

**Pharmacogenomic and
Pharmacokinetic Assessment
of Liposome Encapsulated
SN-38 (LE-SN38) in
Advanced Cancer Patients**

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Irinotecan (CPT-11)

- **Topoisomerase I inhibitor**
- **Significant anticancer activity**
- **Prodrug hydrolyzed to active metabolite SN-38**
 - **Conversion rate ~3-12%**

SN-38

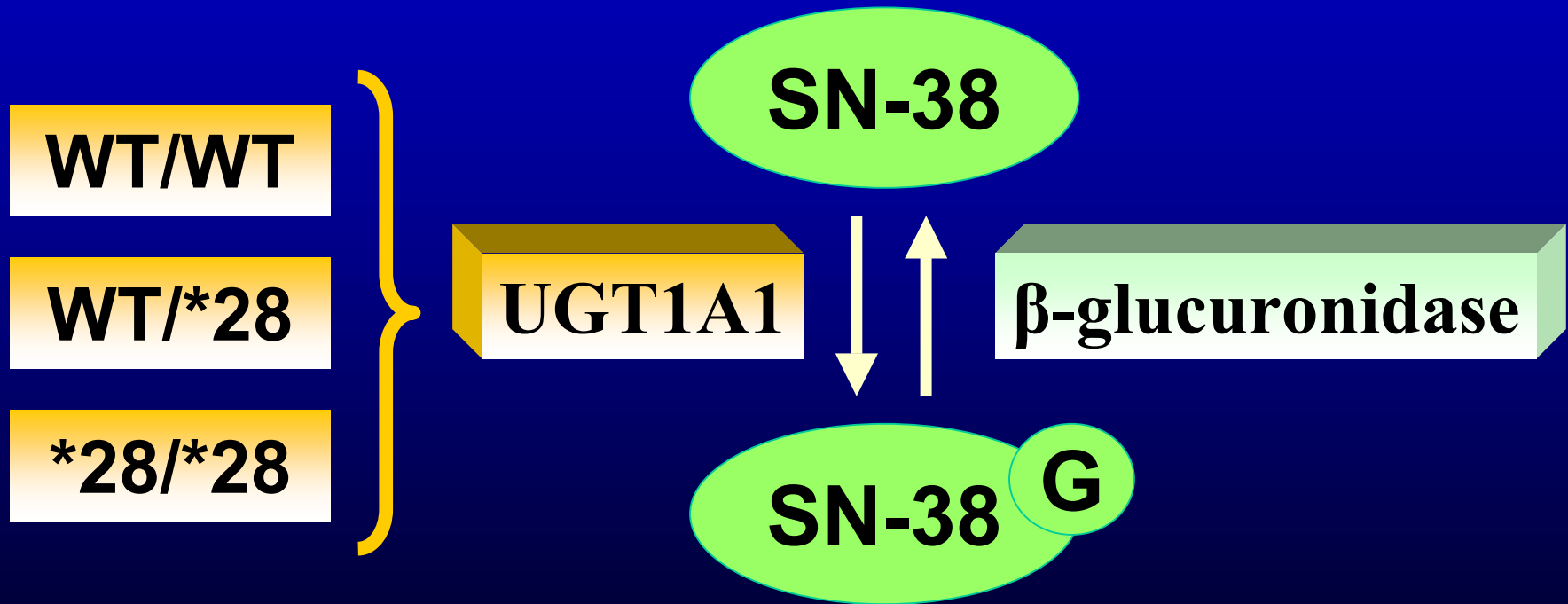
- *In vitro* ~250-1000x more cytotoxic than CPT-11 against tumor cell lines
- Poorly soluble
 - Delivery requires use of prodrug CPT-11

SN-38 Metabolism

- Metabolized to inactive SN-38G by hepatic enzyme UGT1A1
- Enzyme promoter polymorphisms
 - ↓ UGT1A1 expression
 - ↑ neutropenia and diarrhea after CPT-11 administration

UGT1A1 = uridine diphosphate glucuronosyltransferase
isoform 1A1

*UGT1A1**28 Variants Decrease SN-38 Glucuronidation



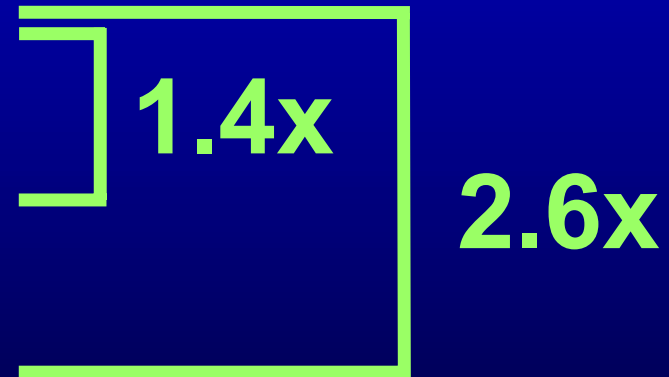
UGT1A1*28 Variants Increase SN-38 AUC

Average SN-38 AUC after 300 mg/m² CPT-11:

