JX-594, a Tumour-selective, GMCSF-Armed Oncolytic Poxvirus

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CGE
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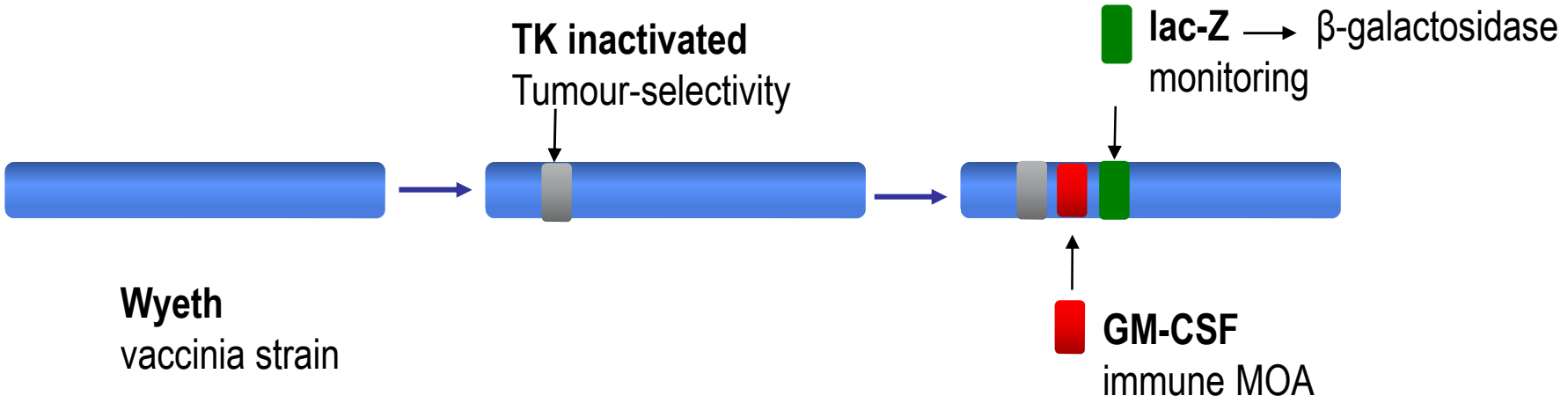
Transgene's Clinical Products as of September 2011: immunotherapeutics against cancer and infectious diseases

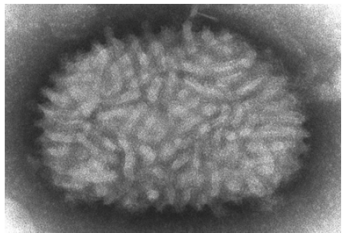
PRODUCT	INDICATION	PRE-CLINICAL	PHASE I	PHASE II	LATE STAGE CLINICAL TRIALS	PARTNERSHIP STRATEGY	CURRENT STATUS & NEXT MILESTONES
TG4010 (MVA-MUC1-IL2)	Non Small Cell Lung Cancer ("NSCLC")					NOVARTIS	Phase IIb/III in NSCLC to start **Q4 2011**
JX594/TG6006	Hepatocarcinoma ("HCC") and Other Solid Tumors					JENNEREX BIOTHERAPEUTICS	Phase IIb in HCC started **Q4 2011** and Phase I/II to start in CRC **Q4 2011**
TG4001 (MVA –HPV-IL2)	Pre-cancerous Lesions of the Cervix Caused by HPV					New co-development partnership contingent on Phase IIb results	Phase IIb Interim Data **Q1 2012**
TG4040 (MVA-HCV)	Chronic Hepatitis C ("HCV")					New co-development partnership contingent on Phase II results	Phase II Interim Data **Q4 2011**

Oncolytic viruses in advanced stage of clinical development

Company	BioVex	Oncolytics Biotech Inc	JennerEx Biotherapeutics
Product	OncoVex^{GMCSF}	Reolysin®	JX-594
Virus/Payload	Herpes simplex virus/human GMCSF	Respiratory Enteric Orphan virus	Vaccinla virus/human GMCSF
Mode of administration	IT only	IT/IV	IT/IV
Lead indications	Melanoma and head & neck cancer	Head & neck cancer	HCC, colorectal cancer

