Supplementary Materials:

Treatment regimen

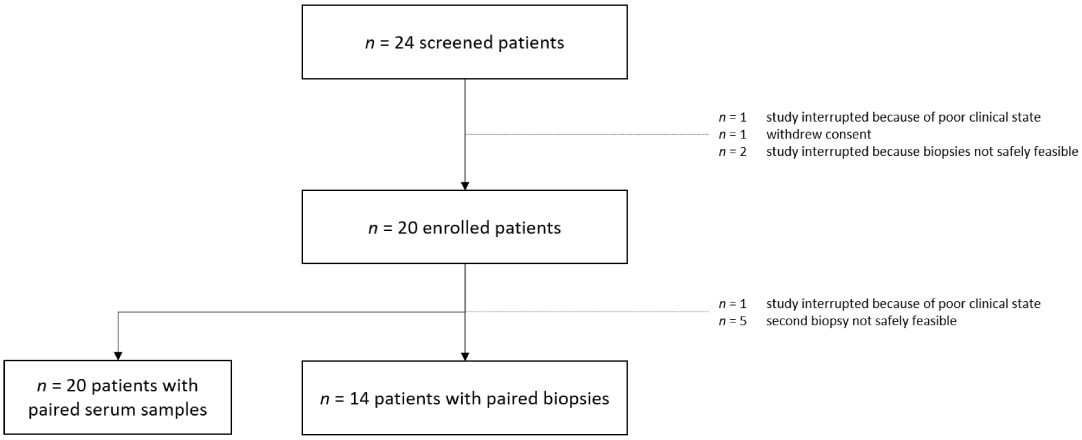
The rationale for the dosing schedule is based on safety data obtained after repeated administration of olaptesed pegol to healthy subjects and multiple myeloma patients. In the repeated dose Phase I study in healthy volunteers[1], olaptesed pegol was administered daily for 5 days at doses of 2 or 4 mg/kg. The daily dosing schedule resulted in plasma accumulation. Dose limiting liver toxicities were observed at the 4 mg/kg dose level when applied on 5 consecutive days, for which peak plasma concentrations of about 20 µM and a weekly exposure of approx. 2,100 µM·h were reached. In contrast, the daily dose of 2 mg/kg, which was safe with only mildly increased transaminases, resulted in peak plasma levels of about 10 µM and a weekly exposure of approx. 900 µM·h. Both Cmax and weekly exposure are therefore considered to be relevant parameters to predict dose-limiting toxicity. The weekly exposure expected in the current study is comparable to the safe regimen in this study. Furthermore, the Cmax and weekly exposure in the current study do not exceed the respective values observed in the previous MM study where a dose of 4 mg/kg body weight was administered on top of bortezomib/dexamethasone twice weekly in the first two weeks of each 21-day treatment cycle[2]. This dosing schedule was safe and well tolerated over up to 6 months of treatment and did not add toxicity to the underlying standard treatment.

The rationale for the dosing in combination with Pembrolizumab at the time of study inception was also based on efficacy considerations. In a syngeneic mouse model of colon cancer, plasma levels with peak and trough levels of 4.5 and 0.5 µmol/L olaptesed pegol significantly improved anti-PD-1 therapy. After single i.v. dose of 300 mg olaptesed pegol such levels are maintained in humans for approximately 7 days in a 75 kg patient. The mode of action of olaptesed pegol is to facilitate the influx of immune effector cells into solid tumors to allow effective response to immune checkpoint inhibition. It was assumed that continuous inhibition of CXCL12 by olaptesed pegol is not required since once within the tumor and activated by recognition of the antigen on the target cells, the immune effector cells are able to expand and to perform serial killing for a prolonged period of time. In fact, it had been shown in a preclinical model[3] that a time window of 7 days for infiltration was sufficient to enable immune effector cell activation, tumor cell killing, and expansive proliferation in tumors resulting in significant inhibition of tumor growth. Therefore, a 7-day window of immune effector cell influx into the tumor within a 21-day treatment cycle with pembrolizumab was considered sufficient to meaningfully improve the efficacy of this checkpoint inhibitor.