WT/WT: 205.13 ng·hr/mL

WT/*28: 288.61 ng·hr/mL

***28/*28: 531.37 ng·hr/mL**



LE-SN38

- **Novel liposomal formulation**
 - **Overcomes poor solubility of SN-38**
- **Drug entrapment >95%**
- **Broader antitumor activity than CPT-11 in preclinical models**

Phase I Study of LE-SN38 in Advanced Cancer Patients

- **Pharmacogenomics**
- **Pharmacokinetics**
- **Safety**
- **Antitumor activity**

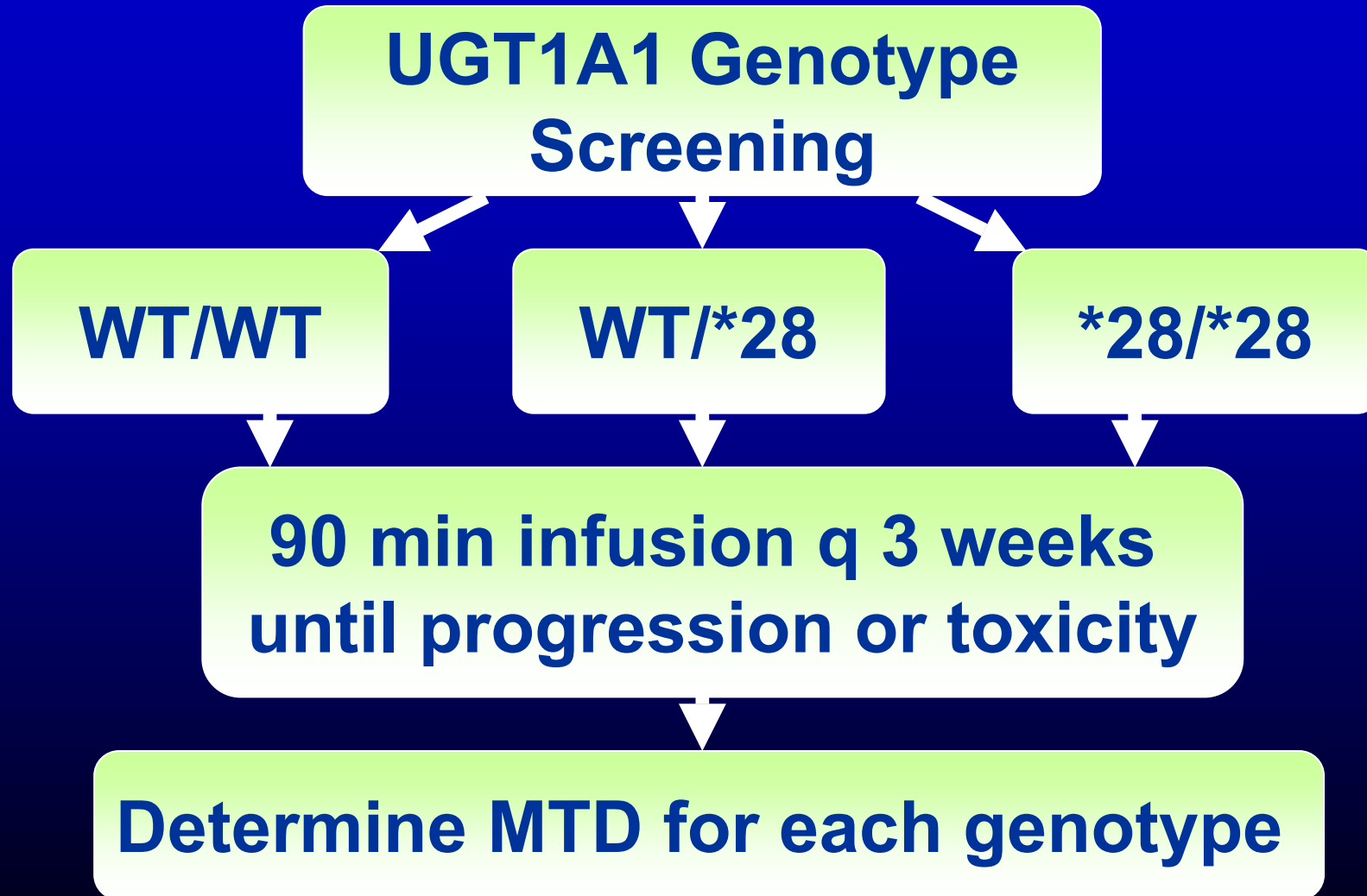
Inclusion Criteria

- Patients with advanced solid tumors
- ECOG PS 0-2
- Laboratory values:
 - $ANC \geq 1,500/mm^3$
 - $Platelets \geq 100,000/mm^3$
 - $Hgb \geq 9 \text{ g/dL}$
 - $Creatinine \leq 2.0 \text{ mg/dL}$
 - $Bilirubin \leq 2.0 \text{ mg/dL}$
 - $ALT \text{ and } AST \leq 1.5x \text{ ULN}$

Exclusion Criteria

- **Known CNS metastasis**
- **On agents interfering with SN-38 metabolism**
- **Known HIV infection**
- **Pregnant or nursing**