JX-594 design: tumour–selective & GMCSF-armed vaccinia



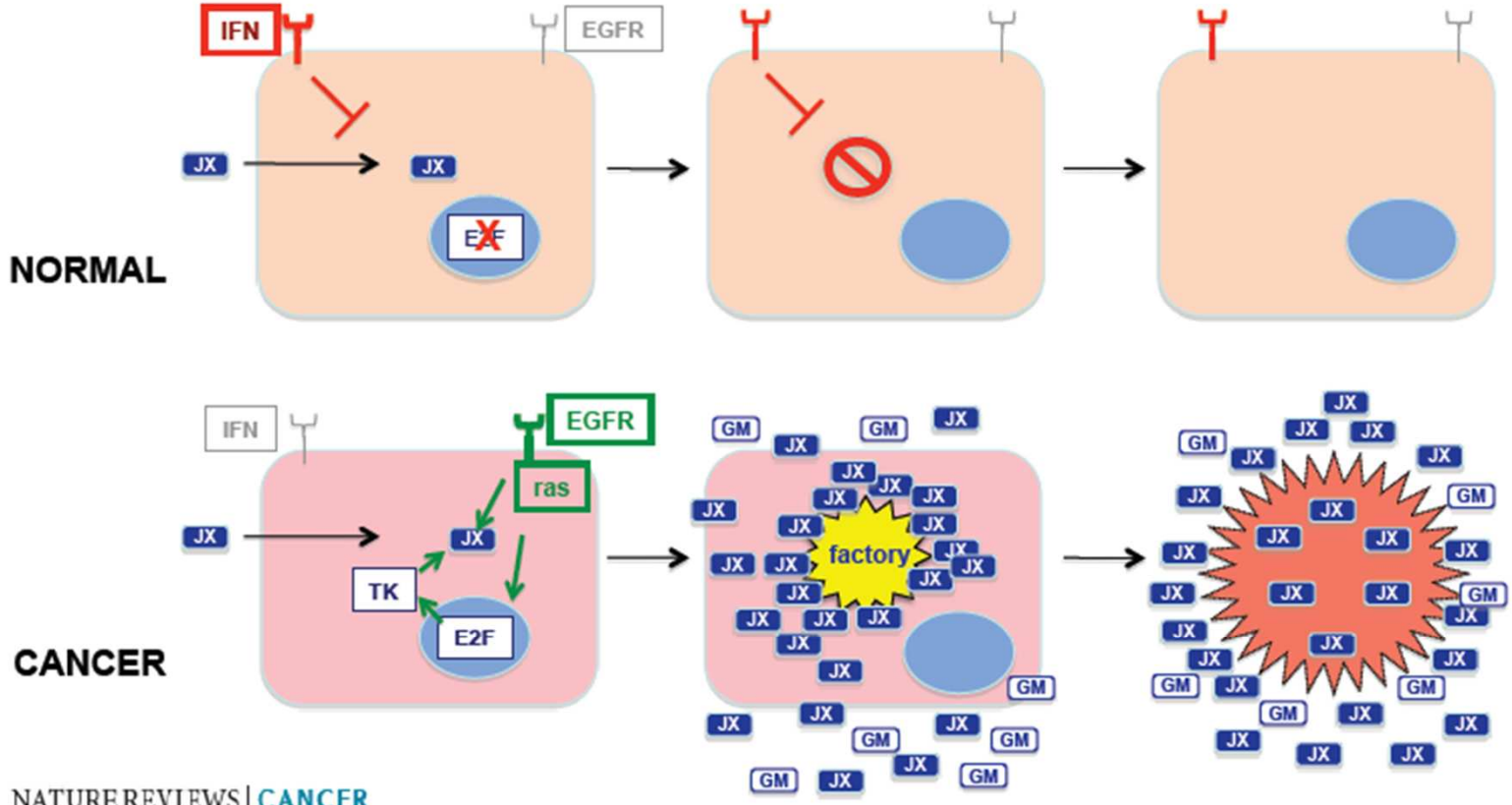


Selective activation:
cancer cells

Transgene expression:
therapeutic relevance

- IV stability & systemic delivery
- Large transgene-hosting capacity

JX-594 oncolytic virus: tumour cell–selective replication and destruction driven by high TK content



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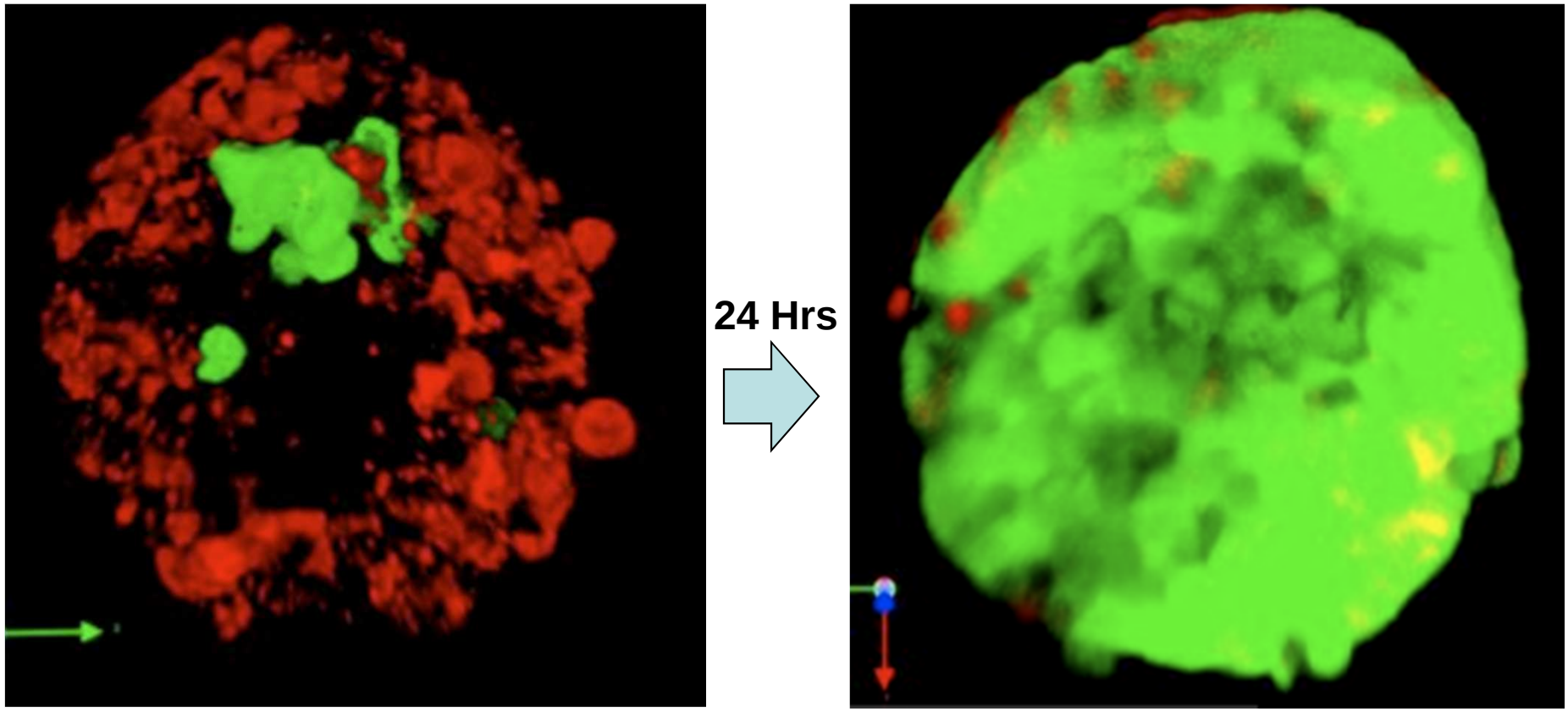
David H. Kirn and Steve H. Thorne

