Supplementary figure 1. Swimmer plot of overall survival and progression-free survival

(**A**) ITT population (n = 31); (**B**) chemotherapy-naïve patients (n = 17)

Control = pemetrexed (500 mg/m^2) in combination with cisplatin (75 mg/m^2) or carboplatin (AUC 5)

ONCOS-102 = ONCOS-102 (3×10^{11} virus particles in 2.5 mL) with pemetrexed (500 mg/m^2) in combination with cisplatin (75 mg/m^2) or carboplatin (AUC 5)

> denotes censoring

PFS, progression-free survival; OS, overall survival

Supplementary figure 2. Selected gene expression profiles stratified by study treatment

Normalized (using DESeq2) expression of genes classified as cytotoxicity (**A**), co-stimulatory (**B**), or checkpoint inhibitor (**C**) genes in tumour biopsies obtained at baseline and Day 36 stratified by study treatment. Values in parenthesis reflect the number of samples for each group at each timepoint.

Control = pemetrexed (500 mg/m^2) in combination with cisplatin (75 mg/m^2) or carboplatin (AUC 5)

ONCOS-102 = ONCOS-102 (3×10^{11} virus particles in 2.5 mL) with pemetrexed (500 mg/m^2) in combination with cisplatin (75 mg/m^2) or carboplatin (AUC 5)

Supplementary figure 3. Serum cytokine concentrations

Circulating concentrations of GM-CSF (**A**), IFNα2 (**B**) and IFN-gamma (**C**) were assessed prior to study medication on Days 1, 43, 85, and 127 in the chemotherapy-alone cohort (upper panels), and on Days 1 Days 4, 8, 36, 78, and 120 in the ONCOS-102 cohort. P-values were calculated by linear regression.

Control = pemetrexed (500 mg/m^2) in combination with cisplatin (75 mg/m^2) or carboplatin (AUC 5)

ONCOS-102 = ONCOS-102 (3×10^{11} virus particles in 2.5 mL) with pemetrexed (500 mg/m^2) in combination with cisplatin (75 mg/m^2) or carboplatin (AUC 5)

***P*<0.01; ****P*<0.001

D, study day, GM-CSF, granulocyte-macrophage colony stimulating factor; IFN, interferon; IL2, interleukin 2

Supplementary figure 4. Selected gene expression profiles stratified by survival at Month 18 (ONCOS-102 group[a])

Normalized (using DESeq2) expression of selected cytotoxicity genes (**A**), co-stimulatory genes (**B**), or checkpoint inhibitor genes (**C**) in tumour biopsies obtained at baseline and Day 36 stratified by 18-month survival. Numbers in parenthesis reflect the number of samples for each group at each timepoint.

[a]ONCOS-102 (3×10^{11} virus particles in 2.5 mL) with pemetrexed (500 mg/m^2) in combination with cisplatin (75 mg/m^2) or carboplatin (AUC 5).

Supplementary figure 5. Tumour transcriptome analysis stratified by survival at Month 18 (ONCOS-102 group[a])

Heatmaps of the top 100 most differentially expressed genes in patients stratified by survival (alive or deceased at Month 18) in baseline (**A**) and Day 36 (**D**) tumour biopsies from patients who received ONCOS-102. Volcano plot depicting change in all tumour-expressed genes at baseline (**B**) and Day 36 (**E**) in patients (alive or deceased at Month 18) (Benjamini-Hochberg adjusted *P*-values). Gene ontology analysis of tumour genes with significant differential expression at baseline (**C**) and Day 36 (**F**) in patients who were alive versus deceased at Month 18.

[a]ONCOS-102 (3×10^{11} virus particles in 2.5 mL) with pemetrexed (500 mg/m^2) in combination with cisplatin (75 mg/m^2) or carboplatin (AUC 5).

Supplementary figure 6. Predictors of survival at Month 18 following (ONCOS-102 cohort[a])

(**A**) Baseline tumour transcriptome levels of *PD-L1*, *CD8A*, *LAG3,* and *STAT1* stratified by survival at Month 18. (**B**) 2x2 contingency table comparing the binomial GLM classifier build on transcriptome data shown in (**A**) with ground-truth survival. (**C**) ROC-analysis of model prediction. (**D**) GLM coefficients reflecting the predictive value for each gene on survival.

[a]ONCOS-102 (3×10^{11} virus particles in 2.5 mL) with pemetrexed (500 mg/m^2) in combination with cisplatin (75 mg/m^2) or carboplatin (AUC 5).

BL, baseline; D, day; GLM, generalized linear model; ROC, receiver operating characteristics