**Supplementary information**

Figure 1 Mean (±SD) serum lumretuzumab profiles following multiple ascending doses from 100 mg up to 2000 mg



Figure 2 Percentage change in standardized uptake value maximum from baseline as assessed by FDG-PET at (a) Cycle 1 Day 14 and (b) Cycle 4 Day 14

(a)



(b)

Table 1 Summary of baseline and change in HER3 expression measured by IHC in skin and tumor biopsy samples pre and post treatment with lumretuzumab

|  |  |
| --- | --- |
| **Lumretuzumab (mg)** | **Membrane HER3 Expression (IRSmedian)** |
| **Skin Biopsies** | **Tumor Biopsies** |
| **Predose (n)** | **ΔIRS (n)****(Day 14, Cycle 1 – Predose)** | **P-valuea** | **Predose (n)** | **ΔIRS (n)****(Day 14, Cycle 1 – Predose)** | **P-valuea** |
| 100 | 1.35 (3) | -0.67 (3) | NA | 0.66 (3) | NA | NA |
| 200 | 0.81 (3) | -0.81 (3) | NA | 2.4 (3) | -2.05 (2) | NA |
| 400 | 1.08 (3) | -1.08 (3) | NA | 2.6 (3) | -2.6 (3) | NA |
| 800 | 0.99 (7) | -0.92 (6) | NA | 1.26 (7) | -0.65 (5) | NA |
| 1600 | 0.49 (5) | -0.49 (5) | NA | 1.2 (5) | -1.2 (5) | NA |
| 2000 | 1.2 (25) | -1.12 (24) | <0.0001 | 1.74 (25) | -1.24 (23) | <0.0001 |
| a P-value has been calculated using Wilcoxon signed-rank test if 10 or more paired samples were available. |

Table 2 Summary of change in expression of HER3, HER2, EGFR and cMET in fresh tumor biopsies compared to primary archival samples

|  |  |  |  |
| --- | --- | --- | --- |
| **Marker** | **Paired cases** | **Median change in IRS from archival tissue** | **Patients (%) with increased IRS compared to archival tissue** |
| HER3 | 34 | 1.06 a | 88.2 |
| EGFR | 34 | 0.48 a | 76.5 |
| HER2 | 34 | 0 | 85.7 |
| cMET | 34 | 0.86 a | 91.2 |
| a P<0.001 Wilcoxon signed rank test. |

Table 3 Peripheral blood immunophenotyping (T, B and NK cells and NK subsets) from patients dosed with 2000 mg lumretuzumab

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Median Baseline Value** | **Cycle 2 – pre-infusion** | **Cycle 3 – pre-infusion** |
| **Population**  | Cells/µL (N) | % change Cycle 1\* | N Changing † | % change Cycle 1\* | N Changing † |
| **Lymphocytes** | 1109 (24) | 6.2 (-40, 61)% | 9/11 | 4.4 (-25, 133)% | 6/13 |
| **B (CD3–CD19+)** | 97 (25) | -11.3 (-38, 95)% | 13/10 | 3.3 (-38, 127)% | 9/11 |
| **CD3 (mature T)** | 674 (25) | 4.9 (-44, 99)% | 10/13 | 3,9 (-33, 239)% | 9/11 |
| **CD4 (helper T)** | 428 (25) | 1.3 (-62, 120)% | 10/13 | 1.2 (-44, 171)% | 9/11 |
| **CD8 (cytotoxic T)** | 233 (25) | -5.8 (-41, 87)% | 13/10 | 3.6 (-20, 271)% | 9/11 |
| **CD8NK (CD3+CD8+CD16+CD56+)** | 38 (24) | -6.9(-64, 301)% | 12/10 | 44\*\* (-53, 370)% | 5/13 |
| **CD56T (CD3+CD56+)** | 43 (24) | 2 (-66, 61)% | 10/12 | 4.2 (-70, 265)% | 9/9 |
| **NK (CD3-CD16/CD56+)** | 173 (25) | 9.8 (-64, 152)% | 11/12 | 27,3 (-60, 384)% | 7/13 |
| **CD16NK (CD3/CD19-CD16/CD56+)** | 164 (24) | 11.1 (-65, 148)% | 10/12 | 30.8 (-61, 400)% | 6/13 |
| **CD16NK MESF1** | 402135 (24) | 16.6 (-22, 126)% | 8/14 | 26.7 (-36, 219)% | 6/13 |
| **CD56bright NK (CD3/CD19-CD16/CD56+)** | 9 (23) | -7.8 (-56, 394)% | 11/10 | -4.5 (-40, 497)% | 9/9 |
| **CD16+CD56-NK (CD3/CD19/CD56-CD16+)** | 10 (23) | 10.7 (-63, 192)% | 8/13 | -0.8 (-57, 190)% | 9/9 |
| **CD56dim NK (CD3/CD19/CD16-CD56+)** | 8 (23) | -22.3 (-53, 110)% | 12/9 | -8.5 (-66, 249)% | 11/17 |
| **CD56 NKp46 NK (CD3/CD19-CD56/CD335+)** | 145 (24) | 14.3\*\* (-57, 442)% | 8/14 | 32.1 (-56, 385)% | 5/14 |
| **CD56 NKp46 NK MESF1** | 4230 (24) | 16\*\*\* (-26, 213)% | 6/16 | -3.8 (-31, 75)% | 11/8 |
| **CD56dimCD16brightNK(CD3/CD19-CD16/CD56+)** | 145 (24) | 9.1 (-67, 133)% | 10/12 | 34.9 (-63, 457)% | 6/13 |
| \*Median percentage change in cells/μL from pre-infusion Cycle 1 (Day 1) (range: min, max). P>0.05\*\*, < 0.005\*\*\*.† Number of patients showing change consistent with the median change from baseline on Day 1 of Cycle 1 or Cycle 2 (for example, a negative change).1 Mean Equivalent Soluble Fluorescence (MESF) intensity of CD16 of the CD3–/CD19-/CD56+/CD16+ and CD56/NKp46 populations. |

