Supplementary material:

Paper	Cytostatic drug	Combinations	Route of administration and dosage	Time & treatment cycles	Measurements	Mouse strain, cell line, tumor entity	Results	Side effects	Other remarks
(1)	**P, D, E**	No	P: i.p., 3 mg/kg/d D: i.p., 5 mg/kg/d E: i.v. ,10 mg/kg/d	P: d1-4/15-18 D: d1-3/15-17 E: d1,5,9/14,19,24	Tumor growth curves, α-Fetoprotein level, histology (liver, kidney, heart), proliferation activity	Female NMRI nu/nu athymic, 6-8 weeks Subcutaneous injection of patient derived hepatoblastoma cells	P and D produced a significant retardation of the mean tumor volume , E demonstrated only a moderate response dependent on the tumor cell entity	Chemotherapy side effects were observed in only 10% of the mice without any lethal consequences D: Necrosis of the renal tubuli in 2 animals, moderate infiltration of the heart muscle with eosinophilic leukocytes and monocytes in 1 animal, areas of regeneration and inflammation in the liver in 6% of the animals especially after D	Drugs were given in equitoxic doses for nude mice, formula for transformation of mg/m^2 to mg/kg: (dose in mg/m^2) = k_mx (dose in mg/kg), k_m = 3 for nude mice
(2)	**E**	No, review!	i.p. or i.v., 7.5-45 mg/kg	Many different schemes, for i.p. 30 mg/kg d1,5,9,13	Increase in life span, curation	Review, many different strains and tumor entities	Best results for i.p. administration with 30 mg/kg every 4 days	Dose limiting toxicity: myelosuppression Others: Aloplecia, mild gastrointestinal toxicity, nausea, vomiting, acute hypersensitivity reactions especially when administered i.v., acute nonlymphocytic leukemia	Synergistic effects of E with P or D, toxicity of E is schedule dependent
(3)	**E, P**	Yes, E & P	Both i.p. P: 5-7,5 mg/kg E: 10 mg/kg	P: d1, P and/or E: d2/4/6 (not clear) Two consecutive cycles	Inhibition of tumor growth, changes in body weight, platinum and Etoposide concentration in serum and tumor tissue	Female KSN nude mice, 7-8 weeks Subcutaneous transplantation of "Ishikawa human endometrial adenocarcinoma cell line"	Combination produced a marked inhibition of tumor growth, 7.5 mg/kg for P and 10 mg/kg for E produce a significantly higher complete remission rate, higher concentrations show higher mortality rates, E alone caused almost no inhibition of tumor growth, with P alone at 10mg/kg 10 of 22 mice died	Synergistic effects, combination has to be set carefully to avoid high mortality rates Combination of P and E resulted in maximum weight losses of ca. 9%, weight was rapidly regained after the completion of chemotherapy	Combination of E and P leads to a higher toxicity, dosages have to be set carefully
(4)	**D, P**	No	P: i.p., 6.6 mg/kg D: i.v., 10 mg/kg	Single dose, single treatment	Primary sensitive testing, assessment of toxicity, survival, growth delay, LD_{50} of D	NMRI nu/nu mice Establishment of more than 30 well-characterized human soft-tissue sarcoma cell lines as xenografts	D administered i.p. causes peritonitis and should be administered i.v., LD_{50} D 14.4 mg/kg	Toxic death (Kaplan-Meier curve), weight loss	Doses were chosen according to the $LD_{10/30}$, use of isotoxic doses