JENNEREX BIOTHERAPEUTICS

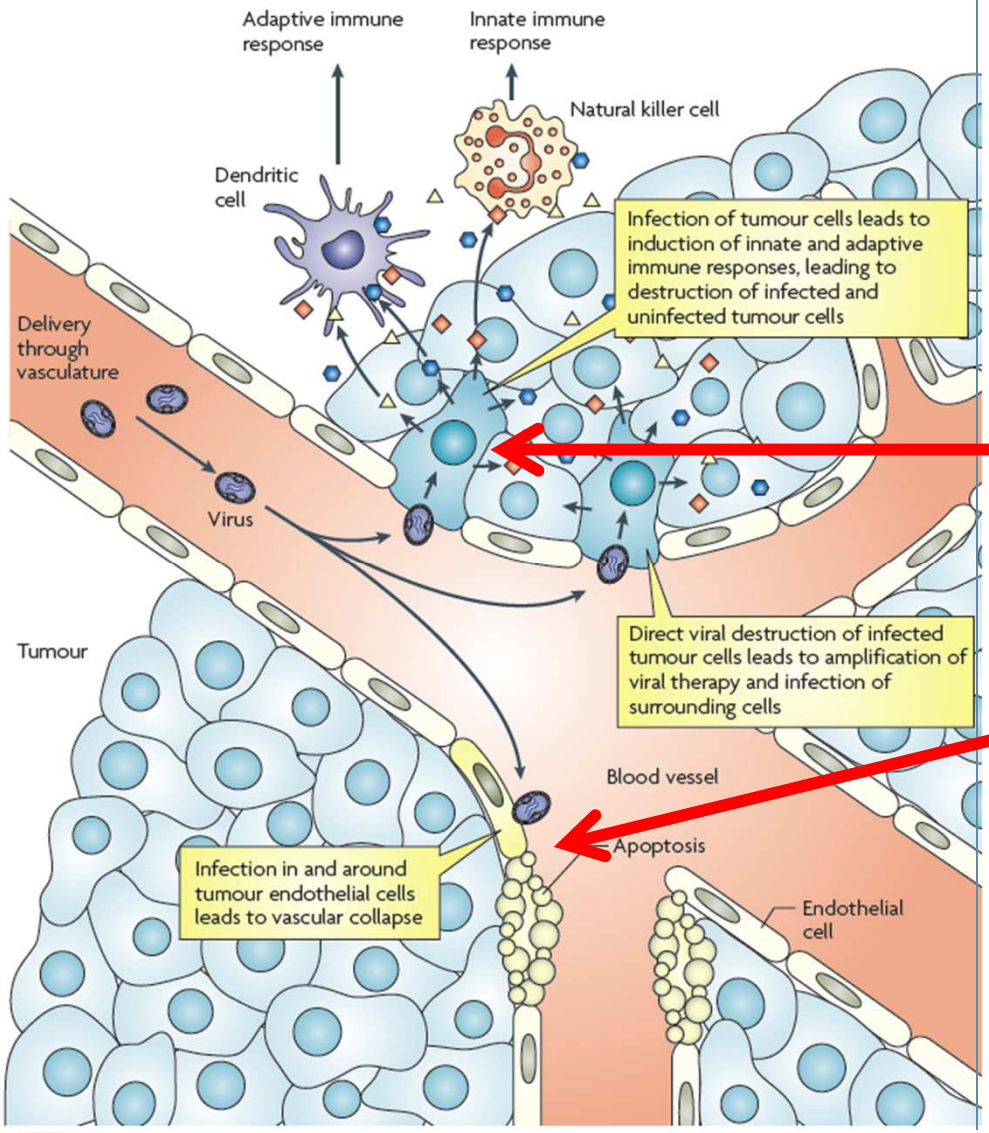
JX-594 activity: Amplification, spread, cell killing within human tumours

3D human tumour spheroid in red, JX594 in *green*



Stanford Bio-Imaging Center by Thorne S

JX-594 three-pronged mechanism of action (MOA)