Table 4 Ex-vivo activation potential of peripheral NK lymphocytes for all patients at baseline and following exposure to lumretuzumab in the 2000 mg dose cohort

|  |  |  |
| --- | --- | --- |
|  | **All Patients** | **2000mg Lumretuzumab Dose Cohort** |
| **Condition** | **Cycle 1 (pre-infusion)** | **Cycle 1 (pre-infusion)** | **Cycle 2 (pre-infusion)** | **Cycle 3 (pre-infusion)** |
| ADCC-independent control (K562 cells)\* |  13.8 (2.1 to 29)% (28) | 12.5 (5.4 to 29)% (14) | 12.3 (5 to 26)% (14) | 11.8 (4 to 27)% (15) |
| + HER3 WT | 13.5 (3.9 to 36)% (37) | 10.9 (3.9 to 36)% (20) | 10.5 (0.7 to 27)% (19) | 15.2 (3 to 25)% (19) |
| + lumretuzumab | 27.2(7.5 to 53)% (41) | 26.5 (7.5 to 53)% (23) | 25.7 (3.2 to 49)% (22) | 29.3 (11 to 47)% (21) |
| Values are median % (range: min‑max) CD3-/CD56+/CD107+ cells and number of patients (n).\* NK lymphocyte activation stimulated directly by the ADCC-independent control cell line K562 (and independent of either HER3 on the target cell, or CD16 on the NK cell).ADCC = antibody-dependent cellular cytotoxicity |

Table 5 Summary of tumor immune effector cell infiltration

|  |  |  |
| --- | --- | --- |
| **Immune effector cell population** | **All patients** | **2000 mg lumretuzumab dose cohort** |
| **Number of patients** | **Median (range) pretreatment****(cells/mm2)a** | **Number of patients** | **Median % change (range)****(Day 14 Cycle 1 – Day 1 Cycle 1)** | **Number of patients with a changeb****(decrease/increase)** |
| CD3+ (mature T) | 44 | 97 (1 to 360) | 23 | -17.4 (-74 to 967) | 12/11 |
| CD68 (macrophage) | 47 | 90 (12 to 275) | 23 | 7.0 (-92 to 181) | 8/15 |
| CD16+ (NK,FCγRIII) | 45 | 135 (7 to 600) | 23 | 17.6 (-68 to 3186) | 8/15 |
| a Values express “number of positive staining cells/mm2” for all evaluable samples.b Number of patients treated with 2000 mg of lumretuzumab showing a change on Day 14 of Cycle 1 from baseline (n: negative/positive) (no missing values). |

Table 6 Tumor response to treatment (RECIST)

|  |  |
| --- | --- |
|  | **No. of patients (%)N = 47** |
| Complete response | 0 |
| Partial response | 0 |
| Stable disease  | 10 (21.3) |
| Progressive disease | 29 (61.7) |
| Clinical progression a | 5 (10.6) |
| Lost to follow up | 3 (6.4) |
| a If the overall response was based solely on symptomatic deterioration, i.e. without confirmation by an imaging method. |