Science Week Conference Presentation

9 July 2021 – Perth, Australia: PharmAust Limited (ASX: PAA), a clinical-stage biotechnology company is pleased to provide the enclosed presentation which will be presented today by Chief Scientific Officer, Dr Richard Mollard, at the Australian and New Zealand College of Veterinary Scientists (ANZCVS) Annual Scientific Conference, "Science Week" being held this week.

This announcement is authorised by the Board.

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About PharmAust (PAA):
PharmAust Limited is listed on the Australian Securities Exchange (code: PAA) and the Frankfurt Stock Exchange (code: ECQ). PAA is a clinical-stage company developing therapeutics for both humans and animals. The company specialises in repurposing marketed drugs lowering the risks and costs of development. These efforts are supported by PAA's subsidiary, Epichem, a highly successful contract medicinal chemistry company that generated $3.5 million in revenue in FY 2020.

PAA's lead drug candidate is monepantel (MPL), a novel, potent and safe inhibitor of the mTOR pathway – a pathway having key influences in cancer growth and neurodegenerative diseases. MPL has been evaluated in Phase 1 clinical trials in humans and Phase 2 clinical trials in dogs. MPL treatment was well-tolerated in humans, demonstrating preliminary evidence of anticancer activity. MPL demonstrated objective anticancer activity in dogs. PAA is uniquely positioned to commercialise MPL for treatment of human and veterinary cancers as well as neurodegenerative disease as it advances a reformulated version of this drug through Phase 1 and 2 clinical trials.

Monepantel: from registered livestock anthelmintic to phase II pet dog anticancer drug

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Disclosure Statement

Presenter: Dr Richard Mollard BSc (Hons) PhD MBA

Disclosure:
I have the following relationships to disclose:
1. PharmAust: Chief Scientific Officer
2. Pitney Pharmaceuticals Pty Ltd: Chief Executive Officer

Off-label Drug Use Disclosure:
I will discuss investigational use of a drug in a clinical trial:
Drug name = monepantel

ABOUT PHARMAUST LTD (ASX: PAA)

- Australian clinical stage oncology, neurodegenerative and antiviral company
- Lead drug monepantel (MPL) being developed ("repurposed") for dog and human oncology and human neurodegenerative diseases and viral infections
- Wholly owned and subsidiary, Pitney – owns rights to MPL and aminoacetonitrile derivatives
- Wholly owned subsidiary, Epichem – fine medicinal chemistry supporting PharmAust work and independent product development

Market cap at $0.93	$29 450 000
Cash June 2021	~ $3 000 000
Debt (Epichem EFIC)	$38 000
Options (Unlisted June 2021)	1 675 000
Top 20 own	37%
Board/Exec own	9.30%

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MONEPANTEL: ANTHELMINTIC

MONEPANTEL: REGISTERED VETERINARY PRODUCT

REGISTRATION > 38 JURISDICTIONS

- European Union: 28 countries
- South Africa
- New Zealand
- Australia
- Argentina
- Uruguay
- Switzerland
- Iceland
- Lichtenstein
- Norway
- Chile

ANTHELMINTIC ACETYLCHOLINE RECEPTORS

- Not present in livestock
- Not present in humans
- Not present in worms that infect humans

COMPREHENSIVE PRECLINICAL TOXICITY & PK REPORT

- EMA Scientific Discussion Dossier
- APVMA Public Release Summary

https://apvma.gov.au/sites/default/files/publication/14141-prs-monepantel.pdf;
https://www.ema.europa.eu/documents/scientific-discussion/zolvix-epar-scientific-discussion_en.pdf

EXCELLENT SAFETY PROFILE

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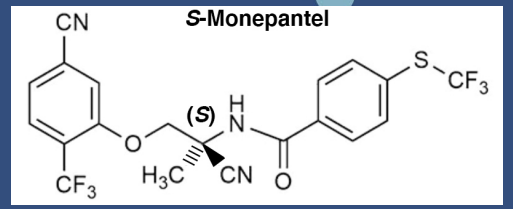
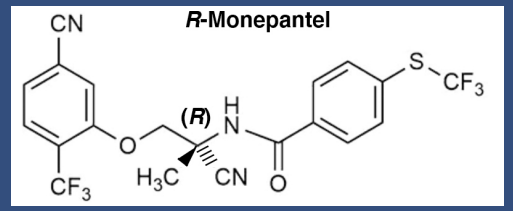
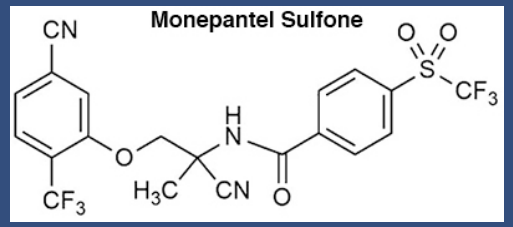
MONEPANTEL: MOLECULE

CHEMICAL/ PHYSICAL PROPERTIES







Monepantel (Mpl)
MW 473 Da
S- and *R*- enantiomers

Monepantel sulfone (MplS)
MW 504 Da

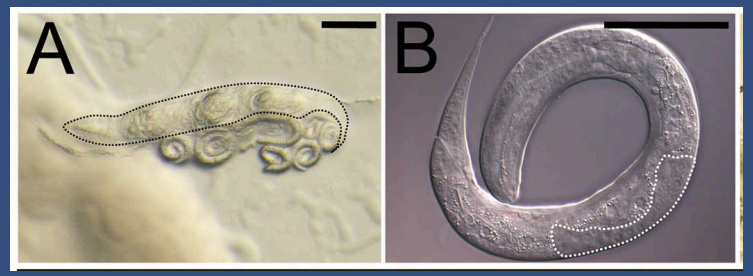
<u>*S*-Mpl</u>
White powder
Solubility water = 0.08 mg/L
MP = ~ 148ºC (<u>*B*</u>), = ~125 ºC (A)
Stability = > 1 year (4 - 30 ºC)

Small hydrophobic insoluble molecule

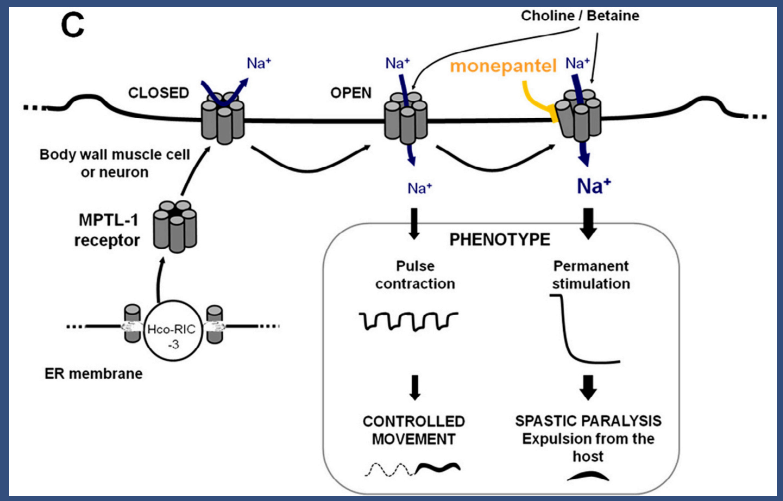
MONEPANTEL: ANTHELMINTIC

Deg-3 NICOTINIC ACETYLCHOLINE RECEPTOR (AchR) AGONIST

Deg-3 nicotinic acetylcholine receptor (AchR) subfamily
(i) Acr-23 (*Caenorhabditis elegans: Cel-arc-23)*
(ii) Des-2 (*Haemonchus contortus: Hco-des-2)*
(iii) Mptl-1 (*Haemonchus contortus: Hco-mptl-1*



