



# NDA 201848 Melblez Kit

FDA Presentation  
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# Main Points

- Melblez Kit treatment demonstrates anti-tumor activity against hepatic metastases of ocular melanoma
- The clinical benefit of this activity is uncertain
- Risks of Melblez Kit treatment are substantial and life-threatening
- A REMS program cannot eliminate inherent toxicities of Melblez Kit treatment

# Presentation Outline

- Regulatory History
- Review of Randomized Study 1
- Efficacy
- Safety
- Summary
- Issues

# Melblez Kit

- Drug-Device combination product
- Primary mode of action mediated by drug
- CDER is lead review center
- CDER and CDRH collaborative review
- Drug-Device combination is subject to both regulatory provisions
- 505(b)2 application

# Standard for Marketing Approval

Combination product for which marketing approval is being sought must be safe and effective in its proposed use

Substantial evidence of effectiveness in adequate and well-controlled trials

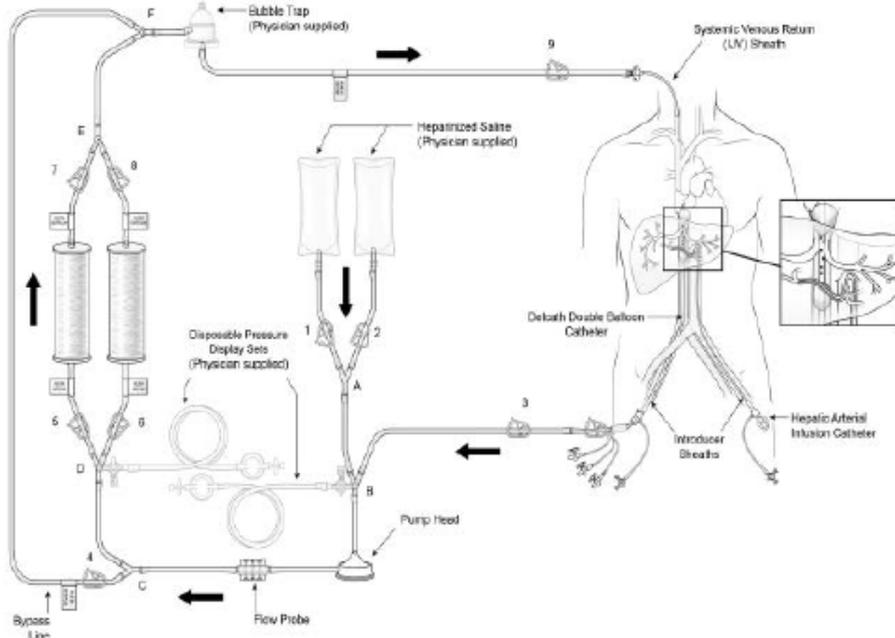
Demonstrate a favorable benefit-risk profile