LE-SN38 Phase I Study Design



Dose-limiting Toxicity

- Neutropenia Gr 4 for ≥ 3 days, Gr 3 + fever
- Thrombocytopenia Gr 4, Gr 3 for ≥ 7 days
- Diarrhea Gr ≥ 3 for ≥ 24 hours despite treatment
- Nausea/vomiting Gr ≥ 3 for ≥ 24 hours despite treatment
- Hepatic transaminase Gr 4, Gr 3 for ≥ 7 days
- Infusion-related reaction Gr ≥ 3 , Gr 2 + bronchospasm

Dose Escalation Plan

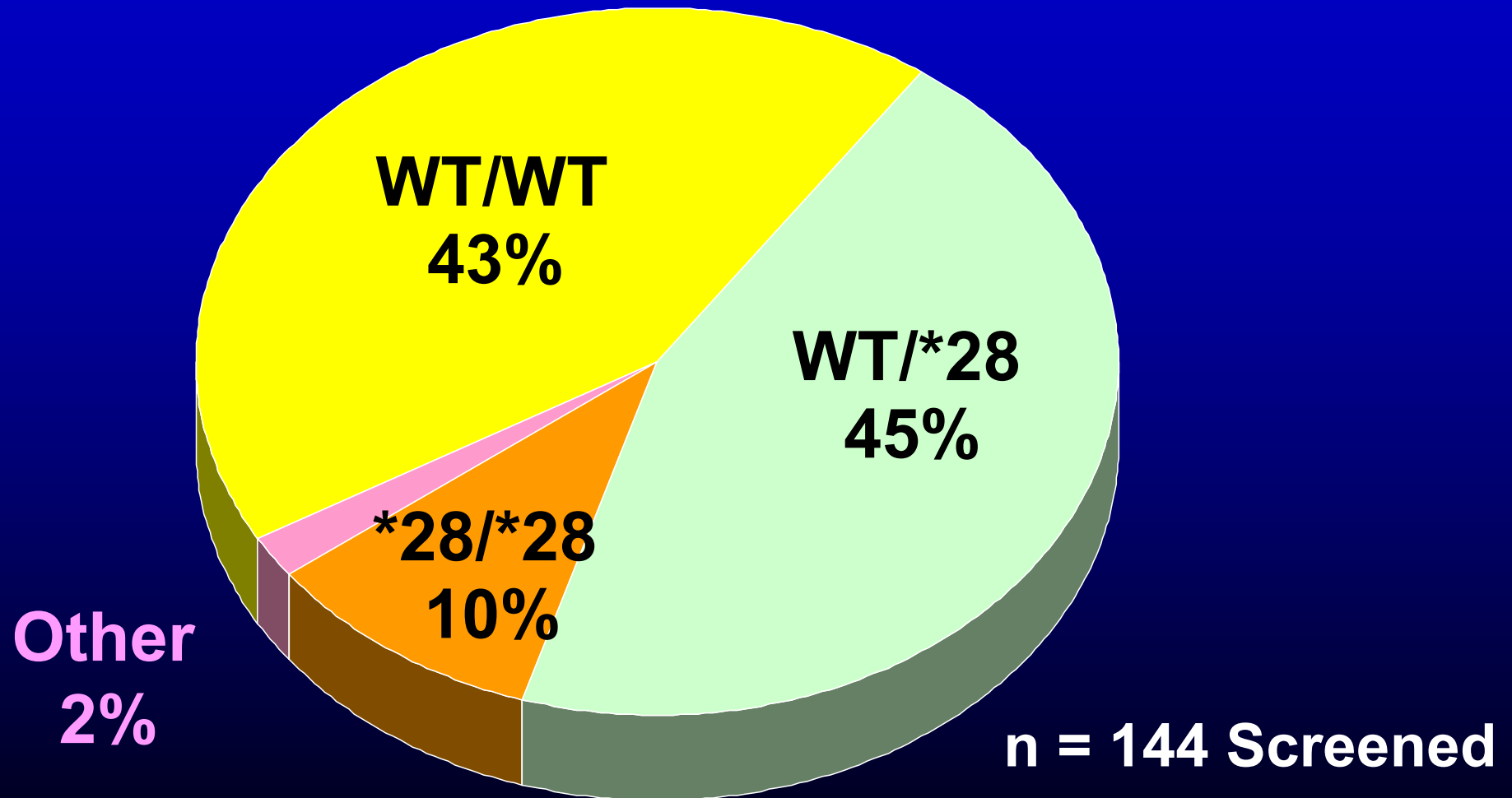
Current dose:

*28/*28 

WT/WT 
WT/*28

Dose (mg/m ²)	Increment (%)
2.5	---
5	100
10	100
20	100
30	50
40	33
50	25
62.5	25
75	20
90	20

UGT1A1 Genotyping Results



Patient Characteristics

(n=56)

		WT/WT	WT/*28	*28/*28
Enrolled		28	25	3
Gender	Male	13	12	1
	Female	15	13	2
Age	Median	60.5	62	45
	Range	40-75	40-84	40-73
ECOG PS	0-1	25	22	3
	2	3	2	--
Prior Chemos	0-3	18	16	2
	≥4	9	8	1

