**Supplementary Table 1.** The activity of nazartinib, TNO155, and their combination in EGFR mutant NSCLC cell lines. IC50 was calculated from either 3-day (for nazartinib) or 6-day (for TNO155) anti-proliferation assays. The synergy scores between nazartinib and TNO155 were determined from 6-day anti-proliferation assays as described in Figure 1C.

**Supplementary Figure 1.**

(**A**) Immunoblots of RKO cells treated with 0.5 μM selumetinib alone or in combination with 3 μM TNO155 or 0.5 μM indicated RTK inhibitors or MDST8 cells treated with 0.1 μM dabrafenib (Dab), 0.5 μM selumetinib (Selu), or Selu+Dab alone or in combination with 10 μM SHP2 inhibitor SHP099 or 1 μM indicated RTK inhibitors. Both cell lines were treated for 24 h. (**B**) Combination dose matrix of RTK inhibitors and dabrafenib plus trametinib (Dab + Tram, maximal dose: Dab = 10 μM, Tram = 0.5 μM, followed by 3-fold serial dilutions) evaluating their anti-proliferative effects against RKO (capmatinib and erlotinib) and MDST8 (infigratinib and erlotinib) for 3 days. The mean (n = 3) of percentages of inhibition relative to the DMSO-treated control and synergy scores of the two treatments are shown.

**Supplementary Figure 2.**

(**A**) Immunoblot of NCI-H2122 and SW837 cells that were treated with TNO155, Cpd 12a, or the combination for 2, 24, or 48 h. (**B**) Growth kinetics of NCI-H2122, SW1463, MIA PaCa-2, and SW837 cells treated with DMSO, 0.2 μM Cpd 12a, 0.3 µM TNO155, or the combination measured by IncuCyte imaging over 14 days. Mean percentages of confluency are shown, error bars denote standard deviation,*n* = 3. (**C**) Combination dose matrix of TNO155 and Cpd 12a evaluating their anti-proliferative effects against indicated cell lines in a 3-day assay. The mean (n = 3) of percentages of inhibition relative to the DMSO-treated control and synergy scores between the two compounds are shown

**Supplementary Figure 3.**

(**A**) Immunoblot of GDM-1 cells that were treated with DMSO, 1 µM TNO155, 50 nM trametinib (Tram), or 0.5 µM BLZ945 for 2 h. (**B**) Mean percentage of proliferation of CD14+ monocytes isolated from healthy donors (Donor ID: 1011, 1070 and E347) in the absence or the presence of 50 ng/mL M-CSF in a 6-day assay, relative to the cell number for each donor on the seeding day (Day 0, set as 100%). Error bars denote standard deviation,*n* = 3. (**C**) Schematic illustration of the process of cell isolation, compound treatment, co-culture, stimulation, and cytokine measurement in the co-culture of M-CSF-differentiated monocyte-derived macrophages and T cells as described in Methods. (**D**) Mean percentage of viability of monocytes-derived macrophages treated with TNO155, trametinib (Tram), or BLZ945 in the absence or the presence of 50 ng/mL M-CSF relative to the M-CSF and DMSO treated control (the second bar, set as 100%). Cell number on the seeding day (Day 0) is marked as a dotted line. Error bars denote standard deviation,*n* = 3. (**E**) Mean percentage of tumor-associated macrophages relative to CD45+ cells in MC38 tumors from C57BL6 mice treated and analyzed as in Figure 5D. Error bars denote standard error of mean, *n* = 6. n.s., not significant; \*, p < 0.05; \*\*, p < 0.01; \*\*\*, p< 0.001.