# To-be-Marketed Device Differs From Clinical Trial Device

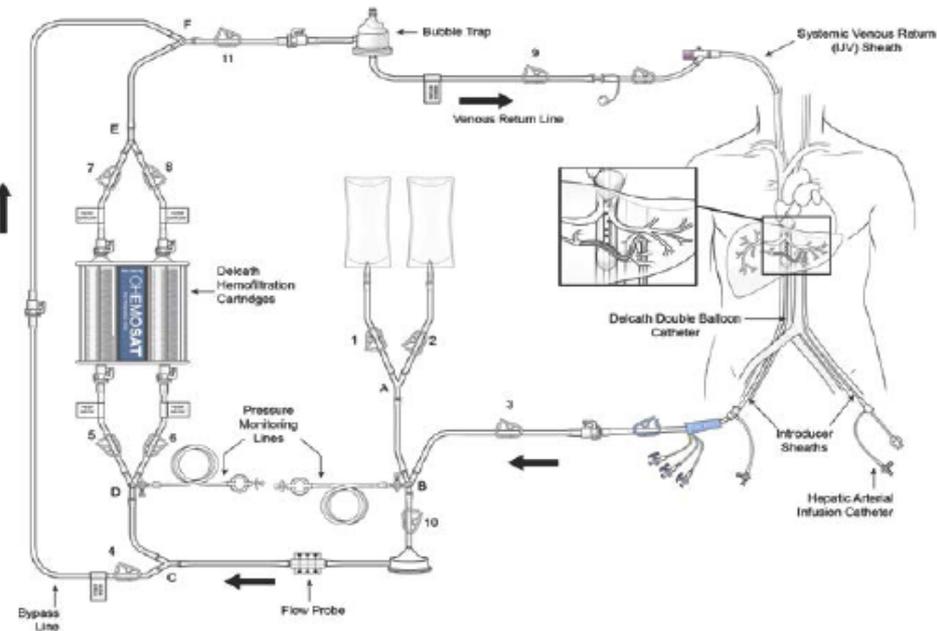
Clinical Trial Version

To-be-Marketed Version

Assembled System



Assembled System



# Proposed Indication

The Melblez Kit is a drug/device combination product containing melphalan hydrochloride and the Delcath Hepatic Delivery System, which is indicated for the treatment of patients with unresectable metastatic ocular melanoma in the liver

# Ocular Melanoma

Rare disease

No approved agents for specific indication

No BRAF V600 mutations

Liver most common site of metastases

# Melblez Kit Supportive Studies

<b>Study</b>	<b>Design/ Population</b>	<b>Study Treatment</b>	<b># Subjects</b>
Study 1	Multicenter/Phase 3 Randomized/Open Label Melanoma	Melblez Kit 3.0 mg/kg IBW vs. BAC	All: 93 NCI: 44 Other: 49
Study 2	NCI Single arm/Phase 2 Mixed Histology	Melblez Kit 3.0 mg/kg IBW	56
Study 3	NCI Single arm/Phase 1 Mixed Histology	Dose escalation Melblez Kit 2.0-3.5 mg/kg IBW	34

# Study 1

Patients with unresectable, hepatic-dominant metastatic ocular or cutaneous melanoma

1:1 Randomization

Melblez Kit  
3.0 mg/kg IBW  
(N=44)

Treatment discontinued at hepatic progression, extra-hepatic progression if systemic therapy required, 4 cycles if stable disease, or 6 cycles if response

Best Alternative Care  
(N=49)

Treatment discontinued at hepatic progression

Optional Melblez Kit treatment if eligible  
N=28

# Eligibility

Unresectable hepatic metastases with limited extrahepatic disease

Prior therapy allowed

A number of eligibility revisions made in response to adverse reactions encountered

# Efficacy Outcome Measures

## Primary

Hepatic progression free survival as assessed by independent review committee

## Secondary

Overall progression free survival

Hepatic response rate

Overall survival

# Study Patients (n=93)

89% ocular melanoma

60% hepatic lesions only

46% enrolled at NCI

# BAC Treatments

<b>Treatment Administered</b>	<b>% Patients (N=49)</b>
<b>Systemic single agent chemotherapy</b>	<b>43%</b>
<b>    Temozolomide</b>	<b>41%</b>
<b>    DTIC</b>	<b>2%</b>
<b>Intrahepatic chemotherapy</b>	<b>22%</b>
<b>Supportive care</b>	<b>18%</b>
<b>Systemic combination chemotherapy</b>	<b>8%</b>
<b>Intrahepatic Y-90 chemoembolization</b>	<b>6%</b>
<b>Radiofrequency ablation</b>	<b>2%</b>