(5)	**P, D, E, Pa**	No	i.v. P: 2-8 mg/kg E: 17,5-70 mg/kg D: 5-10 mg/kg Pa: 10-40 mg/kg 0,1 ml/10g body weight	P: d7 & 14 E: d7 & 10 & 14 D: d7 & 14 Pa: d7 & 14	Histological study, tumor development	Female athymic BALB/c nude mice, two metastatic models of human NSCLC (NCIh460 & A549), injection of tumor cells into the pleural space	P: dose-dependent activity in the NCIh460 tumor model when administered at 2-8 mg/kg and E at 35 and 70 mg/kg respectively, antitumoral activity of D when administered at 5 and 10 mg/kg, antitumoral activity of Pa when administered at 20 and 40 mg/kg, none of the drugs was found to be curative, poor response to monotherapy	--	--
(6)	**P, E**	Single substanc	i.p. E : 8-16	E: d1,2,3 P: d1	Tumor developme	Female Swiss nu/nu mice, 6-	Single studies: P: 6mg/kg/d	Weight loss, death	P and E show synergistic effects,

		es & combination of P and E	mg/kg/d P : 6/9 mg/kg/d 0,2 ml per injection		nt, combined chemotherapy	10 weeks, subcutaneous implantation of patient derived SCLC tumors	E: 12mg/kg/d Combined E-P led to complete regression of tumors		higher dosages for E (16 mg/kg) and P (9mg/kg) show more side effects and do not improve therapeutic effects, fractionation of drug dosage does not improve the antitumoral effect, no dose dependency for E or P here
(7)	**Pa, P, E, D**	Combination of Pa with P or E or D	i.v. Pa: 24mg/kg/d P: 2-4 mg/kg/d E: 18-26 mg/kg/d D: 10 mg/kg/d 0,01 ml/g body weight	Pa d1-5 & E d6-10 Pa d1-5 + P d6-10 Pa d1-5 + D d6-10 Or both on the same days d1-5	Antitumor activity, evaluation of toxicity	Adult male CDF_1 mice, M-109 murine lung carcinoma were maintained in adult female BALBc mice and subcutaneously implanted in CDF_1 mice	Combination of Pa (24 mg/kg/d, d1-5) followed by P (2mg/kg/, d 6-10) showed a significant tumor growth delay, additive effect of P! Reverse sequence of this combination or a higher dose of P caused toxic deaths of all mice, also possible to administer Pa and P at the same time (d1-5) P alone causes no toxic deaths (2 and 4 mg/kg) Combination of Pa (24 mg/kg d1-5) and E (18mg/kg, d6-10) is optimal but also sequence dependent!! Reverse sequence or administration of E at 36 mg/kg caused toxic death of all mice. Pa and D combinations do not reveal any toxic deaths, no sequence dependency	Toxic death of the mice if the drugs are given in a reverse combination, Pa has to be administered before E or P!!	Maximum tolerable dose (MTD) of E 18mg/kg (d1-5) To avoid toxic deaths, MTDs should not be used if drugs are combined. Often the administration on the same day is more toxic compared to an administration on different days Pa was administered over a period of about 1 min, the other drugs and saline about 15s
(8)	**D**	No	i.p. or i.v. i.p. 4 mg/kg q4dx3 or 8 mg/kg q7dx2 i.v. 8 mg/kg q4dx3, 10 mg/kg q7dx2	Q4dx3 (4 days with 3 cycles) or q7dx2 (7 days with 2 cycles)	Antitumor activity, tumor regression	Female Balb c nu/nu mice, implantation of human tumor cell lines (L2987, MCF7)	Maximal antitumoral activity of D when administered i.v. 6-8mg/kg Q4dx3 or 8-10mg/kg q7dx2, maximum tolerable dose depends on application route and dose, with higher doses also higher lethality	Single injection of 12 mg/kg causes a lethality of 22%	--
(9)	**P, E, D, Pa**	No	i.v. P: Q1d: 8-12mg/kg, Q1dx5: 2,5-5 mg/kg E: Q1dx5 12,5 mg/kg D: Q1d 12-16 mg/kg, Q4dx3 7,5 mg/kg Pa: Q4dx3: 11, 22, 33mg/kg	See route of administration and dosage	Antitumoral activity	Female nude mice with BALB/c background, inoculation of mice with many different tumor cell lines (subcutaneous or intradermal)	Antitumoral activity dependent on substance and tumor, dose schedules are important!!	D: Q1d 16mg/kg 4/7 Mäusen dead P: Q1d, 1/7 Mäusen dead	Dosage of Pa is quite high?