Primary Tumor Type

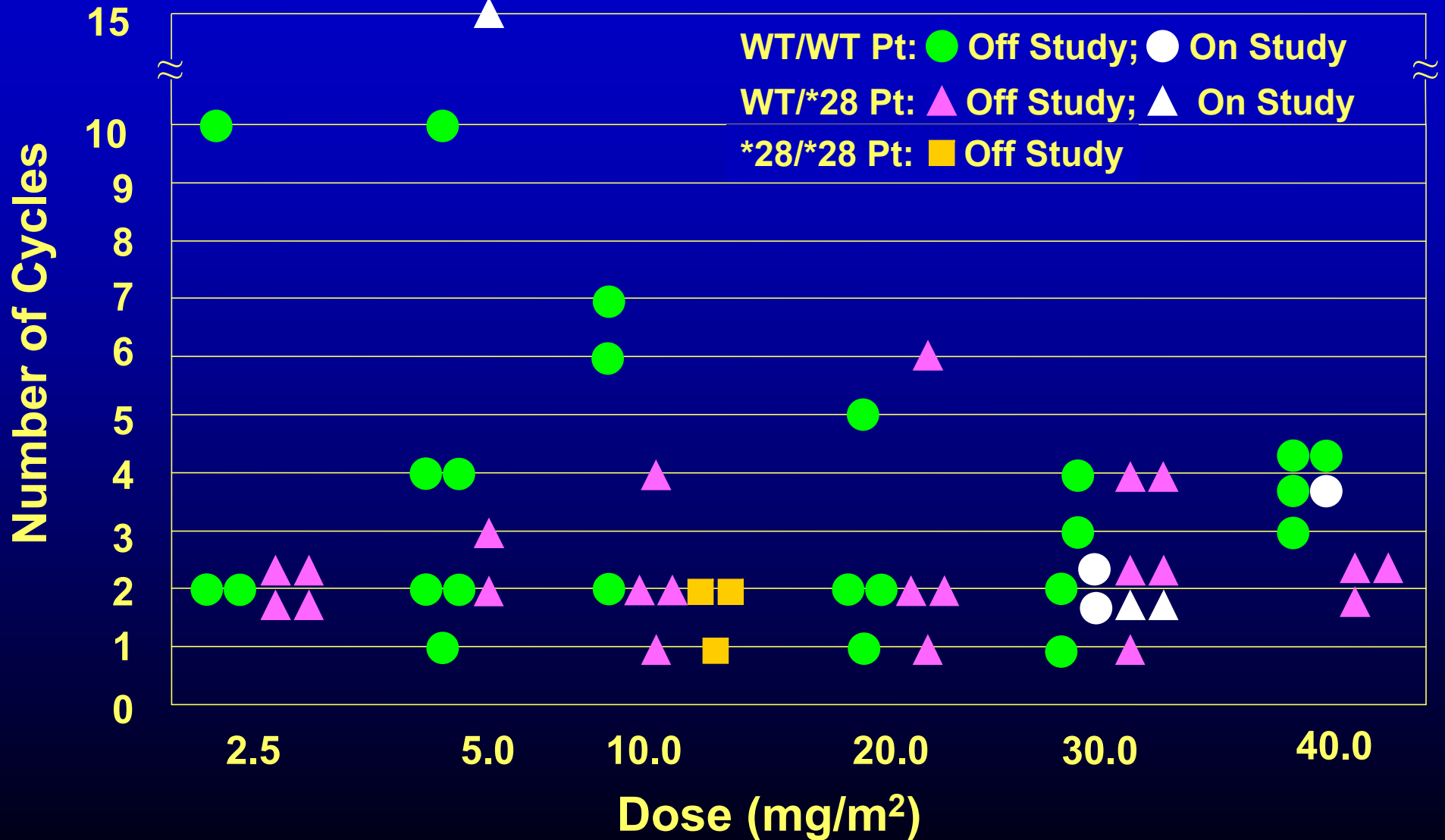
Tumor Type	Number of Patients			
	WT/WT	WT/*28	*28/*28	Total
Colorectal	10	3	--	13
Lung	4	6	--	10
Breast	4	2	1	7
Pancreatic	2	1	--	3
Thyroid	2	1	--	3
Melanoma	--	3	--	3
Other	6	9	2	17