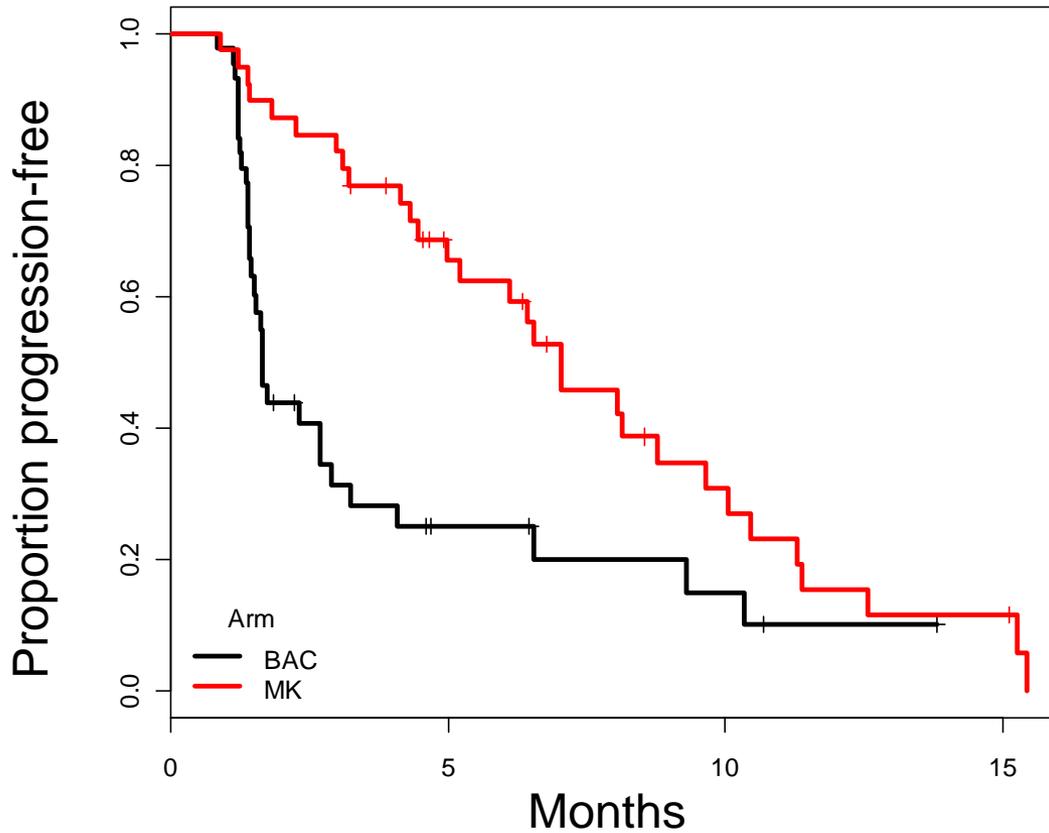


# Efficacy in Ocular Melanoma

# Hepatic PFS

<b>hPFS</b>	<b>Melblez Kit (N = 39)</b>	<b>BAC (N = 44)</b>
<b>Patients with hepatic progression or death</b>	77%	73%
<b>Median hPFS in months (95% CI)</b>	7.0 (5.0, 9.7)	1.6 (1.4, 2.7)
<b>Hazard Ratio 95% CI</b>	0.42 (0.25, 0.72)	
<b>p-value (Log-Rank Test)</b>	0.001	