(10)	**D**	No	i.v. D: 2x 8mg/kg, d10 and 17 0,2 ml/20g body weight	d10 & 17	Comparison to an albumin-bound prodrug, tumor development	Female NMRI nu/nu, subcutaneous implantation of MDA MB 435 tumor cells	Standard and maximum tolerated dose of doxorubicin 2x 8mg/kg in nude mice models!	Higher doses than 2x8mg/kg lead to unacceptable toxicity and mortality	---

(11)	**D, LD**	No	i.v., 2x 4,8,12 mg/kg	Q7dx2	Antitumoral activity	NMRI nu/nu, different solid human tumor xenografts i.e. renal RXF944	---	D at 12 mg/kg toxic, 5/7 mice dead, no toxic deaths at 8 mg/kg, but body weight loss of 8%	---
(12)	**D**	No	i.v., 6.5 mg/kg	d1,8,15	Plasma and doxorubicin levels after 1,4,24h i.v. injection	Male DD/S strain, SC115 subcutaneous injection	Higher tumor-associated drug level with LD, dose dependent decrease in the tumor growth rate	Maximum tolerable dose in a multiple dose therapy regimen is 6.5 mg/kg, resulted here in one toxic death. 13 mg/kg cause a 70% mortality rate	---
(13)	**Pa**	No	i.v. 2-20mg/kg	Single bolus injection	Pharmakokinetic parameters, plasma samples, testing of different vehicles for paclitaxel	Female FVB mice, 10-14 weeks	Pharmakokinetic parameters dependent on solvent, nonlinear pharmacokinetic parameters with Cremophor EL	Maximum dose that can be administered to mice by i.v. bolus injection is 20mg/kg, dictated by the acute lethal toxicity of the vehicle Cremophor EL	Formulations for Pa: - Cremophor EL + EtOH - Tween 80 + EtOH + NaCl - Dimethylacetamide
(14)	**Pa**	No	i.p., 13 mg/kg	5 times, intervals of 3 days, controls were treated with distilled water	Tumor development, immunohisto-chemical expression of CD31 and VEGF, real-time PCR	Female BALB c nude mice, 6-8 weeks old, human OSCC cell line	Pa showed an inhibitory effect on the growth of transplanted human OSCC and reduced the immunohistochemical expression of VEGF and CD31 and VEGF-RNA	--	Mice were killed 30 days after drug treatment
(15)	**Pa**	No	i.p. 4.5, 18, 36 mg/kg	d1,5,9	60-day cures	CDF femal mice, intraperitoneal implantation of P388 murine leukemia cells	Combination of Pa with Vinorelbine can improve survival	--	Highest nontoxic Pa dose was 36 mg/kg, 43% increase in live span
(16)	**P, E**	Single substances & combination of P and E	i.p. P: 2-5 mg/kg E: 10-30 mg/kg	Single treatment	Tumor volume, growth ratio	BALBc nu/nu mice, inoculation with SBC-1, SBC-3 and SBC-5 cells	Neither P nor E showed significant effects against any tumor, marked antitumoral effects were observed in the groups treated with 5mg/kg P and 30mg/kg E	5mg/kg P and 30 mg/kg E were considered to be the maximum acceptable doses in nude mice	--
(17)	**P**	No	i.p. P: 6mg/kg	d1,5,9	Tumor development	BALB c nu/nu mice, different human lung tumor xenografts	--	Weight loss, when P is combined with CPT-11, dose is 3 mg/kg!	With this dosage all mice in all the treatment groups survived during the experiments
(18)	**D, Pa**	Single substances & combination of D and Pa	i.v. D: 10mg/kg Pa: 25 mg/kg	--	Pharmakokinetic studies, investigation of serum and heart, lung, liver, kidneys and spleen	Male CDF1 mice	Much higher accumulation in the organs when D and Pa are combined	Higher incidence of cardiotoxicity when Pa and D are combined, pharmacokinetic interaction	D was injected just before Pa was injected
(19)	**D, Pa**	Single substances & combination of D and Pa	i.v. D: 6mg/kg Pa: 10mg/kg	Single treatment, determination of experiment after 24h	Pharmakokinetic studies, investigation of serum and heart, liver, kidneys and intestine	Female BALB/c mice, 8-10 weeks	Combined treatment has effects in drug levels in liver and intestine but not in kidney and heart	--	Interaction of D and Pa is due to both drugs being substrates for PGP and each drug serves as a competitive inhibitor, but there are controversial studies! Sequence dependency, D should be given before Pa
(20)	**D, Pa**	No	i.p. D and Pa: repeated administration 2 mg/kg single administration 15 mg/kg	d1-9	Effects in ko-mice, apoptosis analysis, tumor development	P53 -/- mice, C57Bl6	--	MTD for a single injection 10mg/kg D and 20mg/kg Pa	--