1. ***Oncolysis***

   Cancer cell infection & lysis

2. ***Immune response stimulation***

   Invasion of cancer-targeted cytotoxic T-cells and production of antibodies

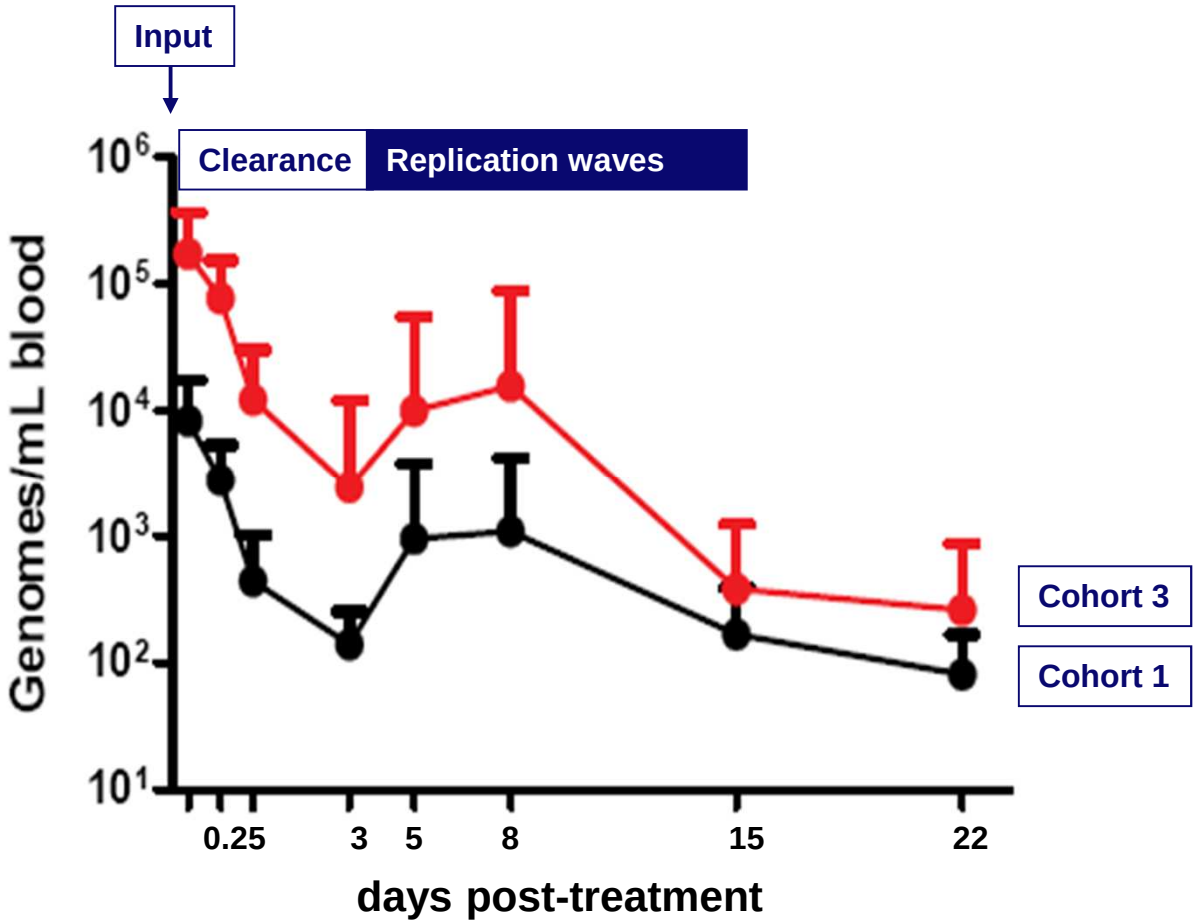
   Production of immune-stimulatory GMCSF

3. ***Tumour vascular shutdown***

   Within as little as five days after treatment

Kirn DH, et al. *Nature Reviews, Cancer.* 2009

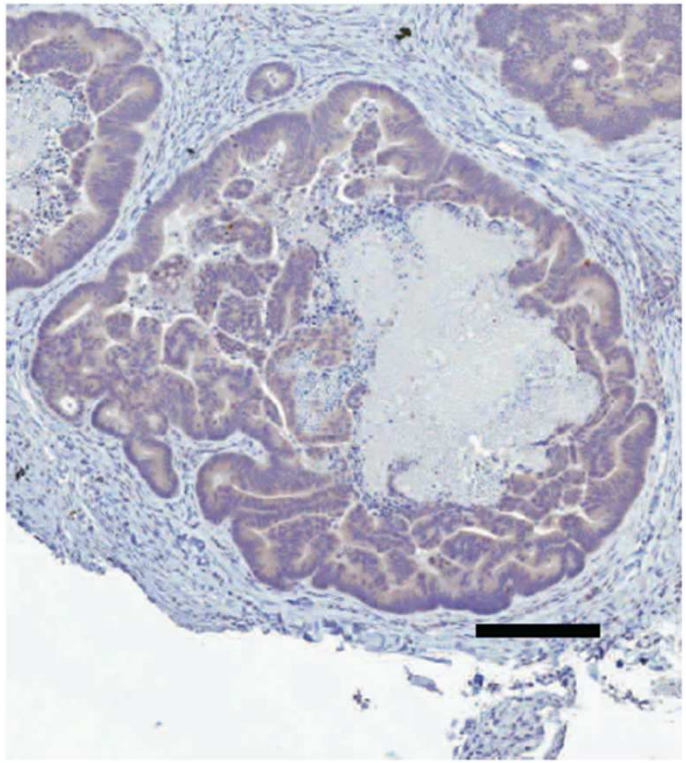
Pharmacokinetics: unique replication-dependent PK