## Hepatic Progression Free Survival in Study 1: Patients with Ocular Melanoma



	Number at risk			
BAC	44	6	3	0
MK	39	21	8	3

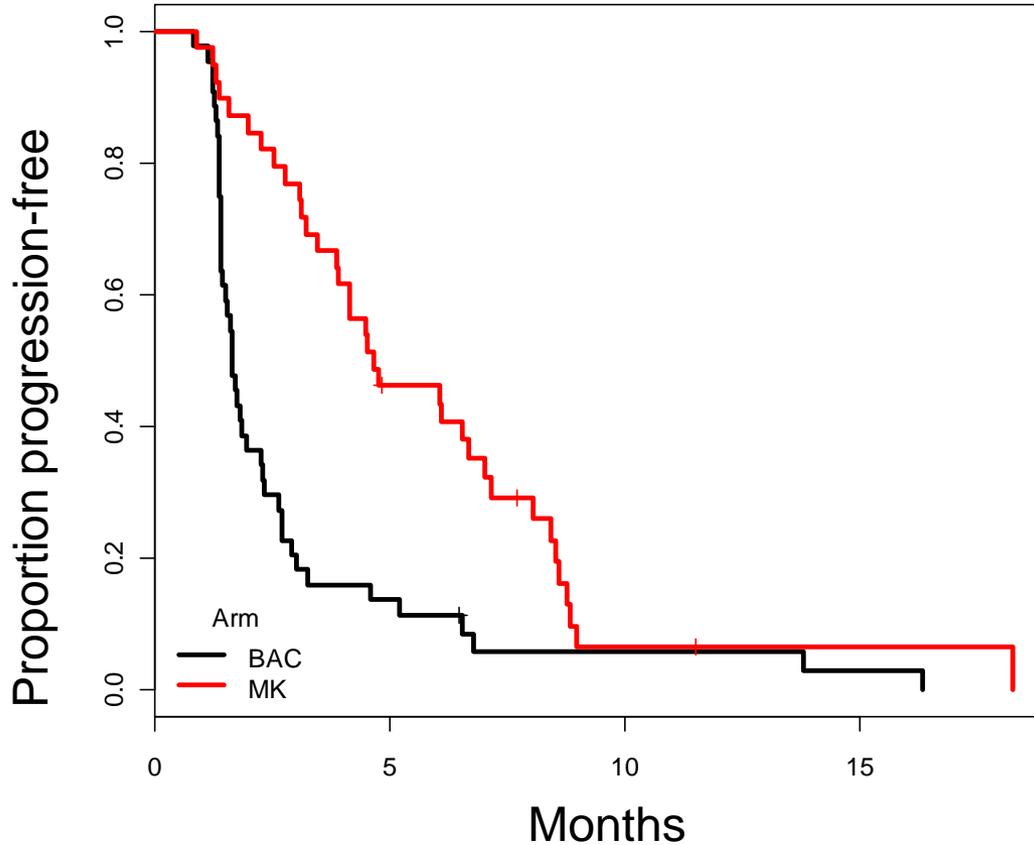
# Hepatic PFS – Investigator

<b>hPFS</b>	<b>Melblez Kit (N = 39)</b>	<b>BAC (N = 44)</b>
<b>Patients with hepatic progression or death</b>	79%	98%
<b>Median hPFS in months (95% CI)</b>	7.9 (5.2, 8.8)	1.6 (1.4, 2.3)
<b>Hazard Ratio 95% CI</b>	0.31 (0.19, 0.50)	
<b>p-value (Log-Rank Test)</b>	< 0.0001	

# Overall PFS

<b>Overall PFS</b>	<b>Melblez Kit (N = 39)</b>	<b>BAC (N = 44)</b>
<b>Median PFS in months (95% CI)</b>	4.7 (3.5, 7.0)	1.6 (1.4, 2.3)
<b>Hazard Ratio 95% CI</b>	0.40 (0.25, 0.63)	
<b>p-value (Log-Rank Test)</b>	<0.0001	