DLTs by Dose Level

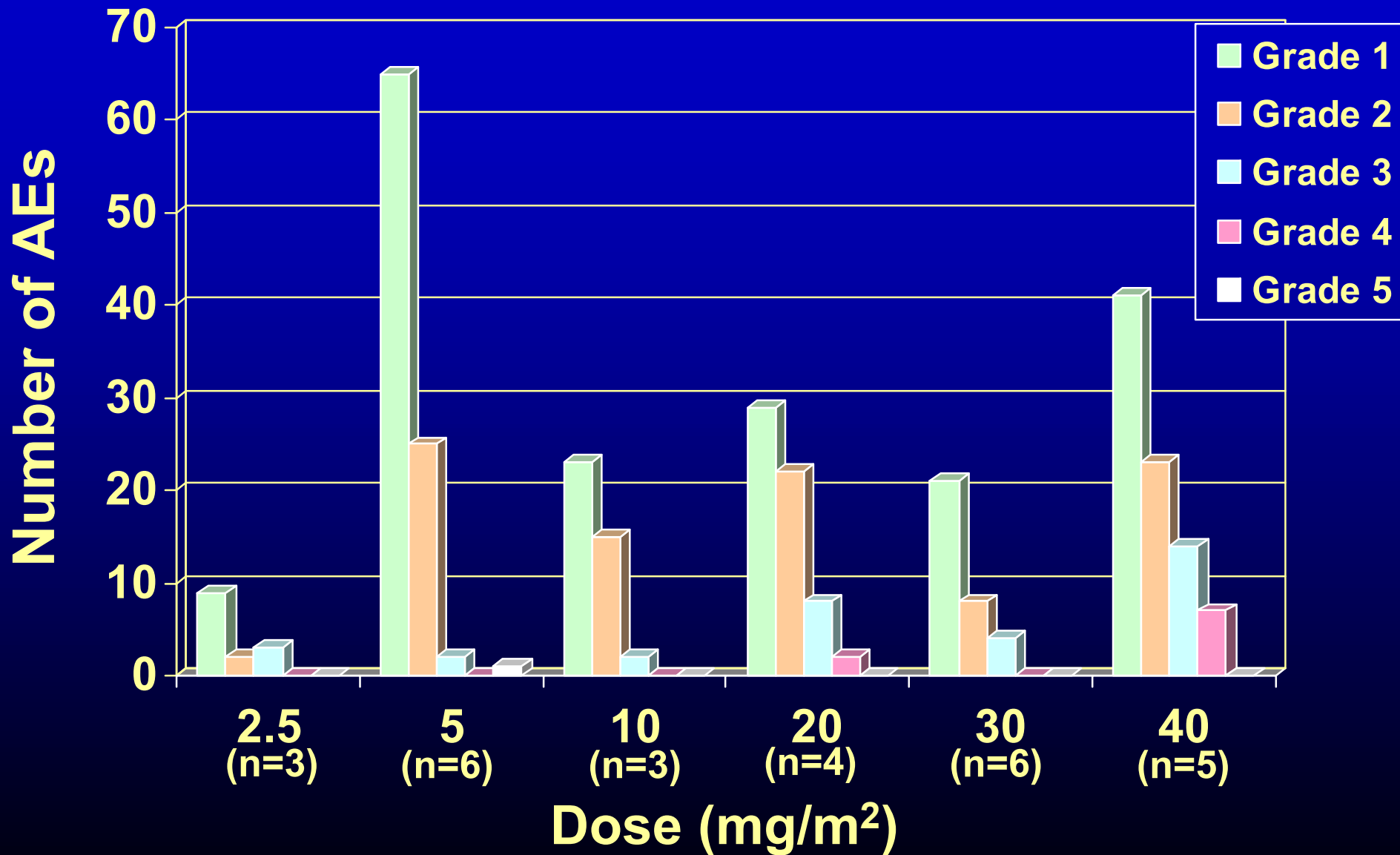
Dose (mg/m ²)	DLTs / No. of Pts	
	WT/WT	WT/*28
2.5	0/3	0/4
5	1/6	0/6
10	0/3	0/4
20	0/3	0/4
30	0/6	0/6
40	*2/5	0/3