Rufener et al., 2013, PLOS doi.org/10.1371/journal.ppat.1003524
Kaminsky et al., 2008 Parasitol Res doi: 10.1007/s00436-008-1080-7



Klotz et al., 2014 Int J Parasitol Drugs Drug Resist
doi.org/10.1016/j.ijpddr.2014.07.007

Only *S*-enantiomer and MPLS have activity
***R*- enantiomer has no activity**

MONEPANTEL: ANTHELMINTIC

ANTHELMINTICS AND ANTICANCER DRUGS

	ANTHELMINTIC		
	BENZIMIDAZOLES	IMADOZOTHIAZOLES	MACROCYCLIC LACTONES
	Albendazole[1]	Levamisole[6]; N276-12, -14, -17[7]	Ivermectin[11,12]
ANTHELMINTIC MODE OF ACTION	Tubulin polymerization inhibitor[1]	Nicotinic acetylcholine receptor agonist[6], drug efflux inhibition[7]	Nicotinic acetylcholine receptor agonist[11,12]
CELL LINES TESTED	Colorectal[2], mammary[3] and ovarian[4] adenocarcinoma and hepatocellular[5] carcinoma	Cervical adenocarcinoma[7], bladder cell carcinoma[7], renal cell carcinoma[7]	Ovarian and breast caricinoma[13,14] and ovarian, breast and colon adenocarcinoma[13,14,15], melanoma[15], glioblasoma[15], Schwannoma[13]
XENOGRAFTS TESTED	Colorectal[2], mammary[3] and ovarian[4] adenocarcinoma and hepatocellular[5] carcinoma	Colorectal and breast adenocarcinoma[8,9],	Breast and colon adenocarcinoma[i,j], metastatic lung bronchioalveolar carcinoma[i]
EFFICACY IN THE CLINIC		Colon cancer[10]	

1 Chu et al., Anticancer research 29, 3791-3796 (2009)
2 Pourgholami et al., Canc chemo pharma 55, 425-432 (2005)
3 Castro et al. Red biol 10, 90-99 (2016)
4 Pourgholami et al., Clin canc res 12, 1928-1935 (2006)
5 Pourgholami et al., Canc let 165, 43-49 (2001)
6 Levandoski et al., Euro j pharmacol 471, 9-20 (2003)
7 Naito et al. Oncol res 10, 123-132 (1998)
8 Van Ginckel et al., Eur j canc 28a, 1137-1139 (1992)
9 Friis et al., Angiogenesis 8, 25-34,(2005)
10 Moertel et al., NEJM 322, 352-358, (1990)
11 Krause et al., Mol pharmacol 53, 283-294 (1998)
12 Collins et al., Mol pharmacol 78, 198-204,(2010)
13 Hashimoto et al, Drug disc thera 3, 243-246 (2009)
14 Dou. et al. Canc res 76, 4457-4469,(2016)
15 Melotti et al., EMBO molecular medicine 6, 1263-1278v(2014)

Hypothesis: monepantel will display anticancer activity

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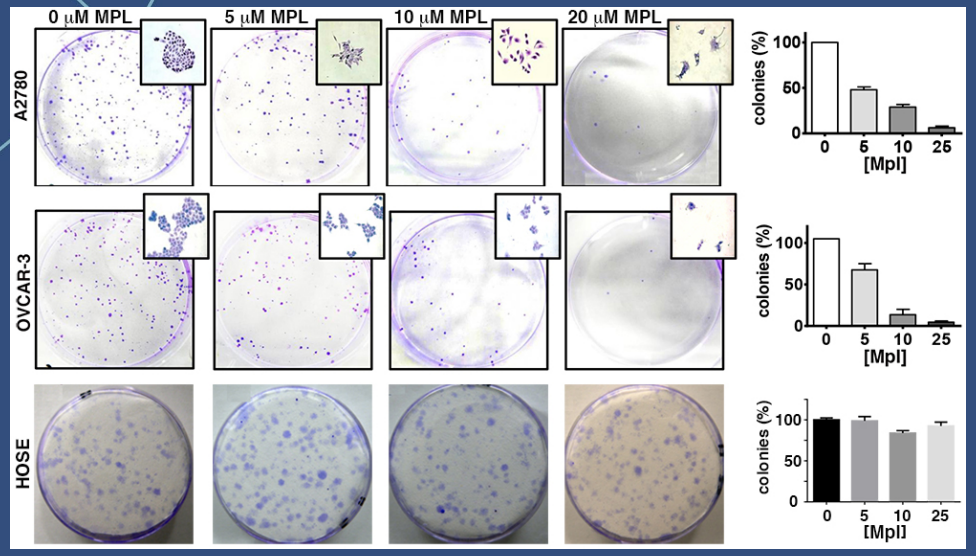
MONEPANTEL: ANTICANCER DRUG

IN VITRO CANCER AND NON-CANCER CELL LINE EC50S



Human Malignant Cell Line IC_{50} (∝M)				
Cell Type	Tissue Origin	Cell Line/ Cell Name	MPL Alone	MPL Sulfone Alone
Malignant	Breast	T47-D	5.3 ± 0.0	10.2 ± 0.6
Malignant	Colorectal	HT-29	5.3 ± 0.2	2.8 ± 0.7
Malignant	Gastric	MKN45	8.19	ND
Malignant	Glial	LN-18	9.4 ± 0.8	6.6 ± 0.7
Malignant	Mesothelial	REN	2.5 ± 0.2	ND
Malignant	Ovarian	1A9	2.5 ± 0.5	3.4 ± 0.1
Malignant	Ovarian	A2780	10.0 ± 3.8	4.2 ± 2.1
Malignant	Ovarian	IGROV-1	4.4 ± 0.3	4.4 ± 1.5
Malignant	Ovarian	OVCAR-3	6.3 ± 0.8	5.5 ± 1.3
Malignant	Pancreatic	AsPC1	7.2 ± 0.3	ND
Malignant	Prostatic	LNCaP	7.3 ± 0.0	ND
Non-malignant	Endothelial	HUVEC	87.0 ± 0.0	47.0 ± 0.0
Non-malignant	Glial	Human Fetal Astrocytes	85.6 ± 2.7	ND
Non-malignant	Ovarian	HOSE	> 100	ND