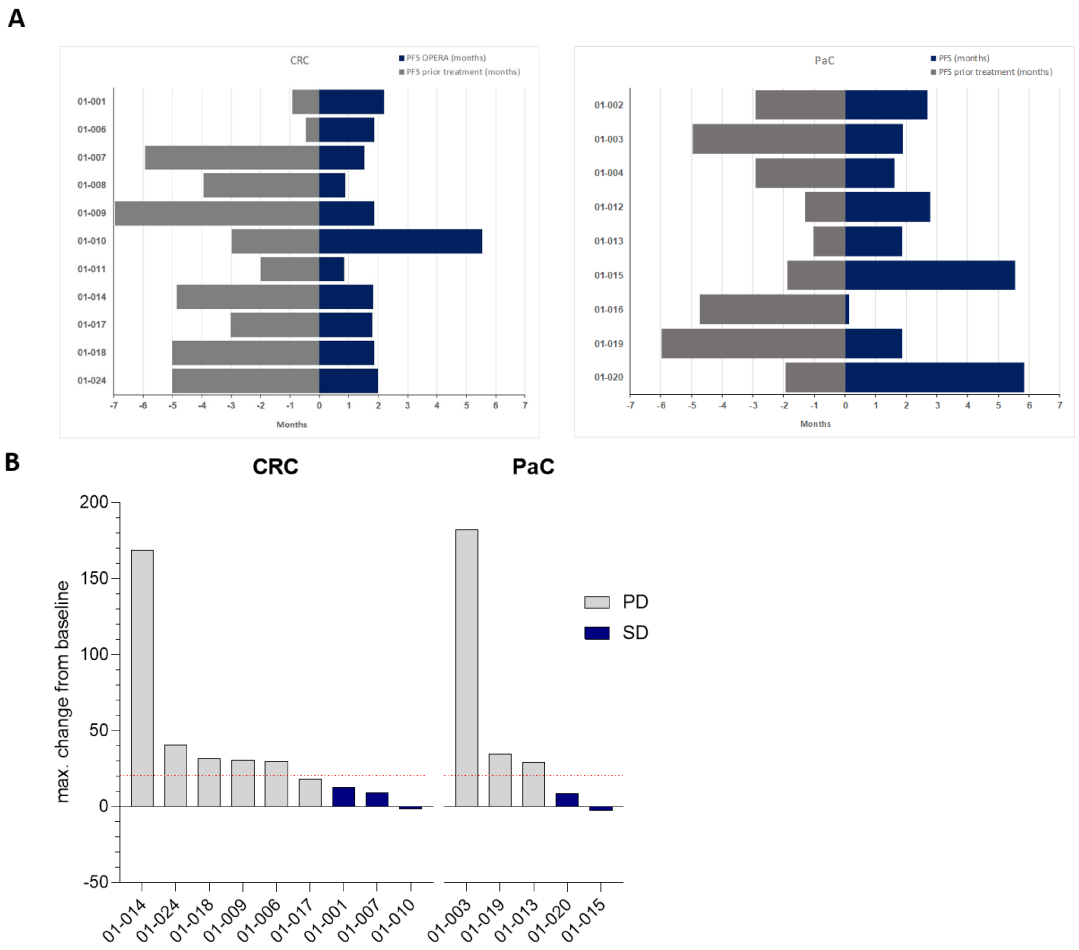
Supplementary Table 1

Table 1: 90% Confidence Intervals for the true response rate in the OPERA trial.

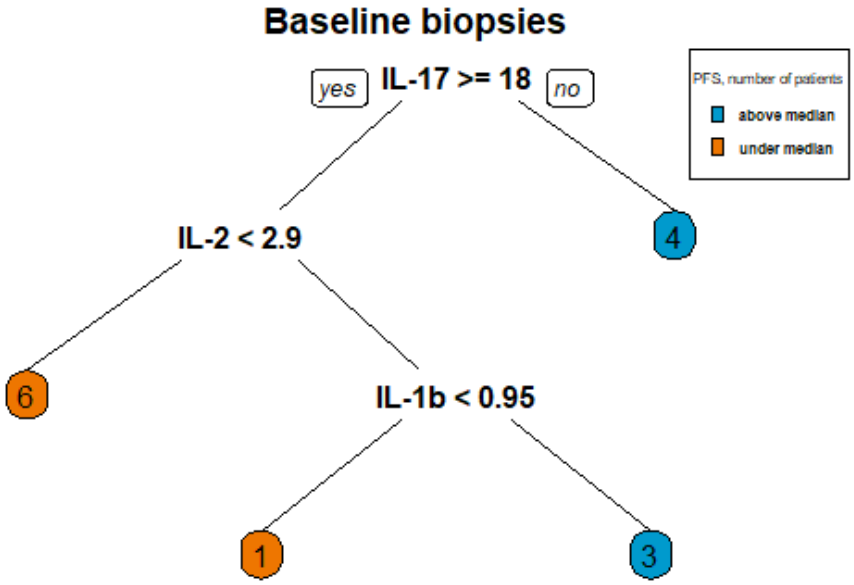
90%CI for response rates Responses out of 10 patients	Exact 90% confidence interval
1	(0.51%, 39%)
2	(3.7%, 51%)
3	(8.7%, 61%)



