage reduced to below 5%. The 12-month overall survival (OS) estimate for all patients was 74.7% (95% CI=49.4 – 88.6) and that for the responders (n=15) was 86.7% (95% CI=56.4 – 96.5). The overall response rates and 12-month OS estimates for patients with or without prior hypomethylating agent (HMA) and with or without MPN are summarized in Table 1. A Kaplan-Meier curve showing OS for responders vs. non-responders is shown in Figure 1. The median time to best response was 30 days (range: 23 - 169). Only 2/14 patients who achieved CR/CRi have died [disease progression (n=1), acute hepatic failure (n=1)].

Conclusions: Venetoclax (600 mg RP2D) plus LDAC demonstrated an acceptable safety and pharmacokenitic profile in patients aged ≥65 years with treatment-naive AML who are not eligible for an intensive anthracycline-containing induction chemotherapy. Clinical remission was achieved in the majority of patients. The median OS has not been reached. A substantially better survival in responders as compared to non-responders suggests that the improvement is likely due to treatment with venetoclax plus LDAC. Updated responses and survival estimates for all patients, including those in dose expansion phase that were enrolled after the preliminary data cut, will be presented.

References

1. Wei A.*et al*. Safety and Efficacy of Venetoclax Plus Low-Dose Cytarabine in Treatment-Naive Patients Aged ≥65 Years with Acute Myeloid Leukemia. Oral Abstract #102: ASH 58th Annual Meeting and Exposition, San Diego, CA.