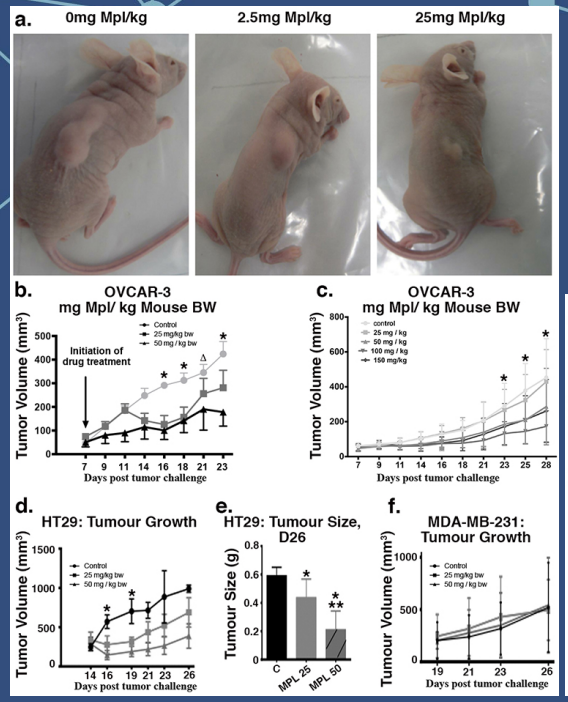
Bahrami et al., 2014, Am J Cancer Res PMCID: PMC4163619
PharmAust unpublished data

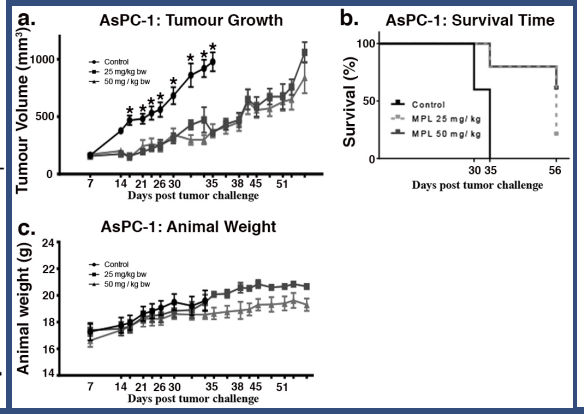
Monepantel demonstrates a 10 fold therapeutic index relevant to numerous cancer cell lines (compare malignant cell line IC50s to non-malignant cell line IC50s)

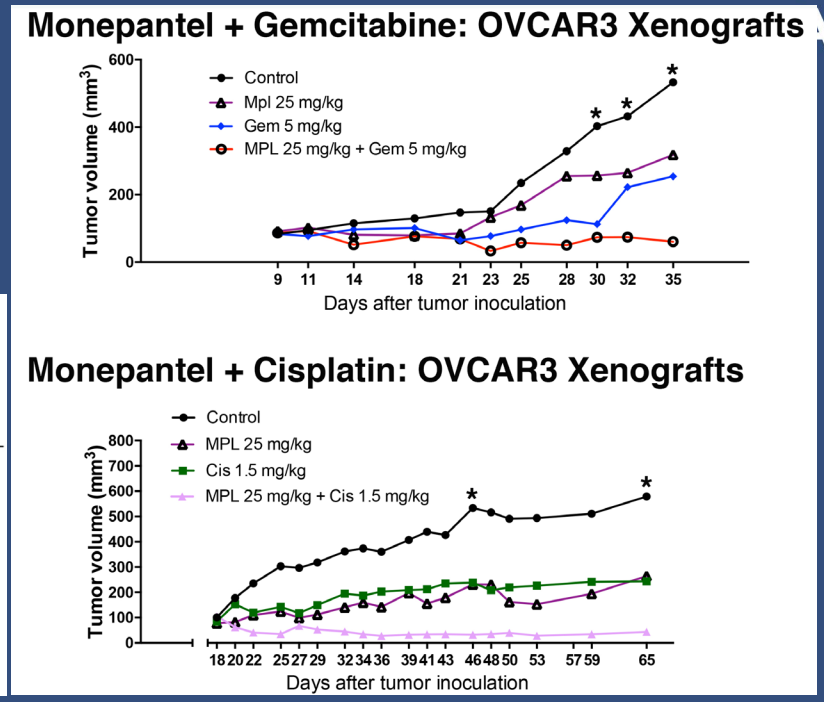
Now demonstrated activity > 40 cancer cell lines in 4 different laboratories
***S*- and *R*- enantiomers have equivalent activity**

MONEPANTEL: ANTICANCER DRUG

MONEPANTEL *IN VIVO* XENOGRAFT NOD SCID MOUSE CANCER CELL LINE STUDIES







Ataie-Kochoie et al., 2018, Am J Cancer Res PMCID: PMC6220142
PharmAust unpublished data

- Monepantel demonstrates activity against ovarian, colorectal, pancreatic cancers in vivo
- Increased xenoengrafted mouse life expectancy
- Amenable to profound synergy with gemcitabine and cisplatin

Demonstrated activity against ovarian, colorectal and pancreatic cancer cell line xenografts

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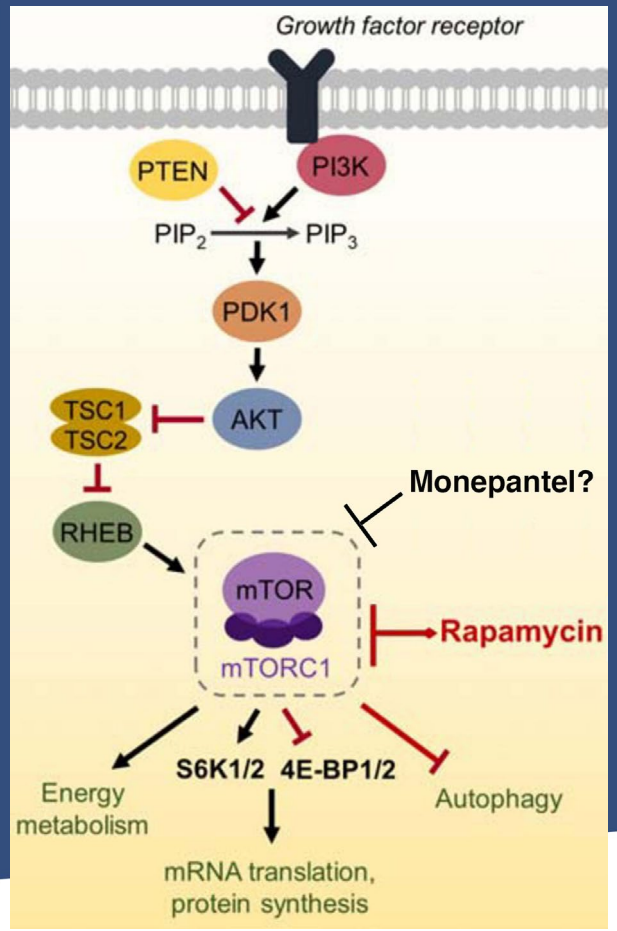
MONEPANTEL: ANTICANCER DRUG

MTOR PATHWAY CHANGES *IN VITRO* AND *IN VIVO* POST MONEPANTEL

Data from Western Blot analyses demonstrates, consistent dampening of p-RPS6KB1 (S6K1/2 in the adjacent figure) levels in numerous cells lines and quickly.