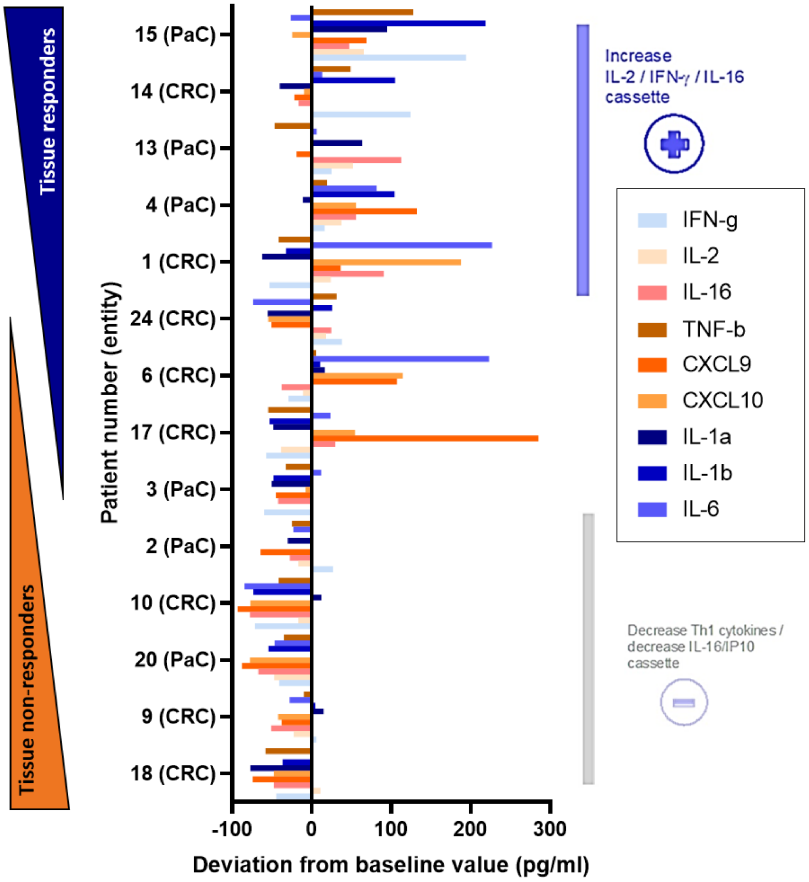
Supplemental Figure 1: diagram of the OPERA trial. This diagram illustrates the numbers patients who were screened, enrolled and who completed the trial.