(21)	**E, P, D**	No	i.v. or i.p. E: 0.3-30 mg/kg P: 0.1-10 mg/kg	Single or repeated injection (for 10d)	Tumor development, toxicity	female CDF_1 mice, BDF_1 and CD-1 mice	--	LD50 in CDF_1 mice single injection E: 88 mg/kg D: 45 mg/kg P: 15 mg/kg	--

			D: 0.3-10 mg/kg					LD50 in CDF_1 mice repeated injection (for 10d) E: 14 mg/kg D: 9 mg/kg P: 3 mg/kg	
(22)	**Pa**	No	i.p. 10mg/kg	Single dose	Tumor growth delay, effect of protein deficient diet on therapeutic activity	Female swiss albino mice i.p. inoculated with Ehrlich ascites cells	Significant tumor reduction in normally-fed animals	24h after Pa administration there was a significant increase in serum LDH activity, after 72h the LDH return to nearly normal level	Pa treatment is known to open the L-type Ca channels and can cause cardiac damage and contraction failure. Blood samples after 24, 48 and 72h
(23)	**Pa, P**	Single substances & combination of Pa and P	Pa: i.v., 40mg/kg P: i.p., 10mg/kg	Different settings	Investigation of drug combinations and application interval, tumor growth, histology	Male C3Hf/mice,3-4 months old, transplantation of OCa-I	--	Sequence dependence of Pa and P! Pa and P as single agents cause no mortality, Pa caused no observable morbidity, P showed transient signs of toxicity with ruffling of the hair. Pa + P 2/47 mice dead, P + Pa 11/47 dead	Pa followed by P was more effective than P followed by Pa, maximum enhancement of cisplatin effectiveness was achieved by treatment with paclitaxel 48 earlier
(24)	**D, LD**	No	i.v. D: MTD 18 mg/kg LD: 55mg/kg	Single dose	Pharmakokinetic studies, tumor development	Female BDF-1 mice, subcutaneous Lewis Lung Carcinoma	--	Estimated maximum tolerable dose around 20mg/kg	--

Abbreviations: D: Doxorubicin, P: Cisplatin, E: Etoposide, Pa: Paclitaxel, i.p.: intraperitoneal, i.v.: intravenous, mg/kg/d: milligram per kilogram bodyweight per day, d: day, MTD: maximum tolerable dose

1. Fuchs J, Wenderoth M, von Schweinitz D, Haindl J, Leuschner I. Comparative activity of cisplatin, ifosfamide, doxorubicin, carboplatin, and etoposide in heterotransplanted hepatoblastoma. Cancer. 1998;83(11):2400-7. Epub 1998/12/05.
2. Hainsworth JD, Greco FA. Etoposide: twenty years later. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 1995;6(4):325-41. Epub 1995/04/01.
3. Suzuki M, Aida I, Sekiguchi I, Tamada T, Nishida M. Anticancer activity of the combination of cisplatin and etoposide in endometrial cancer-bearing nude mice. Gynecologic oncology. 1991;41(1):41-5. Epub 1991/04/01.
4. Budach W, Budach V, Stuschke M, Schmauder B, Reipke P, Scheulen ME. Efficacy of ifosfamide, dacarbazine, doxorubicin and cisplatin in human sarcoma xenografts. British journal of cancer. 1994;70(1):29-34. Epub 1994/07/01.
5. Kraus-Berthier L, Jan M, Guilbaud N, Naze M, Pierre A, Atassi G. Histology and sensitivity to anticancer drugs of two human non-small cell lung carcinomas implanted in the pleural cavity of nude mice. Clinical cancer research : an official journal of the American Association for Cancer Research. 2000;6(1):297-304. Epub 2000/02/03.
6. Nemati F, Livartowski A, De Cremoux P, Bourgeois Y, Arvelo F, Pouillart P, et al. Distinctive potentiating effects of cisplatin and/or ifosfamide combined with etoposide in human small cell lung carcinoma xenografts. Clinical cancer research : an official journal of the American Association for Cancer Research. 2000;6(5):2075-86. Epub 2000/05/18.
7. Fujimoto S, Chikazawa H. Schedule-dependent and -independent antitumor activity of paclitaxel-based combination chemotherapy against M-109 murine lung carcinoma in vivo. Japanese journal of cancer research : Gann. 1998;89(12):1343-51. Epub 1999/03/19.
8. Trail PA, Willner D, Lasch SJ, Henderson AJ, Greenfield RS, King D, et al. Antigen-specific activity of carcinoma-reactive BR64-doxorubicin conjugates evaluated in vitro and in human tumor xenograft models. Cancer research. 1992;52(20):5693-700. Epub 1992/10/15.
9. Sato Y, Kashimoto S, MacDonald JR, Nakano K. In vivo antitumour efficacy of MGI-114 (6-hydroxymethylacylfulvene, HMAF) in various human tumour xenograft models including several lung and gastric tumours. European journal of cancer. 2001;37(11):1419-28. Epub 2001/07/04.