These data suggest mTOR pathway inhibition may represent a primary mechanism of action of monepantel as an anticancer drug



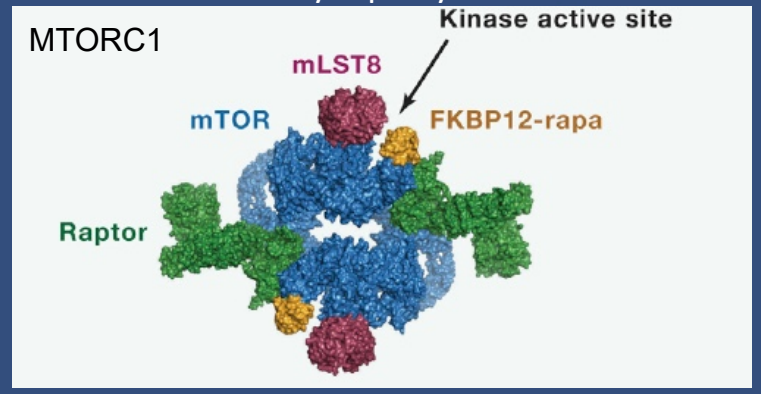
Nguyen et al., 2021, Front Neuroanat doi.org/10.3389/fnana.2021.664695

mTOR Pathway Inhibition

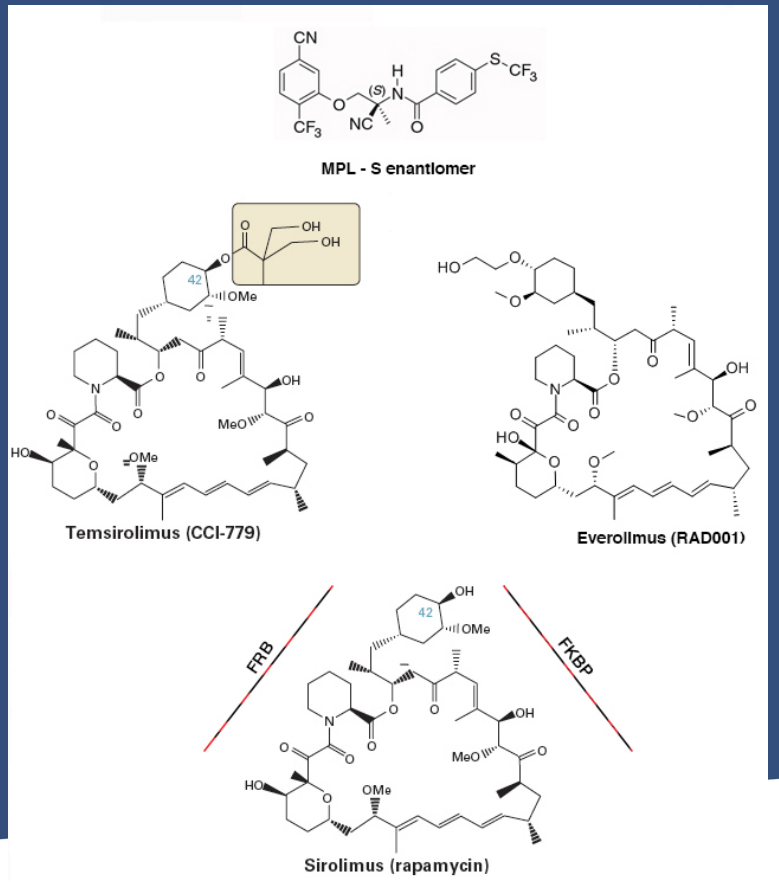
MONEPANTEL: ANTICANCER DRUG

COMPARATIVE STRUCTURE

mTOR inhibition by rapamycin



Monepantel and the rapalogs



Banaszynski et al., 2005 J Am Chem Soc DOI: 10.1021/ja043277y
European Medicines Agency; Wikipedia

Obvious different structure to rapamycin and the rapalogs
Perhaps different mechanism of action

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MONEPANTEL: ANTICANCER DRUG

MONEPANTEL ANTICANCER ACTIVITY CONCLUSIONS

- Nicotinic receptors are apparently not involved: contrary to anthelmintic activity
- Both S- and R-enantiomer possesses anticancer activity: contrary to anthelmintic activity
- Monepantel sulfone possesses anticancer activity: same as anthelmintic activity
- Very early p-RPS6KB1 level reduction implicates mTORC1 signaling pathway inhibition

Monepantel Acts Through the mTOR Pathway but Potentially Differently to the Rapalogs

MONEPANTEL: SAFETY

REPEAT DOSE SAFETY STUDIES IN DOGS

Dose	Species	Route	Dose (mg/kg bw/ d) {m/f}	Effects
4 week diet	Beagles	Feed	0	No effect
4 week diet	Beagles	Feed	161/184	Elevated alkaline phosphatase, increased adrenal weights and reduced thymus weight
4 week diet	Beagles	Feed	566/561	Increased thyroid and liver weight
4 week diet	Beagles	Feed	1217/1472	Decreased food consumption, reduced body weight gain, increased female liver weight.
13 week diet	Beagles	Feed	0	No effect
13 week diet	Beagles	Feed	9.9/10.7	Increase in liver weight and duodedenal and jejunum gland dilation, changes in Alk Phos
13 week diet	Beagles	Feed	97/107	Mild but significantly reduced partial prothrombin time and Ca2+ levels. No change in food consumption, reduced body weight gain females.
13 week diet	Beagles	Feed	963/1176	Increased plasma proteins
52 week diet	Beagles	Feed	0	No effect
52 week diet	Beagles	Feed	2.96	No effect
52 week diet	Beagles	Feed	8.88	Decrease in activated partial thromboplastin times, increase in fibrinogen levels, increase in alkaline phosphatase activity, increase in thyroid, change in liver weight
52 week diet	Feed	Beagles	88.8 (48)	As above, also reduced weight gain, higher alanine transaminase (both sexes) and gamma-glutamyl transpeptidase (males only) activities, lower total protein, albumin and calcium levels and lower albumin/globulin ratios were also observed

- No significant toxicity
- Centrilobular hypertrophy, increased liver enzyme levels and reduced weight gain

https://apvma.gov.au/sites/default/files/publication/14141-prs-monepantel.pdf;
https://www.ema.europa.eu/documents/scientific-discussion/zolvix-epar-scientific-discussion_en.pdf

Excellent safety profile in dogs at very high levels
Liver is the target organ

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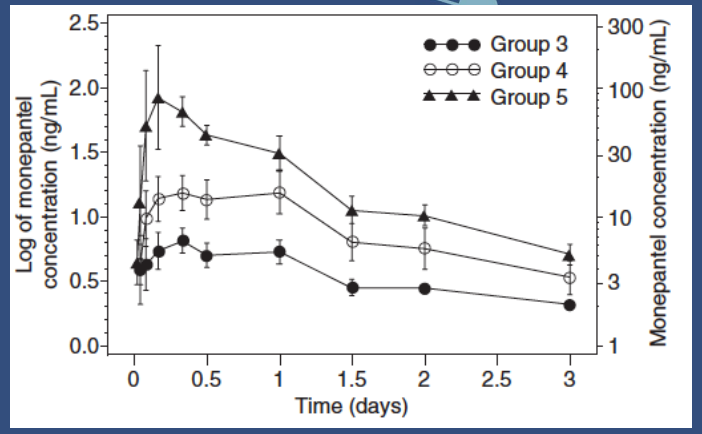
MONEPANTEL: PHARMACOKINETICS