***One patient with a DLT had received 9 prior regimens**

Duration of Treatment



All Adverse Events WT/WT Patients

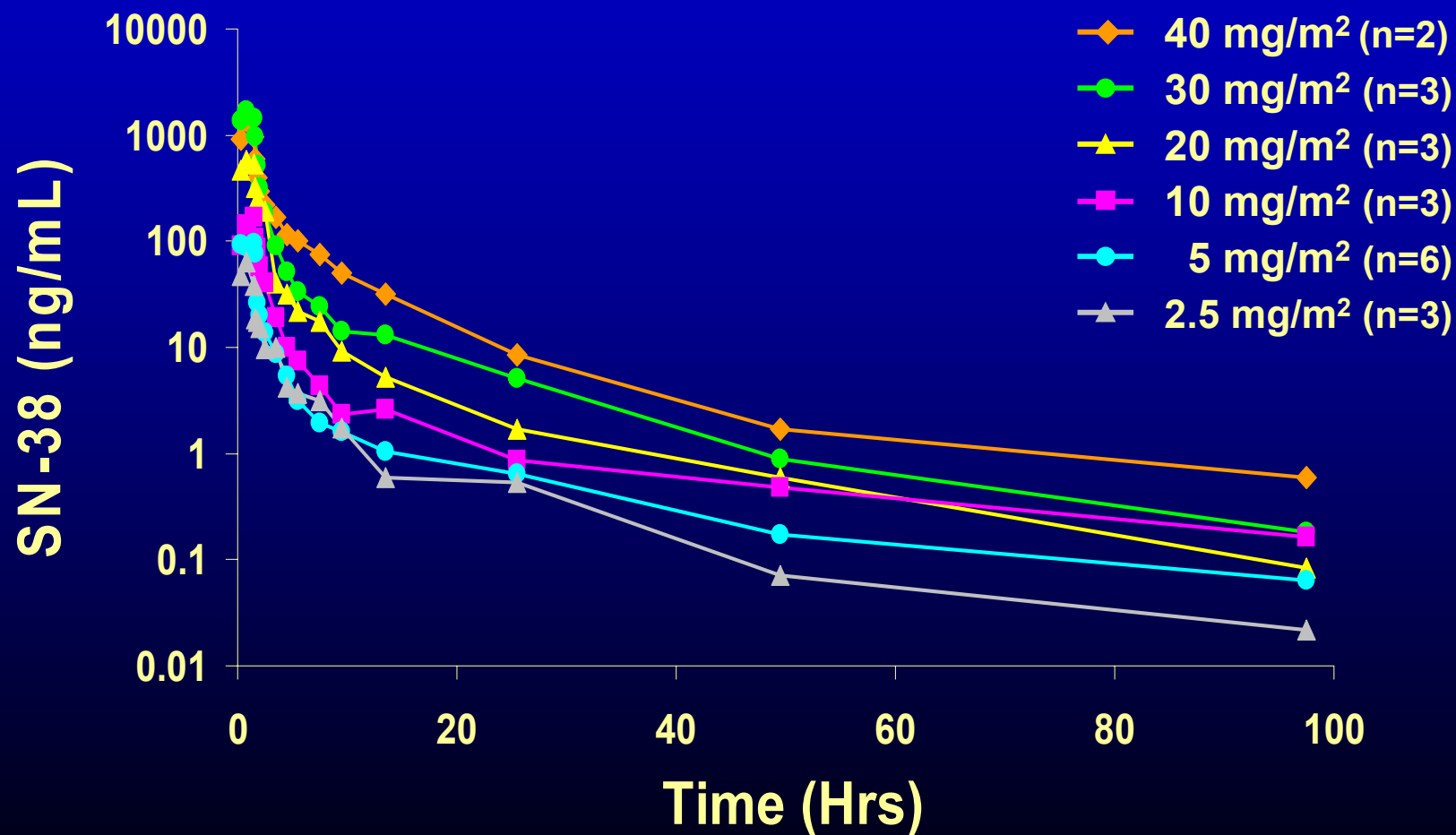


Most Frequent AEs Regardless of Attribution

Adverse Event	Number of Patients			
	WT/WT n=28	WT/*28 n=25	*28/*28 n=3	Total (%) n=56
Fatigue	14	15	3	32 (57%)
Anorexia	13	12	2	27 (48%)
Nausea	13	12	2	27 (48%)
Diarrhea	16	5	1	22 (39%)
Vomiting	11	8	1	20 (36%)
Constipation	6	8	2	16 (29%)
Dyspnea	7	7	1	15 (27%)
Cough	9	2	1	12 (21%)
Insomnia	6	5	1	12 (21%)
Alopecia	7	3	1	11 (20%)
Pyrexia	6	5	0	11 (20%)