# Overall Progression Free Survival in Study 1: Patients with Ocular Melanoma

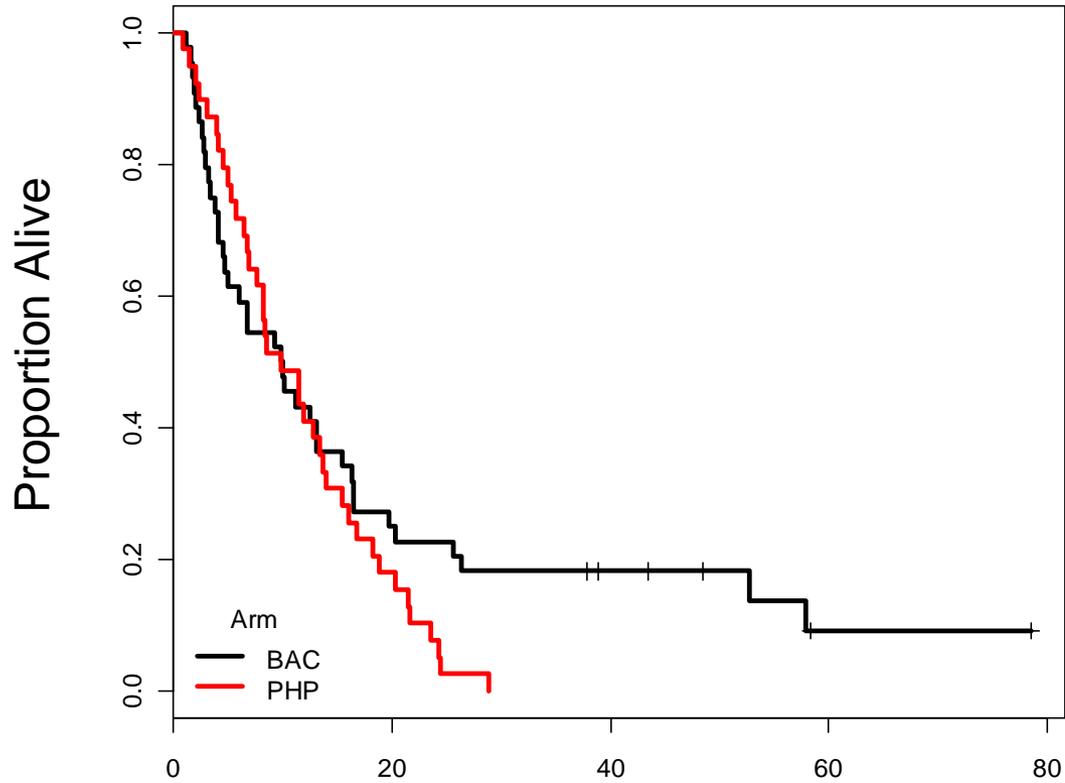


		Number at risk			
		0	5	10	15
BAC	44	44	6	2	1
MK	39	39	17	2	1

# Overall Survival

<b>Overall Survival</b>	<b>Melblez Kit (N = 39)</b>	<b>BAC (N = 44)</b>
<b>Patients who died</b>	100%	86%
<b>Median survival in months (95% CI)</b>	9.8 (6.7, 13.6)	10.0 (4.5, 15.4)
<b>Hazard Ratio 95% CI</b>	1.35 (0.85, 2.15)	
<b>p-value (Log-Rank Test)</b>	0.20	

## Overall Survival in Study 1: Patients with Ocular Melanoma



	Number at risk				
Arm	0	20	40	60	80
BAC	44	11	6	1	0
PHP	39	7	0	0	0

# Efficacy Summary

- Treatment with Melblez Kit demonstrated anti-tumor activity essentially limited to liver
- Magnitude of effect on overall PFS less than effect on hPFS
- Negative trend on OS demonstrated
- Questionable whether magnitude of effect on hPFS represents direct clinical benefit
- Must weigh anti-tumor activity in light of safety results



# Safety

# Safety Concerns

- Rate of toxic deaths
- Severe hypotension with stroke and myocardial infarction
- Incomplete cardiac toxicity risk assessment
- Severe and prolonged bone marrow suppression disproportionate to claimed filtration efficiency
- Severe hepatic injury, hemorrhage, and gastrointestinal perforation
- Role of filtration component

# Study 1 Adverse Reaction During Randomized Treatment Period

	<b>Melblez Kit N=42</b>	<b>BAC N=49</b>
<b>Median days on study</b>	120	62
<b>Median number of cycles</b>	3	NA
<b>Toxic Deaths</b>	10%	0%
<b>Grade 3-4 adverse reaction</b>	95%	41%
<b>Serious adverse reactions</b>	79%	16%
<b>Adverse reaction leading to discontinuation</b>	41%	8%

# Integrated Safety Database

<b>Study</b>	<b>Total in Cohort</b>	<b>Treatment Attempted</b>	<b>Completed 1 Cycle</b>
<b>Study 1 Randomized to Melblez Kit</b>	44	42	40
<b>Study 1 Cross-over to Melblez Kit post-hepatic progression</b>	28	28	25
<b>Study 2</b>	56	52	52
<b>Total</b>	128	122	117

# Toxic Deaths

<b>Fatal Adverse Reactions</b>	<b>N=122</b>
<b>Total</b>	<b>8 (7%)</b>
<b>Hepatic failure</b>	<b>3</b>
<b>Bone Marrow Suppression</b>	
<b>Streptococcal sepsis</b>	<b>1</b>
<b>Neutropenia and thrombocytopenia</b>	<b>1</b>
<b>Hemorrhagic Brain Lesions with     Thrombocytopenia and Renal     Hemorrhage</b>	<b>1</b>
<b>Gastric Perforation</b>	<b>1</b>
<b>Gastrointestinal Hemorrhage</b>	<b>1</b>