SHEEP PHARMACOKINETICS



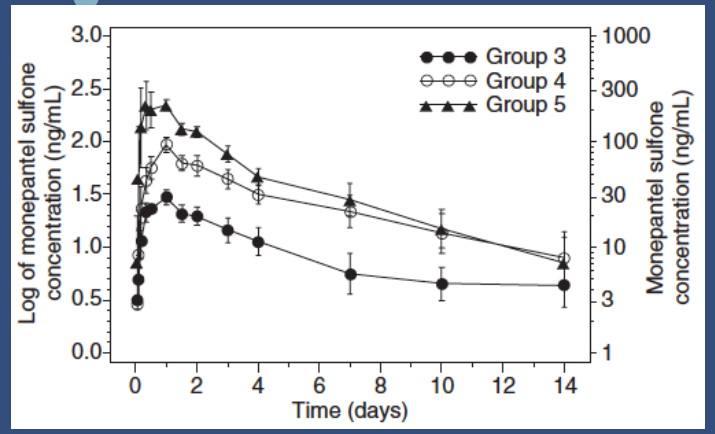


Table 2. Geometric mean ± SD of pharmacokinetic parameters of monepantel and monepantel sulfone after oral administration of monepantel at nominal doses of 1, 3 and 10 mg/kg

	Monepantel			Monepantel sulfone		
Actual dose (mg/kg)	T_{max}* (h)	C_{max}† (ng/mL)	$AUC_{(0-7days)}$† (ng·h/mL)	T_{max}* (h)	C_{max}† (ng/mL)	$AUC_{(0-\infty)}$† (ng·h/mL)
1.35 ± 0.10	8 (2–8)	6.8 ± 1.8	211 ± 91	24 (24–24)	29.9 ± 4.8	3376 ± 1126
3.57 ± 0.09	16 (4–24)	17.9 ± 6.6	671 ± 214	24 (24–24)	94.3 ± 15.6	11125 ± 3279
11.45 ± 0.07	4 (4–8)	98.8 ± 75.5	1920 ± 446	24 (4–24)	276 ± 101	19110 ± 2009

*Median (Minimum–Maximum) is given for T_{max}.
†C_{max} and *AUC*s were normalized to the nominal dose.
SD represents the geometric standard deviation.

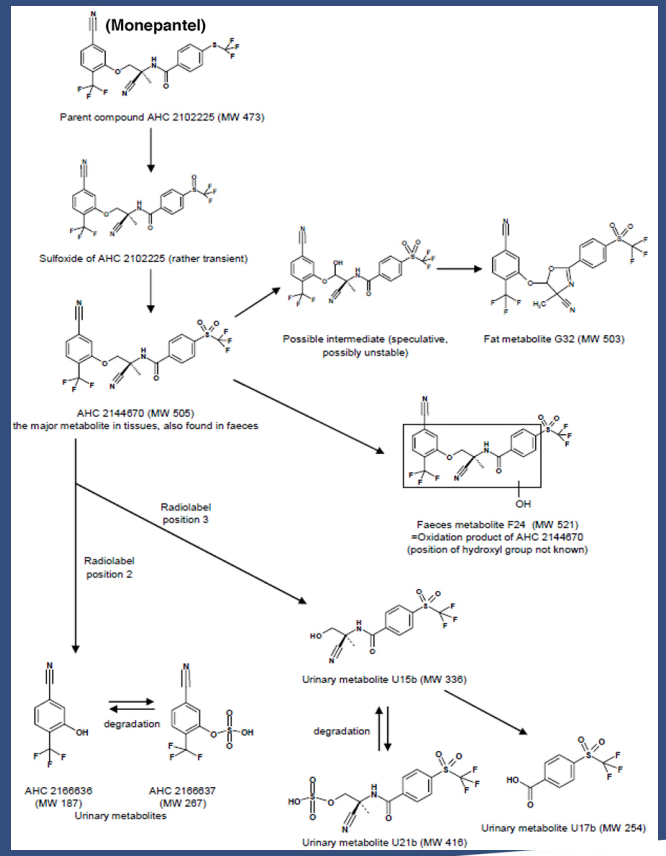
Karadzovska et al., 2009. J. vet. Pharmacol. Therap. 32, 359

Pharmacokinetics in sheep, dogs, rats and mice well known

MONEPANTEL: METABOLISM

METABOLIC PATHWAY AND ELIMINATION

METABOLISM



ELIMINATION

^{14}C-Mpl secreted mainly (90%) through the feces
2.5 mg/kg bw rats = 3 days
5.0 mg/kg bw sheep = 2 – 3 weeks

	Total Tissue MPL + MPLS Residues: Sheep (∝M)	
	Days after single dose 5 mg/kg bw oral administration	
Tissue	**2**	**7**
Fat tissue	27.7	9.7
Liver	11.2	3.8
Kidney	3.3	1.2
Muscle	3.4	0.9

Boison and Sanders, 2012 http://www.fao.org/fileadmin/user_upload/vetdrug/docs/12-2012-monepantel.pdf

Metabolism and elimination in sheep well known

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MONEPANTEL: HUMAN PHASE I/II STUDY

A PHASE I STUDY OF THE TOLERABILITY, SAFETY, AND PHARMACOKINETICS OF ORAL MONEPANTEL (MPL) IN INDIVIDUALS WITH TREATMENT-REFRACTORY SOLID TUMOURS.

Protocol No.: LL1

Principal Investigator:
Site 1: Department of Medical Oncology, Royal Adelaide Hospital:
Professor Michael Brown
Director, Cancer Clinic Trials Unit
Royal Adelaide Hospital
North Terrace
ADELAIDE, SA 5000

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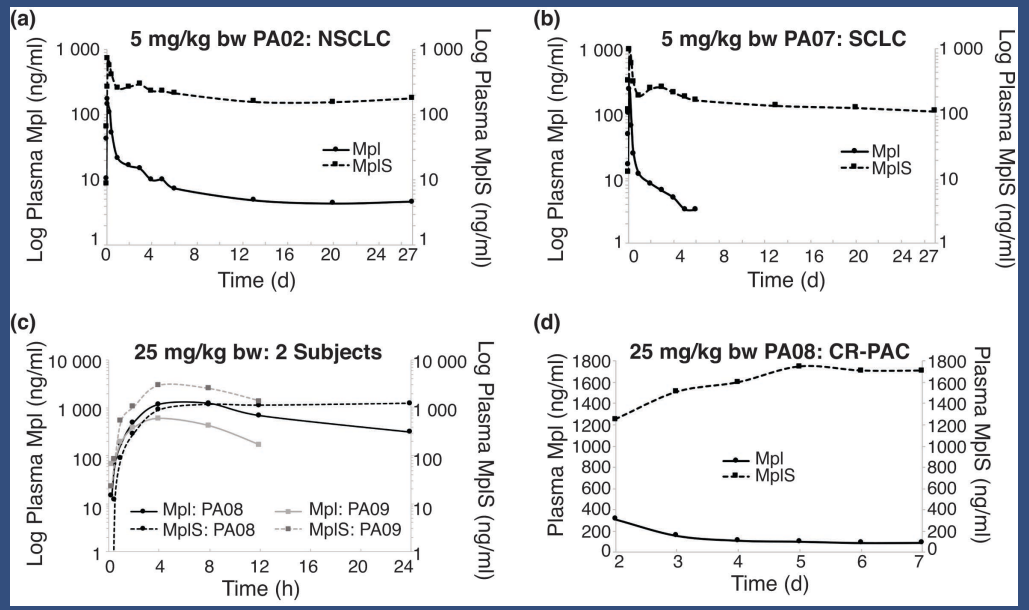
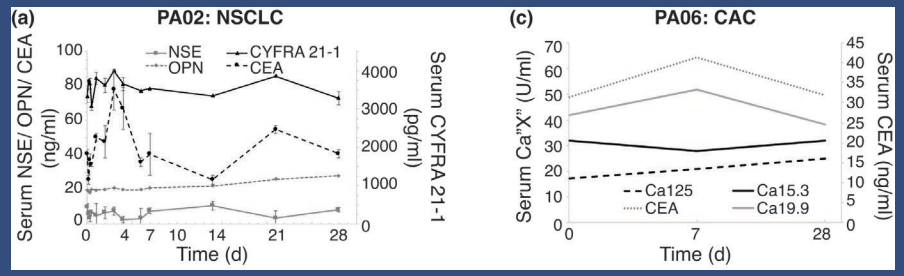
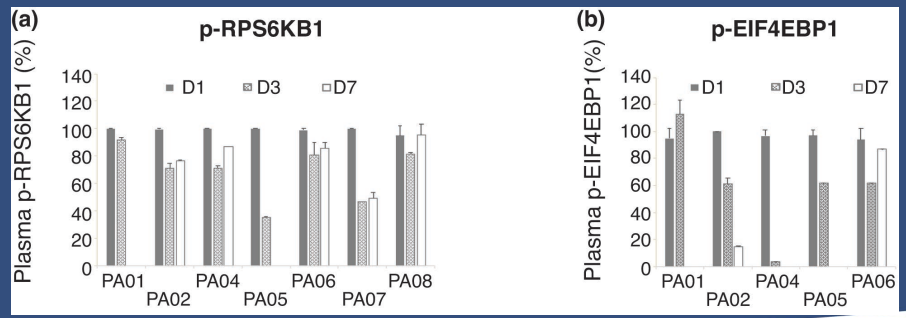
MONEPANTEL: HUMAN PHASE I/II STUDY