10. Abu Ajaj K, Graeser R, Fichtner I, Kratz F. In vitro and in vivo study of an albumin-binding prodrug of doxorubicin that is cleaved by cathepsin B. Cancer chemotherapy and pharmacology. 2009;64(2):413-8. Epub 2009/02/21.
11. Kratz F, Roth T, Fichiner I, Schumacher P, Fiebig HH, Unger C. In vitro and in vivo efficacy of acid-sensitive transferrin and albumin doxorubicin conjugates in a human xenograft panel and in the MDA-MB-435 mamma carcinoma model. Journal of drug targeting. 2000;8(5):305-18. Epub 2001/05/01.
12. Mayer LD, Bally MB, Cullis PR, Wilson SL, Emerman JT. Comparison of free and liposome encapsulated doxorubicin tumor drug uptake and antitumor efficacy in the SC115 murine mammary tumor. Cancer letters. 1990;53(2-3):183-90. Epub 1990/09/01.
13. Sparreboom A, van Tellingen O, Nooijen WJ, Beijnen JH. Nonlinear pharmacokinetics of paclitaxel in mice results from the pharmaceutical vehicle Cremophor EL. Cancer research. 1996;56(9):2112-5. Epub 1996/05/01.

14. Myoung H, Hong SD, Kim YY, Hong SP, Kim MJ. Evaluation of the anti-tumor and anti-angiogenic effect of paclitaxel and thalidomide on the xenotransplanted oral squamous cell carcinoma. Cancer letters. 2001;163(2):191-200. Epub 2001/02/13.
15. Knick VC, Eberwein DJ, Miller CG. Vinorelbine tartrate and paclitaxel combinations: enhanced activity against in vivo P388 murine leukemia cells. Journal of the National Cancer Institute. 1995;87(14):1072-7. Epub 1995/07/19.
16. Kondo H, Kanzawa F, Nishio K, Saito S, Saijo N. In vitro and in vivo effects of cisplatin and etoposide in combination on small cell lung cancer cell lines. Japanese journal of cancer research : Gann. 1994;85(10):1050-6. Epub 1994/10/01.
17. Kudoh S, Takada M, Masuda N, Nakagawa K, Itoh K, Kusunoki Y, et al. Enhanced antitumor efficacy of a combination of CPT-11, a new derivative of camptothecin, and cisplatin against human lung tumor xenografts. Japanese journal of cancer research : Gann. 1993;84(2):203-7. Epub 1993/02/01.
18. Colombo T, Parisi I, Zucchetti M, Sessa C, Goldhirsch A, D'Incalci M. Pharmacokinetic interactions of paclitaxel, docetaxel and their vehicles with doxorubicin. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 1999;10(4):391-5. Epub 1999/06/17.
19. Gustafson DL, Merz AL, Long ME. Pharmacokinetics of combined doxorubicin and paclitaxel in mice. Cancer letters. 2005;220(2):161-9. Epub 2005/03/16.
20. Bearss DJ, Subler MA, Hundley JE, Troyer DA, Salinas RA, Windle JJ. Genetic determinants of response to chemotherapy in transgenic mouse mammary and salivary tumors. Oncogene. 2000;19(8):1114-22. Epub 2000/03/14.
21. Arakawa H, Iguchi T, Morita M, Yoshinari T, Kojiri K, Suda H, et al. Novel indolocarbazole compound 6-N-formylamino-12,13-dihydro-1,11-dihydroxy- 13-(beta-D-glucopyranosyl)-5H-indolo[2,3-a]pyrrolo-[3,4-c]carbazole- 5,7(6H)-dione (NB-506): its potent antitumor activities in mice. Cancer research. 1995;55(6):1316-20. Epub 1995/03/15.
22. Nassier OA. Protein Undernutrition in Tumor-Bearing Mice, Response and Toxicity to Paclitaxel. Int J Pharmacol. 2010;6(3):296-300.
23. Milross CG, Peters LJ, Hunter NR, Mason KA, Milas L. Sequence-dependent antitumor activity of paclitaxel (taxol) and cisplatin in vivo. International journal of cancer Journal international du cancer. 1995;62(5):599-604. Epub 1995/09/04.
24. Parr MJ, Masin D, Cullis PR, Bally MB. Accumulation of liposomal lipid and encapsulated doxorubicin in murine Lewis lung carcinoma: the lack of beneficial effects by coating liposomes with poly(ethylene glycol). The Journal of pharmacology and experimental therapeutics. 1997;280(3):1319-27. Epub 1997/03/01.