# Key Patient Selection

Visceral angiogram with embolization

Brain MRI

Cardiac stress test

Pulmonary function tests

Endoscopy

Liver biopsy

# Key Pre-procedural Steps

Inpatient admission

Intravenous hydration

Proton pump inhibitor

General anesthesia

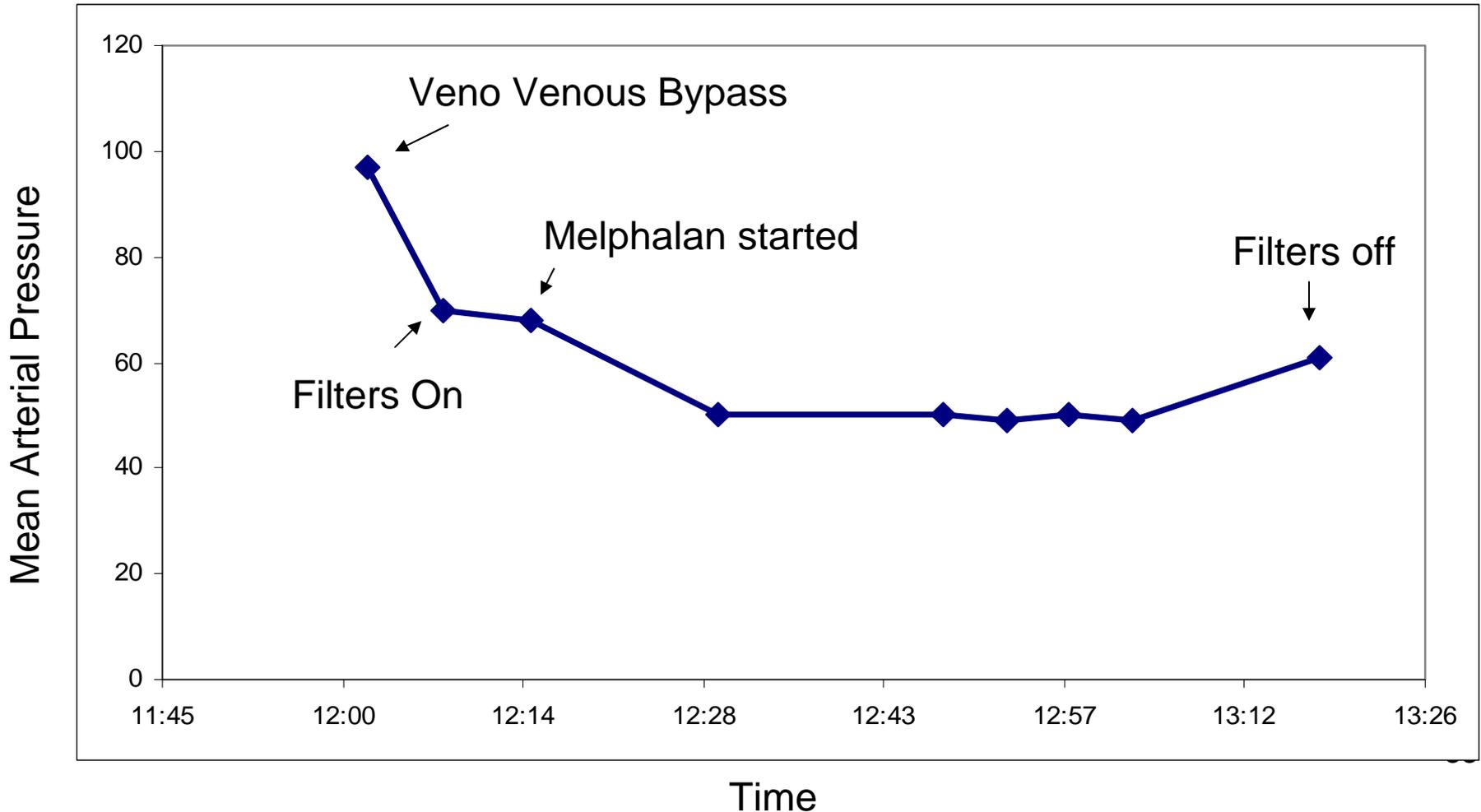
Anticoagulation