HUMAN PHASE I/II PK and PD

- Tolerability, PK, PD and PET-CT
- Daily administration for 28 days
- Level 1: 6 enrolments, 5 mg/kg bw
- Level 2: 2 enrolments, 25 mg/kg bw







Mislang et al., 20201, Cancer Chemother Pharmacol doi: 10.1007/s00280-020-04146-5

Good PK, stable cancer markers, reduced mTOR pathway markers

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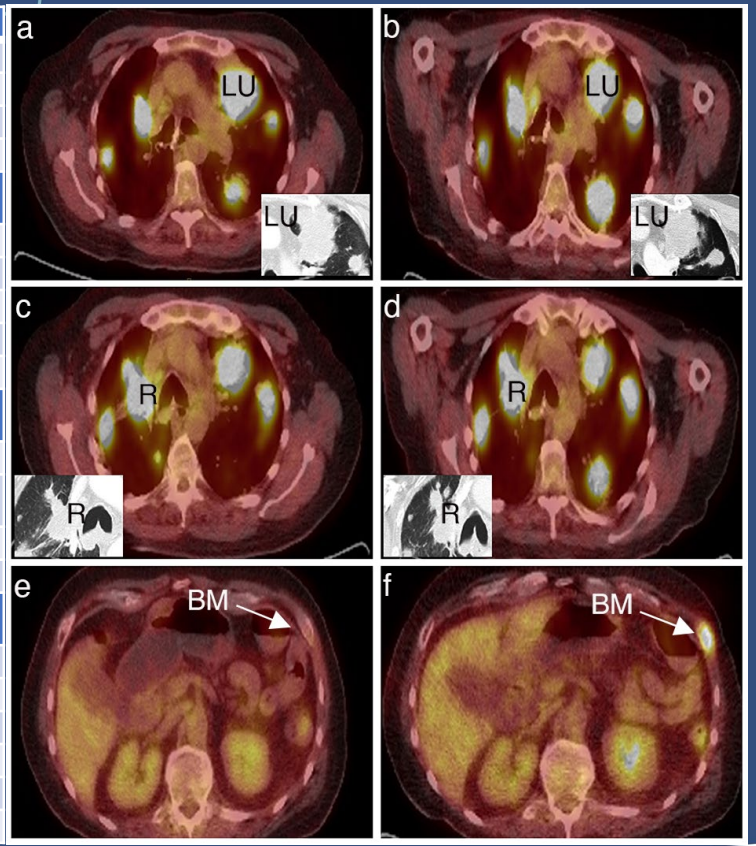
MONEPANTEL: HUMAN PHASE I/II STUDY

HUMAN PHASE I/II TUMOUR MEASUREMENTS

PA02 NSCLC Target Lesions	D(-1)	D29	D (%)
Left upper lobe medial	63	60	-5
Right superior hilum	38	29	-24
Left lower lobe	30	36	20
Sum	131	125	-5
PA04 CR-PAC Target Lesions			
Pre-aortic lymph node	20	22	10
Left para-aortic lymph node	16	17	6
R axillary lymph node	23	23	0
Sum	59	62	5
PA06 CRAC Target Lesion			
Left lung upper lobe	13	12	-8
Rectosigmoid junction	40	42	5
Sum	53	54	2
PA07 SCLC Target Lesions			
Left frontal lobe	16	21	31
Right adrenal	35	53	51
Hepatic	74	85	15
Porta hepatis	42	46	10
Sum	167	205	23



Mislang et al., 20201, Cancer Chemother Pharmacol doi: 10.1007/s00280-020-04146-5

Stable target lesions (when taking drug)

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MONEPANTEL: HUMAN PHASE I/II STUDY

HUMAN PHASE I/II CONCLUSIONS

- Safe
- Unpalatable taste
- No SAEs related to the study drug
- Minor AEs (dysgeusia, dyspepsia, vomiting)
- Good PK for 0 - 24 h
- Poor compliance after D1 (unpalatability)
- Reduction in PD markers
- RECIST1.1 = 2 x SD and 2 x PD
- Target lesions = 3 x SD and 1 x PD

Reformulation of new tablet now completed to:

- eliminate poor taste
- increase dose

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MONEPANTEL: PET DOG PHASE I/II STUDY

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The Use of the Anthelmintic Drug Monepantel

as an Anticancer Drug in Dogs

Principal Investigator:
Dr Angela Frimberger
Director, Cancer Clinic Trials Unit
Animal Referral Hospital
Homebush
Sydney, NSW, 2140

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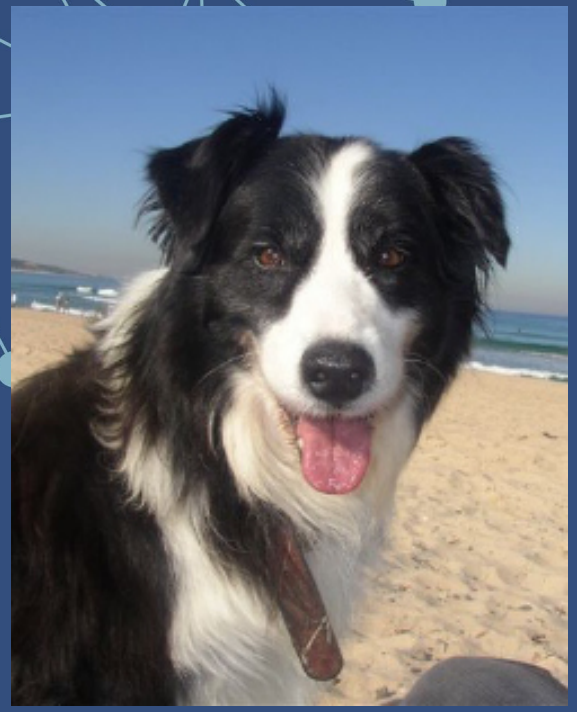
MONEPANTEL: PET DOG PHASE I/II STUDY