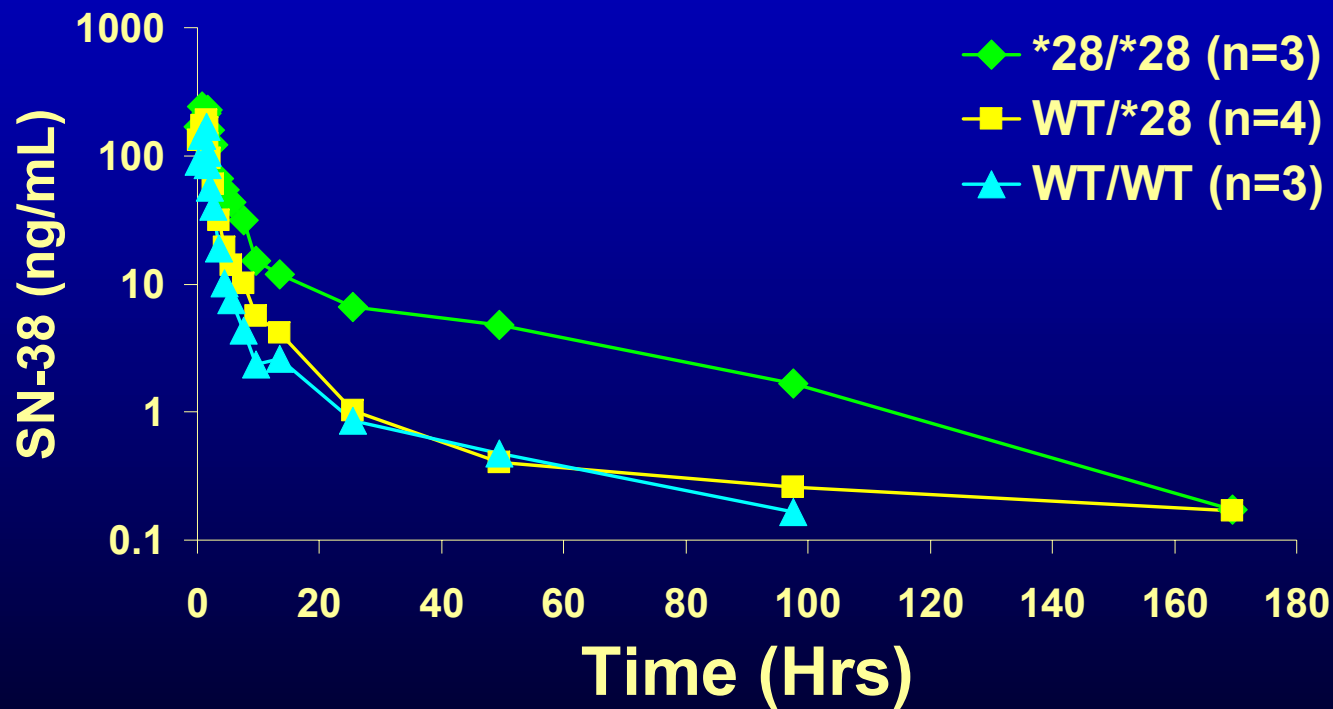
SN-38 Plasma PK - WT/WT Pts

2.5 to 40 mg/m² LE-SN38



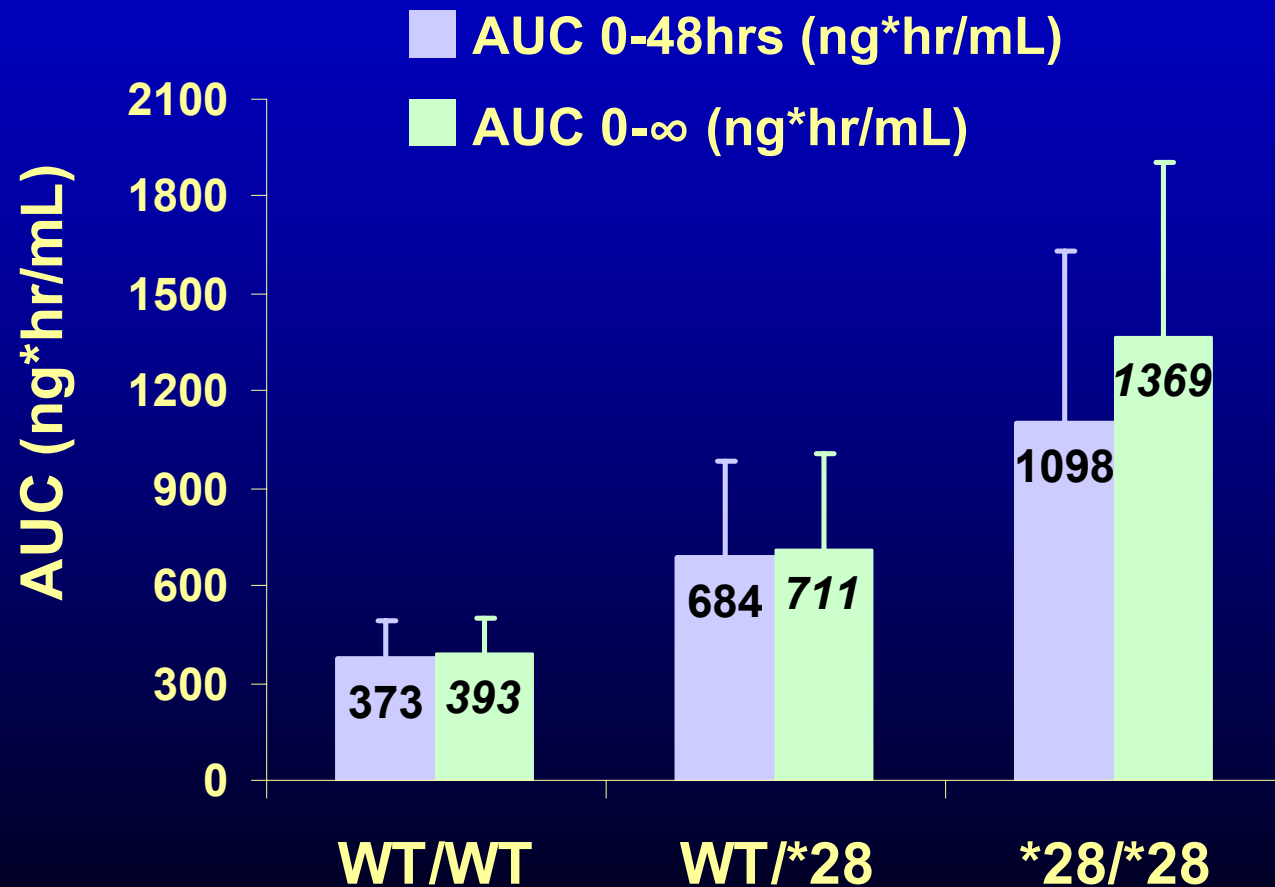
SN-38 Plasma PK By Genotype

10 mg/m² LE-SN38



SN-38 Plasma AUC By Genotype

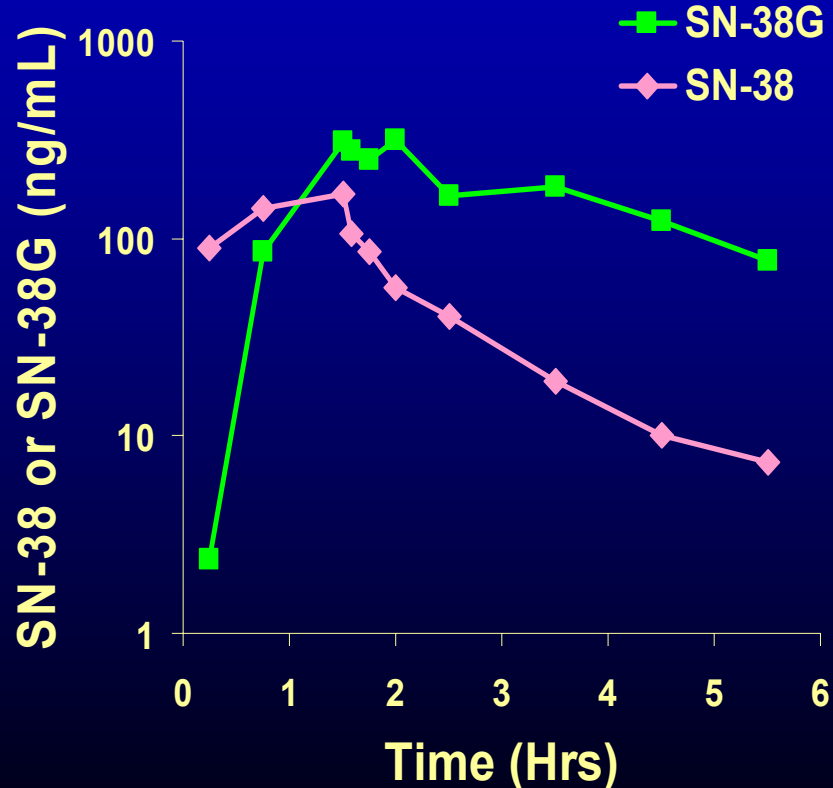
10 mg/m² LE-SN38



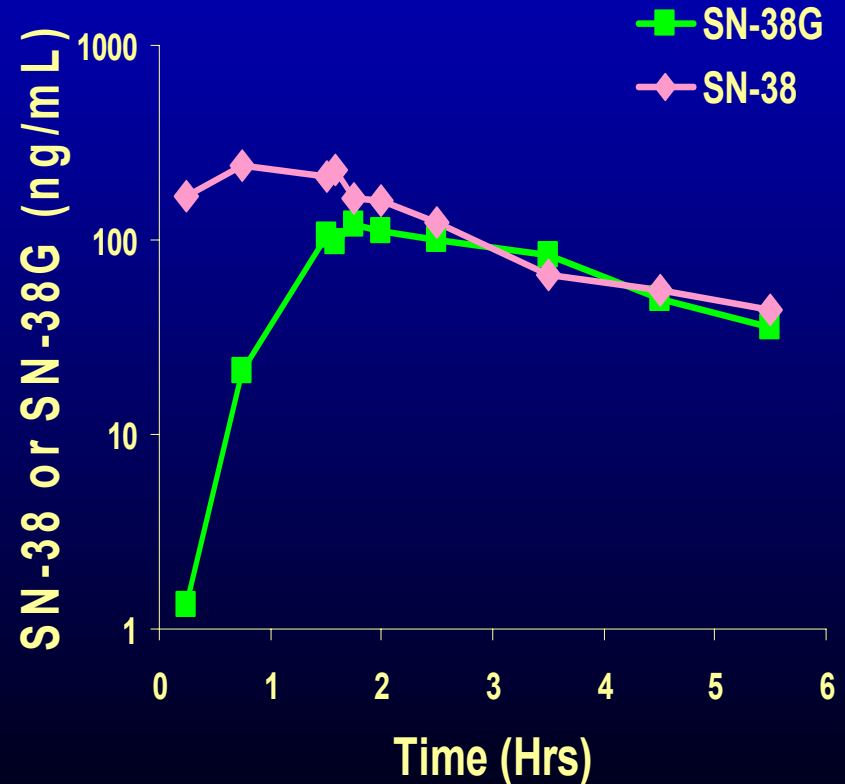
SN-38 & SN-38G Plasma PK

10.0 mg/m² LE-SN38

WT/WT Patients
(n=3)



*28/*28 Patients
(n=3)



LE-SN38 Summary

- Multiple cycles safely administered with >35% of patients receiving >2 cycles
- Dose-limiting toxicity of neutropenia
- No severe diarrhea observed
- SN-38 AUC in WT/WT < WT/*28 < *28/*28
- PK profile of SN-38 and SN-38G altered in *28/*28 patients
- No apparent PK/PD safety correlation for WT/WT and WT/*28 patients to date

Next Steps

- **Dose escalation continues in patients with ≤ 3 prior chemotherapy regimens**
- **Phase II planning underway**
 - **SCLC (NCCTG)**
 - **NSCLC (NeoPharm)**
 - **CRC (CALGB)**

Participants

- **Study Centers**
 - **Ohio State University, Columbus, OH**
 - **H. Lee Moffitt Cancer Center, Tampa, FL**
 - **Karmanos Cancer Institute, Detroit, MI**
- **PK Collaborator**
 - **Cognigen Corp., Buffalo, NY**
- **Pharmaceutical Sponsor**
 - **NeoPharm, Inc., Lake Forest, IL**