

## Supplementary data

**Supplementary Table 1: In vitro cytotoxicity**

| fusion protein    | Bortezomib | Cetuximab | EC <sub>50</sub> (pM) |               |
|-------------------|------------|-----------|-----------------------|---------------|
|                   |            |           | NCI-H460              | Colo205       |
| scTRAIL           | -          | -         | -                     | -             |
|                   | +          | -         | 270 ± 40              | 3,470 ± 1,590 |
| scFv-EHD2         | -          | -         | -                     | -             |
|                   | -          | +         | -                     | -             |
|                   | +          | -         | -                     | -             |
|                   | +          | +         | -                     | -             |
| EHD2-scTRAIL      | -          | -         | 220 ± 90              | 570 ± 50      |
|                   | -          | +         | 280 ± 10              | 530 ± 180     |
|                   | +          | -         | 22 ± 6                | 140 ± 20      |
|                   | +          | +         | 14 ± 2                | 160 ± 0.7     |
| scFv-EHD2-scTRAIL | -          | -         | 28 ± 2                | 31 ± 6        |
|                   | -          | +         | 240 ± 50              | 610 ± 90      |
|                   | +          | -         | 5 ± 1                 | 14 ± 4        |
|                   | +          | +         | 9 ± 0                 | 156 ± 8       |

**Supplementary Table 2: Pharmacokinetic properties of EHD2 fusion proteins**

| construct         | $M_r$ (kDa) | $S_r$ (nm)       | $t_{1/2\beta}$ (h) | $AUC_{0-24h}$ (%h) |
|-------------------|-------------|------------------|--------------------|--------------------|
| scTRAIL           | 67.5        | 3.3 <sup>#</sup> | $3.0 \pm 0.3$      | $127 \pm 30$       |
| scFv-EHD2         | 82.8        | 4.4              | $9.4 \pm 0.5$      | $358 \pm 89$       |
| EHD2-scTRAIL      | 164.6       | 4.6              | $6.5 \pm 0.4$      | $388 \pm 135$      |
| scFv-EHD2-scTRAIL | 218.6       | 5.1              | $7.2 \pm 0.9$      | $508 \pm 112$      |
| Db-scTRAIL        | 187.0       | 5.0              | $3.5 \pm 0.3$      | $326 \pm 29$       |

*The molecular masses were calculated for the dimeric molecules*

<sup>#</sup> *data from (11)*