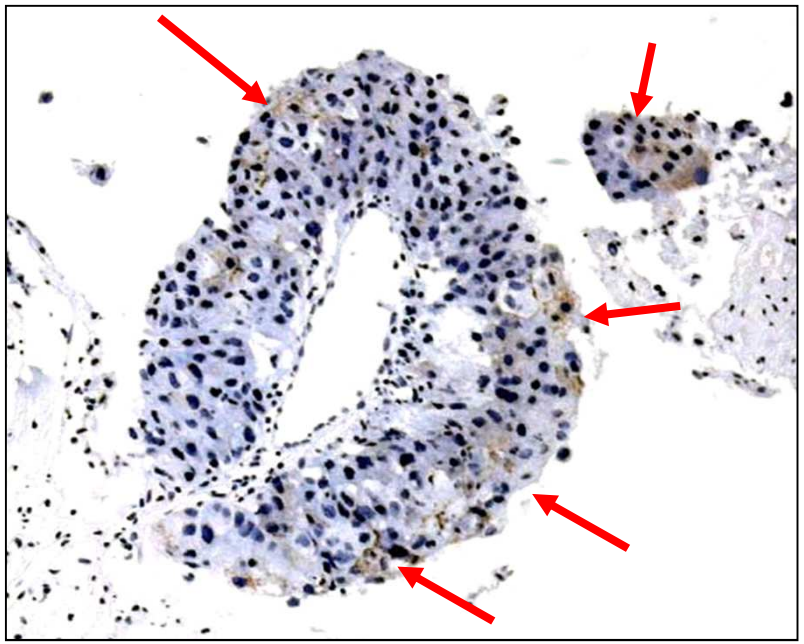
Lancet Oncol 2008; 9: 533–42

Systemic JX-594 delivery to tumours after IV and IT injection

IV injection

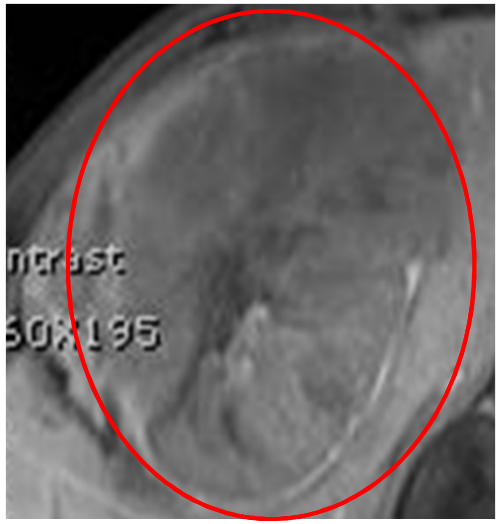


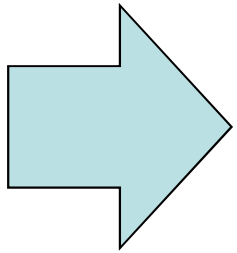
IV spread post-IT injection

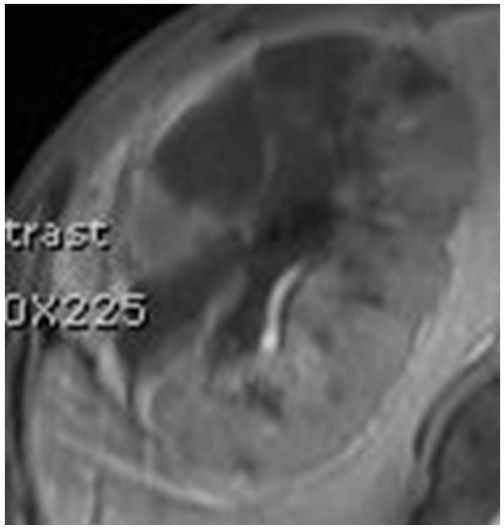


Phase 2/HCC: tumour destruction with JX-594: Acute vascular disruption & shutdown

Pt. 1703





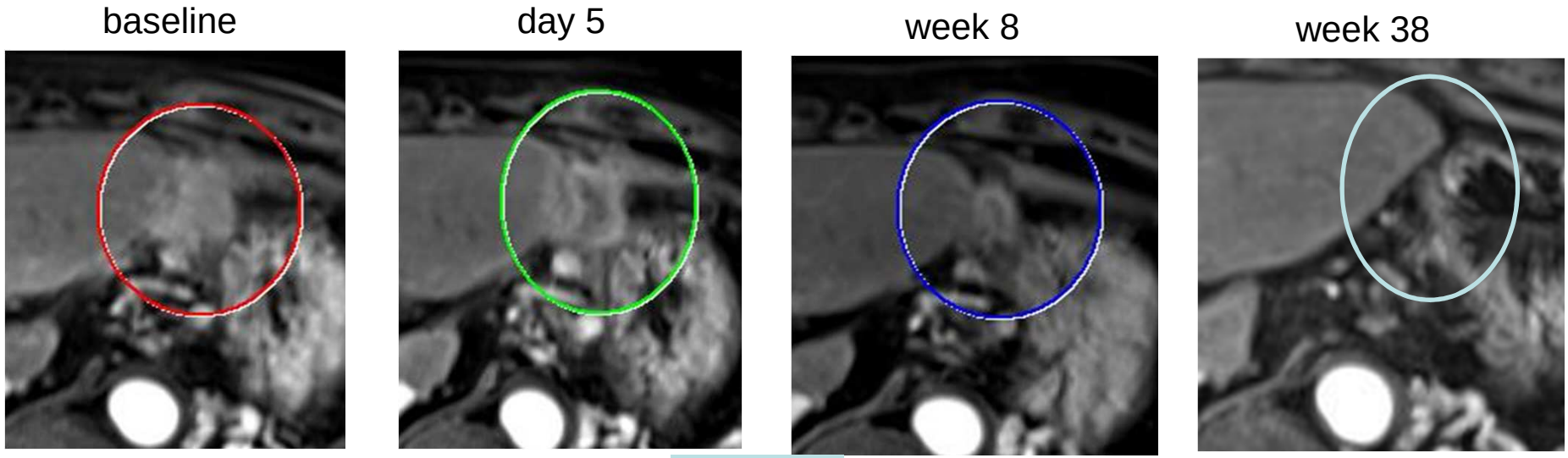


10 cm
massive tumour
highly vascular

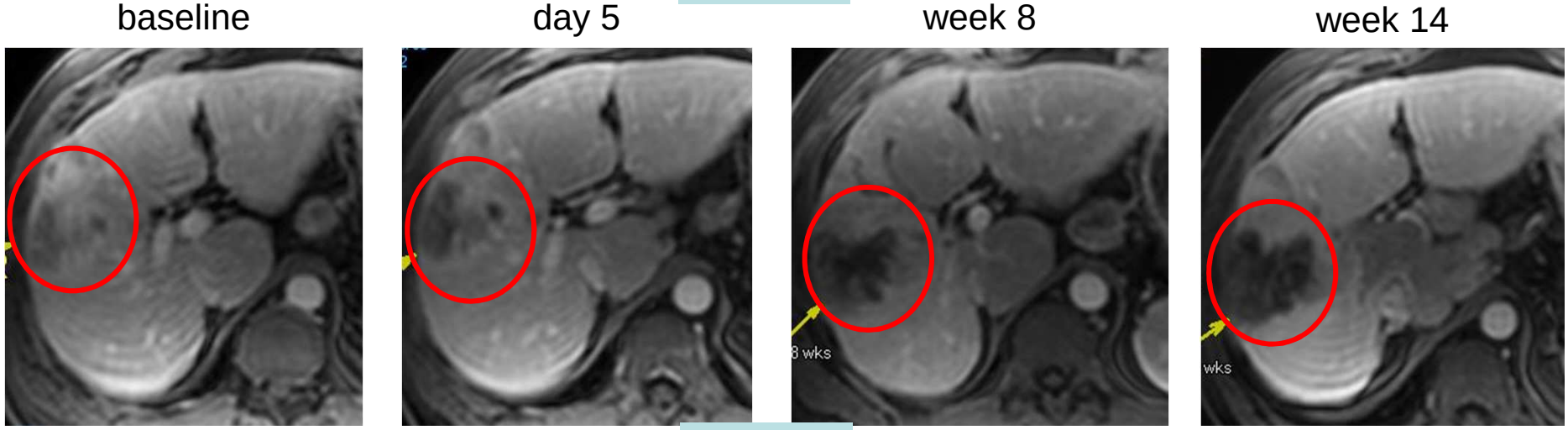
Acute response
diffuse vascular disruption
tumour-specific