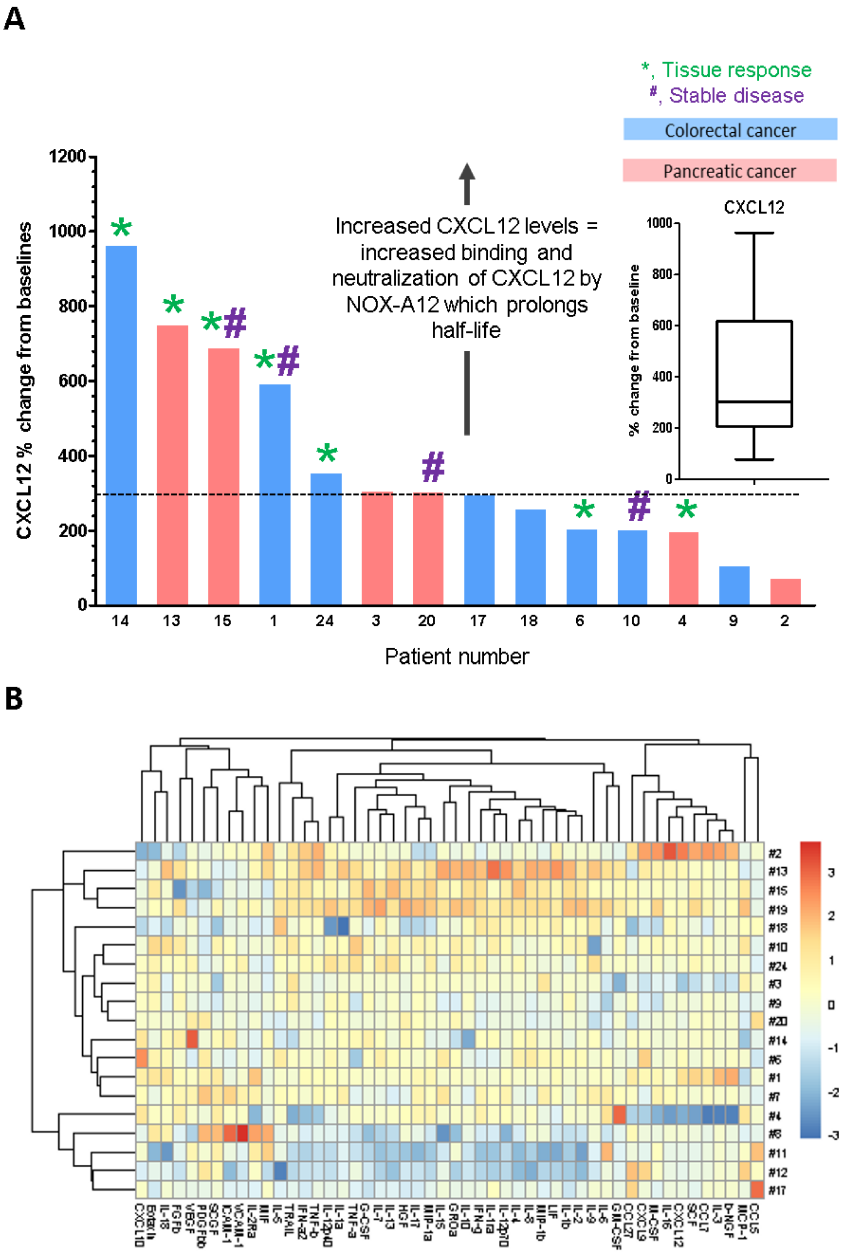
Supplemental Figure 2: Individual progression-free survival and patient responses, by cancer entity. (A) Side-by-side illustration of PFS during the OPERA trial and PFS during the previous treatment, for each tumor entity. (B) Waterfall plot of patients' response, by tumor entity. The maximum change in sum of diameters of target lesions from baseline at the time of best response is illustrated.



Supplemental Figure 3: Recursive partitioning indicates biomarkers predictive of a long PFS (cutoff was set at the median value for all patients, 1.87 months, concentration values are in pg/ml).



Supplemental Figure 4: Clustering of the patients into "tissue responders" and "tissue non-responders" according to the results illustrated in Figure 5A.



Supplemental Figure 5: Relative changes in cytokine concentrations in the biopsies and the serum at the end of the NOX-A12 monotherapy, illustrated patient by patient. (**A**) Relative changes in CXCL12 concentration in the biopsies. Pancreatic cancer patients have a pink bar; colorectal cancer patients have a blue bar. Patients exhibiting a tissue response have a green tag; those benefiting from disease stabilization have a purple tag.
(**B**) Relative serum cytokine concentrations at the end of the monotherapy (d14) compared to baseline (d0). Results are expressed as the Z-score for each cytokine.

1. Vater, A.*, et al.* Hematopoietic stem and progenitor cell mobilization in mice and humans by a first-in-class mirror-image oligonucleotide inhibitor of CXCL12. *Clin. Pharmacol. Ther.* **94**, 150-157 (2013).
2. Ludwig, H.*, et al.* Olaptesed pegol, an anti-CXCL12/SDF-1 Spiegelmer, alone and with bortezomib-dexamethasone in relapsed/refractory multiple myeloma: a Phase IIa Study. *Leukemia* **31**, 997-1000 (2017).
3. Xu, Y.*, et al.* Optogenetic control of chemokine receptor signal and T-cell migration. *Proc. Natl. Acad. Sci. U. S. A.* **111**, 6371-6376 (2014).