DOG PHASE I/II Tolerance, Safety, PK and PD



Seven pet dogs with treatment naïve B cell lymphoma

Tumour Type	Pet Dog Breed	Dog Weight (kg)	Duration (days)	Outcome	Adverse Events
B Cell Lymphoma (4a)	Shi Tzu cross	8	14	SD: 17% reduction	Vomiting (Grade 2)
B Cell Lymphoma (4a)	Staffordhsire Bull Terrior	24	14	SD: 2% reduction	Vomiting (Grade 1)
B Cell Lymphoma (3a)	German Shepherd	30	14	SD: 12% reduction	Anemia (Grade 1)
B Cell Lymphoma (3a)	Rottweiler	42	14	SD: 4% reduction	Nausea (Grade 2)
B Cell Lymphoma (3a)	Terrier	7	14	SD: 3% reduction	Nausea (Grade 1)
B Cell Lymphoma (3a)	Terrier cross	4.2	14	PD: 14% reduction	Spleen/ liver: new sites
B Cell Lymphoma (3a)	Doberman	42	14	SD: 19.9% increase	Vomiting (Grade 1)/ Grade 3 ALP elevation

As with studies in mouse xenografts and cancer cell lines, the mTOR marker p-RPS6KB1 is reduced in these dogs blood cells following monepantel treatment
This demonstrates that monepantel treatment associates with mTOR signaling pathway inhibition in these dogs

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MONEPANTEL: PET DOG PHASE I/II STUDY

DOG PHASE I/II CONCLUSIONS

PharmAust Targeting Regression and Stable Disease

- Safe – achieved endpoint
- Apparent poor taste
- No SAEs related to the study drug
- AEs = nausea and vomiting
- Reduction in mTOR pathway activity marker
- 6/7 dogs with stable disease – achieved endpoint

Reformulation of new tablet now completed to:

- eliminate poor taste
- increase dose

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MONEPANTEL: TABLET DEVELOPMENT

TABLET TASTE: PRECLINICAL AND CLINICAL TESTING

Tablets				
Program	**Condition**	**Females**	**Males**	**Total Dogs Nausea/ Vomiting**
Taste test: Citoxlab	Coated	3	3	0/3
	Uncoated			0/3
Food effect: CRL 1	Fasted	0	3	0/3
	Fed	0	3	0/3
	Fed oil	0	3	0/3
MTD: CRL 2	Single dose	1	1	0/2
		1	1	0/2
		1	1	0/2
		1	1	0/2
Dose escalation: CRL 3	Repeat dose	1	1	0/2
		1	1	0/2
	Total	**9**	**18**	**0/27**

Tablet Stability Data

- GMP batch 1 = 24 months
- GMP batch 2 = 19 months
- No reportable impurities

Poor palatability resolved
Highly stable tablet

MONEPANTEL: PHASE II PET DOG TRIAL: TABLETS

The Use of the Anthelmintic Drug Monepantel

as an Anticancer Drug in Dogs

Principal Investigators:
Dr Claire Cannon
Dr Kim Agnew

Participating Sites

U-Vet Werribee, Melbourne (Claire Cannon)
ARH Homebush, Sydney (Sonya Yu)
UVTHS Camperdown, Sydney (Peter Bennett)
ARH Sinnamon Park, Brisbane (Kathleen O'Connell)
VSS Underwood, Brisbane (Catherine Chan)
WAVES Success, Perth (Sue Bennett)
PVS Osborne Park, Perth (Jessica Finlay)

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MONEPANTEL: PHASE II PET DOG TRIAL: TABLETS

TRIAL DESIGN: PRECEDENT

Pet dogs with treatment naïve B cell lymphoma

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1) CHOP TREATMENT

- PFS in remission upon CHOP completion
- PFS from day of achieving CR on CHOP
- PFS from date of start of treatment

PFS (months)	p_0	p_1
3	0.7	0.9
6	0.6	0.8
12	0.2	0.3
24	0.1	0.2

p_0 = unacceptable response rate for a new drug if comparing to CHOP
p_1 = acceptable response rate for a new drug if comparing to CHOP

References for LMA PFS p_o and p_1 following CHOP
Garrett et al., 2002 J Vet Intern Med 16:704;
Simon et al., 2006 J Vet Intern Med 20:948;
Rassnick et al., 2010 Vet Comp Onc 8(4):243
Hosoya et al., 2007 J Vet Intern Med 21:1355
Curran et al., 2016 Vet Comp Oncol 14 Suppl 1:147
Lautscham et al., 2017 Vet Rec 180(12):303
Desmas et al., 2017 Vet Comp Oncol 15(2):504

2) NO TREATMENT

Treatment Group	No of Dogs	Mn ST (Days)	Md St (Days)
No treatment (A/B)	34	30	29
Chemotherapy (A/B)	47	138	~103
No treatment (A)	24	~39	~30
Chemotherapy (A)	38	~350	~250

Mn ST = mean survival time
Md ST = median survival time
CHOP: Cyclophosphamide, vincristine, cytosine arabinoside, prednisolone

References for LMA PFS p_o and p_1 following no treatment
Theilen et al., 1977 JAVMA 17(6): 607

Fifty % of untreated dogs with LMA will be euthanized by 29 days

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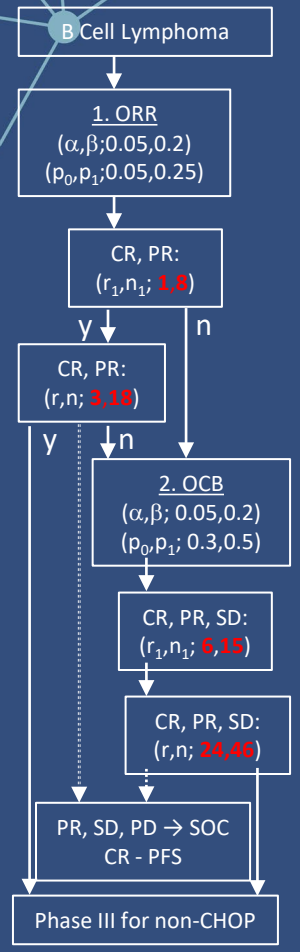
MONEPANTEL: PHASE II PET DOG TRIAL: TABLETS

TRIAL DESIGN: ADAPTIVE BAYESIAN APPROACH



ORR: Hypothesis 1			
p_0 =0.05; p_1 = 0.25; 1-β = 0.8			
S	*n2(S)*	*n(S)*	*r(S)*
0	0	8	0
1	10	18	2
2	8	16	2
≥3	0	8	0

OCB: Hypothesis 2			
p_0 =0.3; p_1 = 0.5; 1-β = 0.8			
S	*n2(S)*	*n(S)*	*r(S)*
≤5	0	15	0
6	31	46	18
7	31	46	18
8	30	45	18
9	28	43	17
10	0	15	0

ORR = overall response rate
OCB = objective clinical benefit

α = 0.05 (Pr incorrectly rejecting the null hypothesis (Type I)
β = 0.8 (Pr incorrectly failing to reject the null hypothesis (Type II)
p_0 = unacceptable response rate
p_1 = acceptable response rate
S = Responders in the first stage
N2(S) = Sample number in the second stage
N(S) = Sample number in the first stage
r(S) = Responders in the second stage