50% necrosis
on day 5

Phase 2/HCC IT-injected tumours: RECIST and Choi responses

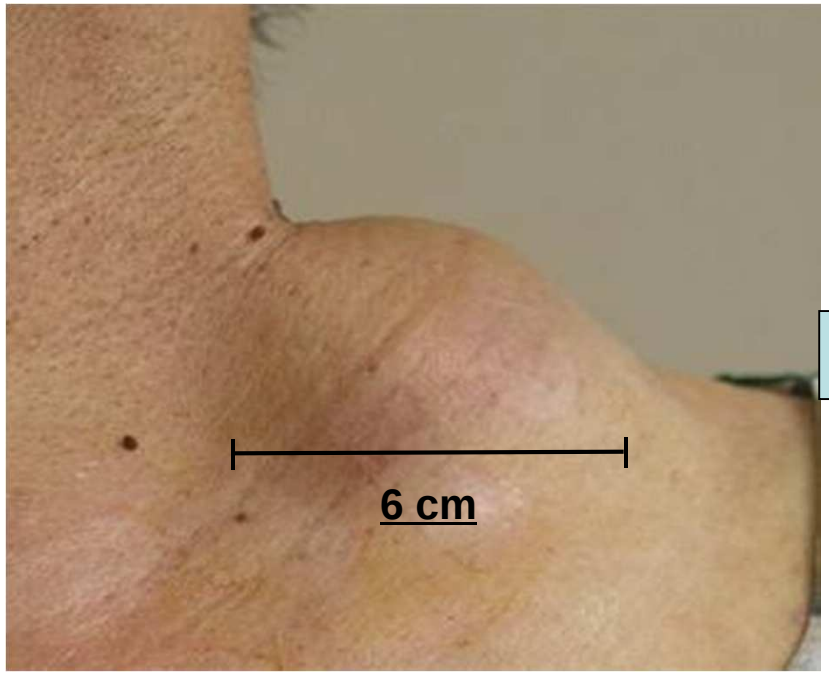


Patient 1715



Patient 1401

Case report following IT JX-594 therapy:
Liver cancer metastasis complete response

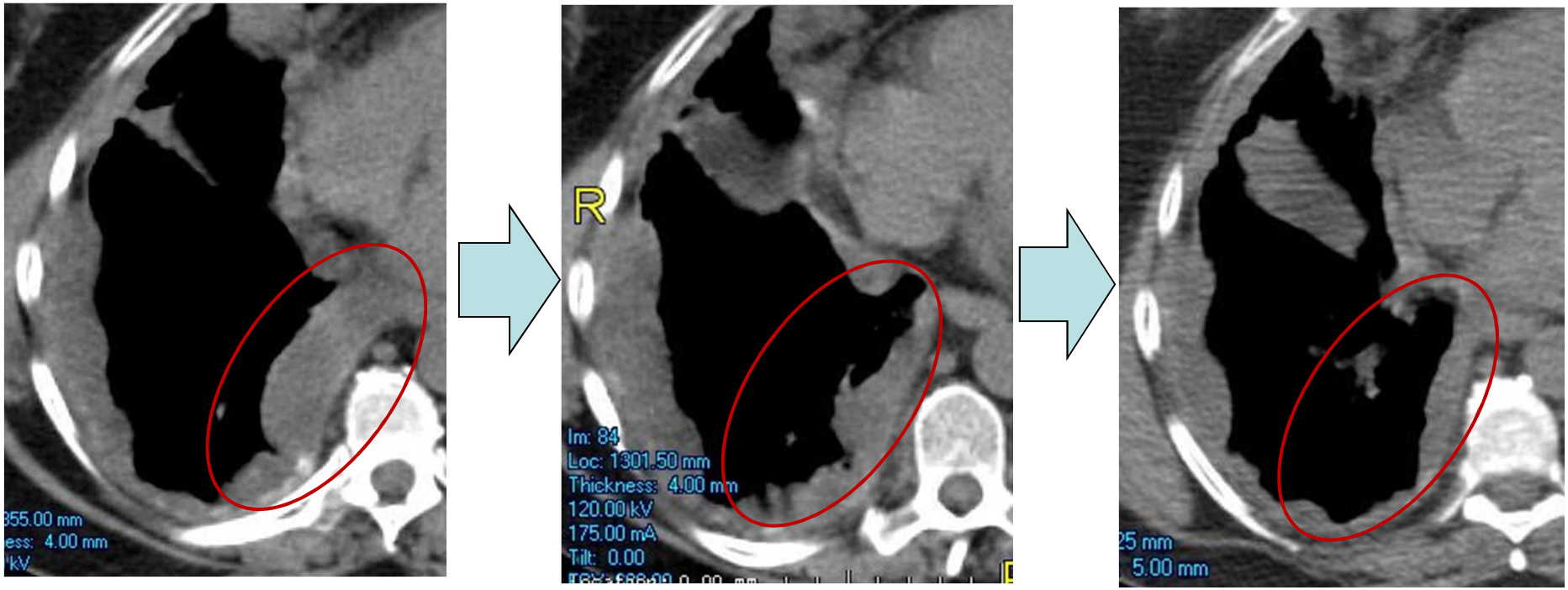


- **Failed 5 prior therapies**
- **Rapidly growing tumour**
- **Severe neck pain**
- **Lack of neck mobility**
- **Severe weight loss**

