Original Article

Phase I study of alvocidib plus cytarabine/mitoxantrone or cytarabine/daunorubicin for acute myeloid leukemia in Japan

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SUPPORTING INFORMATION

TABLE S1 List of participating medical institutions

| Institution name                                                                 | Principal investigator        |
|---------------------------------------------------------------------------------|------------------------------|
| Tokai University Hospital, Tokyo, Japan                                        | Kiyoshi Ando                 |
| University of Tsukuba Hospital, Tsukuba, Japan                                  | Shigeru Chiba                |
| University of Fukui Hospital, Fukui, Japan                                      | Naoko Hosono                 |
| Fukushima Medical University Hospital, Fukushima, Japan                          | Takayuki Ikezoe              |
| National Hospital Organization Kyushu Medical Center, Fukuoka, Japan             | Hiromi Iwasaki               |
| Chugoku Central Hospital, Fukuyama, Japan                                       | Toru Kiguchi                 |
| Kindai University Hospital, Sakai, Japan                                        | Itaru Matsumura              |
| Kyushu University Hospital, Fukuoka, Japan                                      | Toshihiro Miyamoto           |
| Hokkaido University Hospital, Sapporo, Japan                                    | Masahiro Onozawa             |
| NTT Medical Center Tokyo, Tokyo, Japan                                          | Kensuke Usuki                |
| Osaka City General Hospital, Osaka, Japan                                       | Takahisa Yamane              |
**TABLE S2** Summary of pharmacokinetic parameters for cytarabine, mitoxantrone, and daunorubicin (pharmacokinetic population)

|                | C<sub>max</sub> (ng/mL) | t<sub>max</sub> (h) | AUC<sub>0-last</sub> (h*ng/mL) | t<sub>1/2</sub> (h) |
|----------------|--------------------------|---------------------|-------------------------------|---------------------|
| Cytarabine (cohort R1): day 6 |                          |                     |                               |                     |
| n              | 3                        | 3                   | 3                             | 3                   |
| Arithmetic mean<sup>a</sup> | 1401                     | 71.920              | 23063.12                      | 2.28                |
| SD             | 1100                     | 0.119               | 13503.93                      | 0.95                |
| Min, max      | 164, 2270                | 71.75, 71.98        | 7521.4, 31928.6               | 1.3, 3.2            |
| Cytarabine (cohort R2): day 6 |                          |                     |                               |                     |
| n              | 3                        | 3                   | 3                             | 3                   |
| Arithmetic mean<sup>a</sup> | 769.7                    | 71.950              | 27402.21                      | 1.85                |
| SD             | 453.7                    | 27.563              | 6685.38                       | 0.38                |
| Min, max      | 412, 1280                | 24.22, 71.97        | 19791.6, 32327.0              | 1.6, 2.3            |
| Mitoxantrone (cohort R1): day 9 or 10 |                          |                     |                               |                     |
| n              | 3                        | 3                   | 3                             | 3                   |
| Arithmetic mean<sup>a</sup> | 196.6                    | 1.970               | 354.44                        | 5.39                |
| SD             | 113.3                    | 0.068               | 178.75                        | 2.74                |
| Min, max      | 79.7, 306                | 1.87, 2.00          | 159.9, 511.5                  | 3.3, 8.5            |
| Mitoxantrone (cohort R2): day 9 or 10 |                          |                     |                               |                     |
| n              | 3                        | 3                   | 3                             | 3                   |
| Arithmetic mean<sup>a</sup> | 1006                     | 2.000               | 1877.46                       | 20.46               |
| SD             | 1104                     | 0.137               | 2013.46                       | 10.61               |
| Min, max      | 342, 2280                | 1.90, 2.17          | 712.0, 4202.4                 | 10.4, 31.5          |
Daunorubicin (cohort F1): day 5

|     | 3    | 3    | 3    | 3    |
|-----|------|------|------|------|
| n   | 3    | 3    | 3    | 3    |
| Arithmetic mean\(^a\) | 257.7 | 0.500 | 423.26 | 7.28 |
| SD  | 136.3 | 0.053 | 139.35 | 2.87 |
| Min, max | 101, 349 | 0.48, 0.58 | 272.7, 547.7 | 5.6, 10.6 |

Abbreviations: AUC\(_0\)-\(t_{\text{last}}\), area under the concentration-time curve up to the last measurable concentration; \(C_{\text{max}}\), maximum plasma concentration; \(t_{\frac{1}{2}}\), elimination half-life; \(t_{\text{max}}\), time to maximum plasma concentration.

\(^a\)Median is shown for \(t_{\text{max}}\).
**FIGURE S1** Illustration of the mode of action of alvocidib (Sumitomo Dainippon Pharma, data on file).

MCL-1 is an anti-apoptotic protein with a key role in promoting cell survival and its overexpression conveys resistance to apoptosis. Alvocidib potently inhibits CDK9 which, in turn, is able to downregulate MCL-1. This results in sensitization of tumor cells to apoptotic signals.

Abbreviations: BRD4, bromodomain-containing protein 4; CDK9, cyclin-dependent kinase 9; CycT, cyclin T; CTD, C-terminal domain; MCL-1, myeloid cell leukemia-1; P-TEFb, positive transcription elongation factor b.