VCOG V1.0 Peripheral nodal lymphoma

Vail et al., 2010, Vet Comp Oncol DOI: 10.1111/j.1476-5829.2009.00200.x

Simon, 1989, Controlled Clin Trials 10:1
Shan et al., 2016, Stat Med 35(8):1257

ORR and OCB: Vail et al., 2010 Vet Comp Oncol 8(1):28
DOI: 10.1111/j.1476-5829.2009.00200.x

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MONEPANTEL: PHASE II PET DOG TRIAL: TABLETS

TRIAL DESIGN: SCREENING AND TREATMENT SCHEDULE

Variables	Description
Age (years)	≥ 1
Pregnancy (D1 urine test)	No
Dogs used for breeding	No
Tumours	
B cell lymphoma	Yes
Confirmed	Cytology/histopathology
Immunophenotype	IHC, ICC, FCM
WHO stage	1 - 5
Substage	a
Intercurrent disease	None
Previous treatment for lymphoma	None
Corticosteroid use	≤ 8 weeks from trial start, none
Modified Karnofsky	< 2
Life expectancy	> 6 weeks
Hematology, biochemistry, urine	≤ VCOG Grade 1
Lymphocytosis secondary to lymphoma	Yes
Paraneoplastic hypercalcemia	No

Visit and Procedure Number	Procedure
D0 1	Initial consultation*
D0 2	Hem (smear), clin chem, urine (cysto)
D0 3	Sedation for imaging
D0 4	Thoracic X-ray
D0 5	Abd ultra (liver and spleen cytology)
D0 6	LN FNA, cytology
D0 7	Immunophenotype (FACS)
D0 8	Hospitalisation stay if required
D14 1	Consultation/ phys exam (at 14 days)
D14 2	Hem (smear), clin chem, urine (cysto)
D28 1	Consultation/ phys exam (at 28 days)
D28 2	Hem (smear), clin chem, urine (cysto)
D28 3	Sedation for imaging
D28 4	Thoracic X-ray
D28 5	Abd ultra (liver and spleen cytology)
D28 6	LN FNA, cytology
D28 7	Hospitalisation stay if required

* initial consultation and physical exam may be paid for by owners

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MONEPANTEL: PHASE II PET DOG TRIAL: TABLETS

ENROLLED PET DOG CHARACTERISTICS

Breed	Number
Standard Poodle	1
Golden Retriever	1
German Shepherd	1
German Shepherd (cross)	1
Fox Terrier (Mini)	1
Jack Russell Terrier	1
Great Dane	1
Labrador	1
Corgie	1
Boxer	1
Bullmastiff cross	1
American Staffordshire Terrier	1
Fox Terrier (cross)	1
Rhoedesian Ridgeback	1
Daniff	1

Sex	Number
Male	8
Female	7

B Cell Lymphoma	Number
Multicentric, large	10
Multicentric, intermediate to large	4
Multicentric	1

All advanced stage disease pet dogs

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MONEPANTEL: PHASE II PET DOG TRIAL: TABLETS

PERIPHERAL NODAL LYMPHOMA MEASUREMENTS

TARGET LESIONS

HIGH DOSE		LOW DOSE		DOSE 3	
Participant	Outcome	Participant	Outcome	Participant	Outcome
001-001	SD	004-005	SD	002-002	SD
001-002	SD	002-001	PD	005-001	PD
001-003	SD	006-001	SD	002-003	N/A
003-001	PR	004-006	SD	007-001	PD*
004-002	SD	006-002	SD		
004-003	SD				

NON-TARGET LESIONS

HIGH DOSE		LOW DOSE		DOSE 3	
Participant	Outcome	Participant	Outcome	Participant	Outcome
001-001	SD	004-005	SD	002-002	N/P
001-002	SD	002-001	PD	005-001	PD
001-003	SD	006-001	N/P	002-003	N/A
003-001	PR	004-006	SD	007-001	N/A
004-002	SD	006-002	SD		
004-003	SD				

- SD = Stable disease
- PR = Partial response
- PD = Progressive disease
- N/A = no measurements available
- N/P = no measurements provided
- * six lesions included

Monepantel is highly effective in controlling peripheral lymphoma lesions

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MONEPANTEL: PHASE II PET DOG TRIAL: TABLETS

VCOG RECIST v1.0 OUTCOMES FOR PERIPHERAL NODAL LYMPHOMA

- SD = Stable disease
- PR = Partial response
- PD = Progressive disease
- N/A = no measurements available
- N/P = not provided (not measured)
- (x) only D14 available

OUTCOMES					
Outcome by Target Node		Outcome by Non-Target Node		Outcome by VCOG RECIST	
SD	9 (1)	SD	6 (2)	SD	5
PR	0 (1)	PR	0 (1)	PR	1
N/A	1	N/A or N/P	4	N/A	0
PD	2 (1)	PD	1(1)	PD	9
Total	15	Total	15	Total	15

Vail et al., 2010, Vet Comp Oncol DOI: 10.1111/j.1476-5829.2009.00200.x

Quality of Life data available from 12 dogs

- 1 – 10 Quality of life scale (10 is highest)
- "Please rate your dog's overall quality of life today from 1(poor) - 10 (excellent)"

9 of 12 dogs experienced unchanged or better qualities of life on whole during their individual courses of treatment with monepantel

Interim Bayesian primary endpoints attained even when considering monepantel dose levels as an independent variable

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MONEPANTEL: ANTICANCER CONCLUSIONS

MAJOR FINDINGS

- Monepantel inhibits mTOR pathway activity (p-RPS6KB1)
- Stage 1 of Bayesian design demonstrates that monepantel tablets provide objective anticancer activity
- Stage 1 of Bayesian design demonstrates that monepantel tablets provide objective clinical benefit
- Inappetence, weight loss and increased liver enzymes represent dose limiting toxicities
- Acceptable, relatively low toxicity at levels that exert anticancer activity
- Lack of apparent immune suppression
- Long term at home administration is feasible and convenient
- High activity is against target peripheral nodular lesions
- Benefit to quality of life
- Further investigation in Phase III trial in combination with CHOP or prednisolone warranted
- Continue with dose optimisation prior to embarking on Phase III trial

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ACKNOWLEDGEMENTS

Human Studies
Prof Michael Brown, Royal Adelaide Hospital
Dr Anna Mislang, Royal Adelaide Hospital
Dr Gonzalo Tapia Rico, Royal Adelaide Hospital

Gelatin Capsules
Juniper Pharma Services, UK

Tablet Manufacture
BRI Pharmaceuticals, Canada
Citoxlab, Canada (taste test)
Catalent San Diego, USA

Zolvix Pet Dog Trial
Dr Angela Frimberger, Veterinary Oncology Consultants

Tablet Pet Dog Trial
Dr Claire Cannon, U-Vet, Melbourne
Dr Kim Agnew, KAP Consulting, Sydney

Assoc Prof Peter Bennett, UTVHS Camperdown, Sydney
Dr Sue Bennett WAVES Success, Perth
Dr Catherine Chan, VSS Underwood, Brisbane
Dr Jessica Finlay, PVS Osborne Park, Perth
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