- **Cancer-free ~ 1 year later**
- **Pain gone**
- **Normal mobility regained**
- **10 kg weight gain**

Case report following IV JX-594 therapy

Mesothelioma partial response

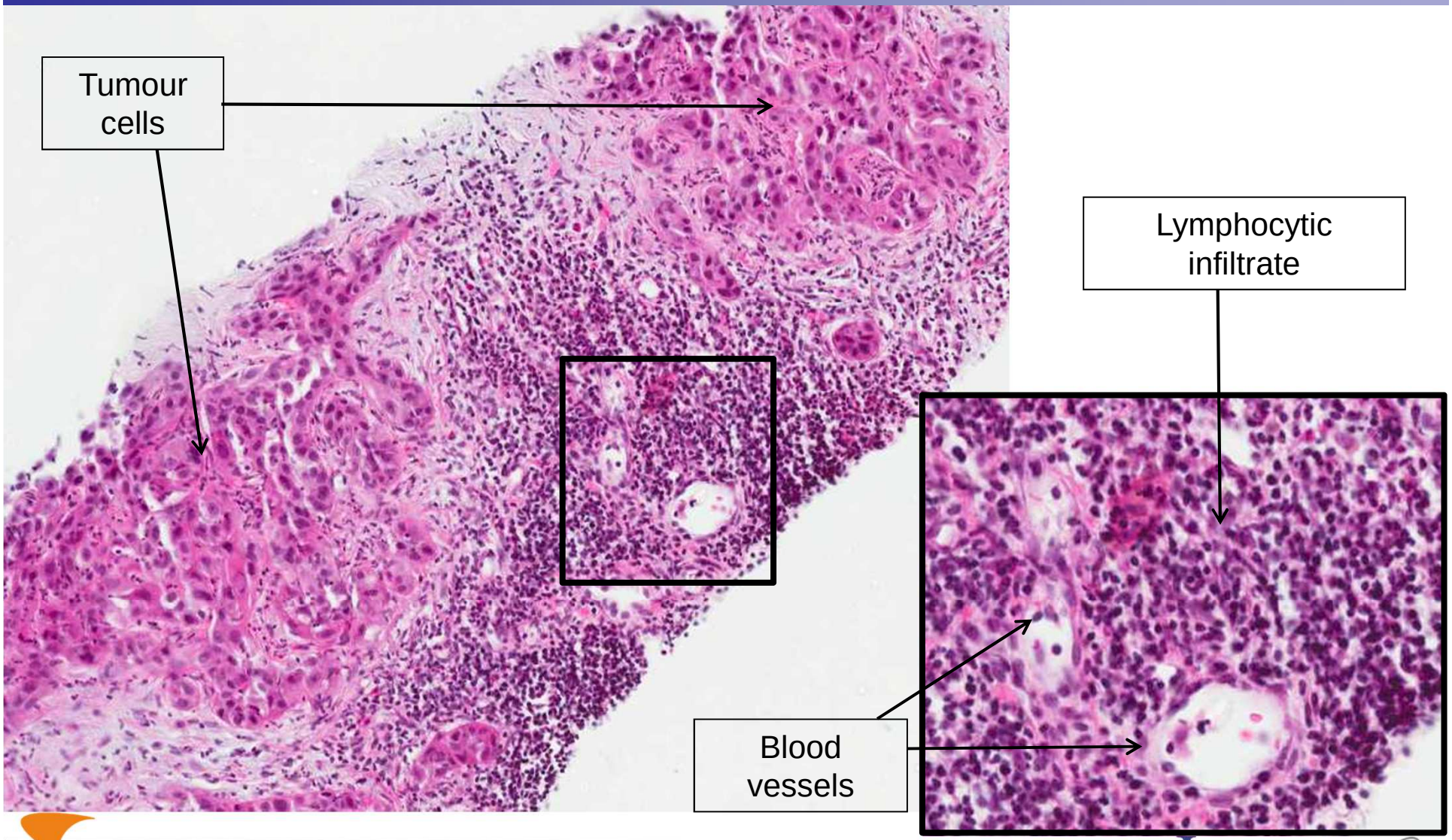


Baseline

Day 29

Week 10

Phase2/HCC Tumour destruction: dense lymphocyte infiltration of non-injected tumour after ~ 1.5 years



Randomised Phase 2 Trial Design: Advanced HCC

JX-594 high dose vs low dose (active) control

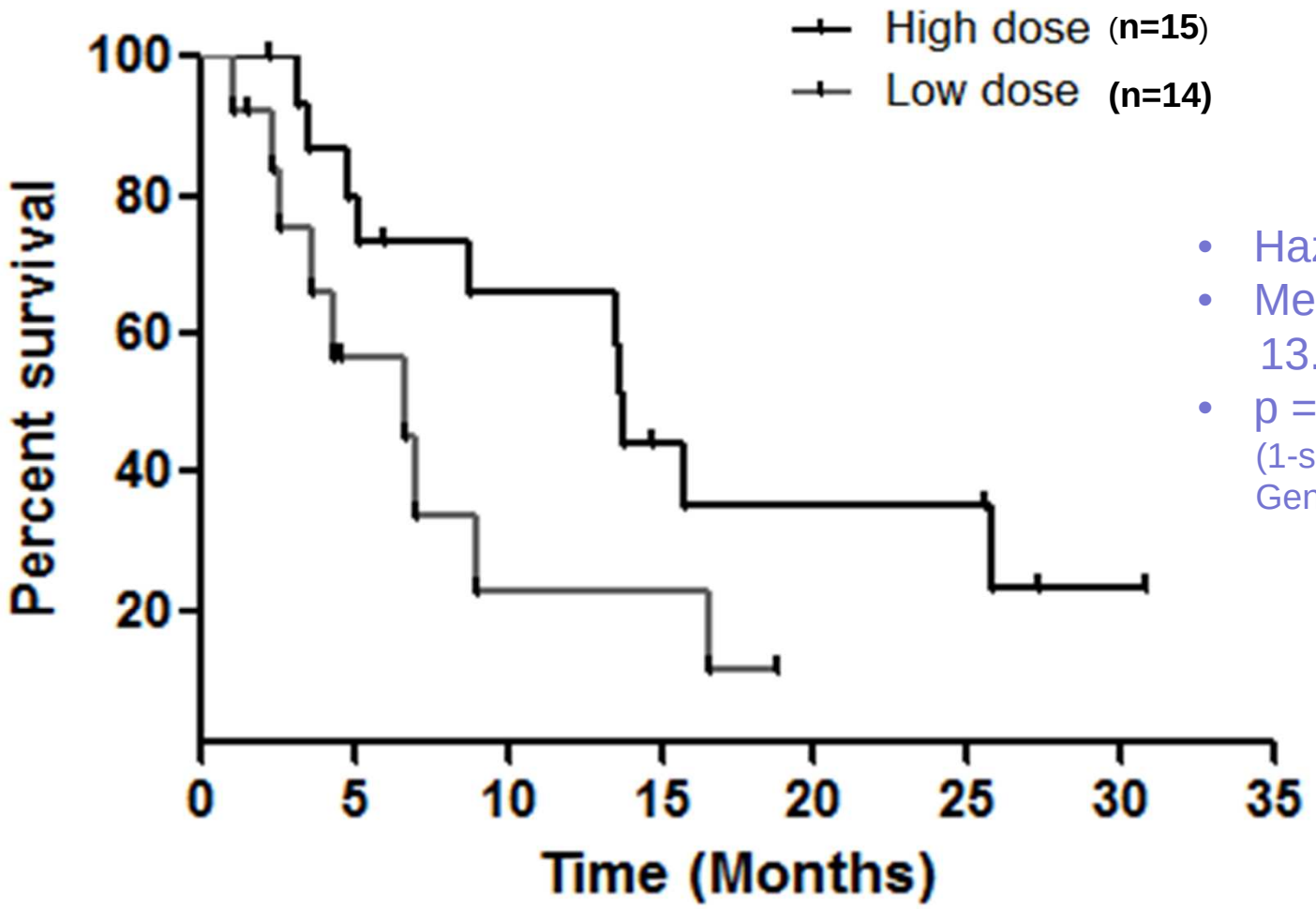
- ***Advanced HCC***
  - *n = 30*
  - *Heavily pre-treated; 80% sorafenib-naïve*
- ***Randomised, stratified enrolment : viral /non-viral etiology***
  - *High dose JX-594 (1 x 10^9 pfu)*
  - *Low dose JX-594 (1 x 10^8 pfu)*
- ***Three total IT doses (day 1, 15, 29)***
- ***Proof Of Concept for MOA: necrosis, vascular ablation, active immunotherapy***
- ***Survival, tumour response, PFS, safety***
- ***Multi-national: US, Canada, S. Korea***

Phase 2/HCC safety profile: flu-like symptoms for 24 hrs

Most common adverse events (regardless of relationship)

	1×10^8 pfu (n=11)			1×10^9 pfu (n=15)			Total (n=26)
	Grade 1/2	Grade 3	Grade 4/5	Grade 1/2	Grade 3	Grade 4/5	All
Fever	10 (91%)	0	0	14 (93%)	2 (13%)	0	24 (92%)
Chills	8 (73%)	0	0	11 (73%)	0	0	19 (73%)
Injection site pain	6 (55%)	0	0	8 (53%)	0	0	14 (54%)
Vomiting	7 (64%)	0	0	6 (40%)	0	0	13 (50%)
Nausea	3 (27%)	0	0	8 (53%)	0	0	11 (42%)
Abdominal pain (+upper)	3 (27%)	1 (9%)	0	7 (47%)	2 (13%)	0	11 (42%)
Headache	4 (36%)	0	0	5 (33%)	0	0	9 (35%)
Anorexia	1 (9%)	1 (9%)	0	7 (47%)	0	0	9 (35%)
Fatigue	2 (18%)	0	0	6 (40%)	0	0	8 (31%)

Phase 2/HCC: survival benefit for high dose patients



- Hazard Ratio = 0.41
- Median OS:
  13.7 vs. 6.8 months
- p = 0.029
  (1-side high dose;
  Gen Wilcoxon)

JX-594 clinical development: next steps

HCC (1st & 2nd line) randomised Ph 2b / 3 trials

	Single Arm Phase 1-2	Randomised Phase 1-2	Randomised Phase 3
Advanced HCC 1st & 2nd line	Ph 1 melanoma single agent IT (n=10)	Advanced HCC single agent IT JX-594 high vs low dose (n=30)	1st line HCC JX-594 IV-IT vs Nexavar
	Ph 1 liver tumours single agent IT (n=15)		
	Ph 1 solid tumour single agent, single dose IV (n=23)	2nd line HCC ("TRAVERSE"): JX-594 IV-IT vs BSC (n=120)	
	Ph 1-2 HCC Nexavar combo IV-IT (n~20)		
Metastatic CRC 3rd line	Ph 1-2 CRC 3rd line single agent multiple IV (n ~15)		
	Ph 1-2 CRC 3rd line single agent & irinotecan combo multiple IV (n ~ 30-50)		

Acknowledgements

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The Patients and their Families