Vasopressors and vasopressor response

# Hypotension in Study 1

<b>BP Parameter (n=70)</b>	<b>Median Nadir Value (mmHg)</b>	<b>Median Change (mmHg)</b>
<b>Systolic Blood Pressure</b>	63	↓ 40
<b>Diastolic Blood Pressure</b>	40	↓ 20
<b>Mean Arterial Pressure</b>	49	-

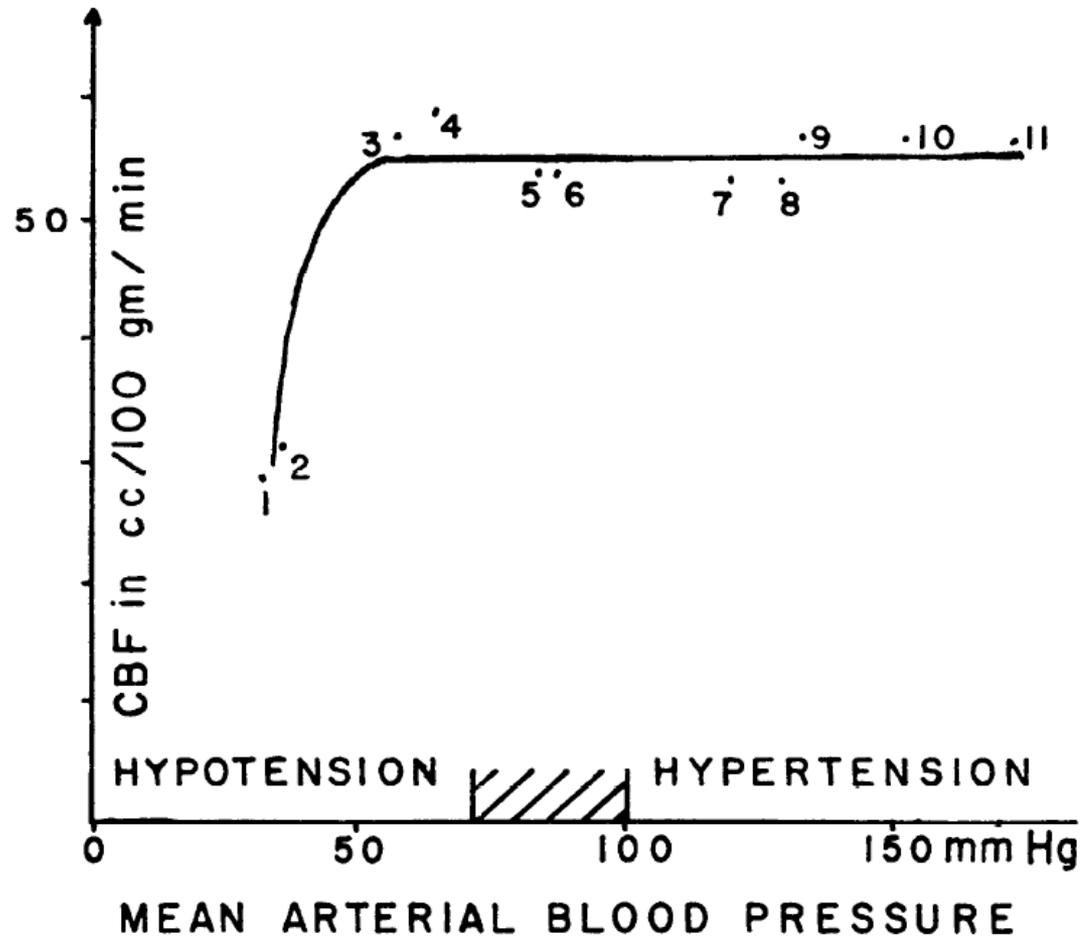
# Mean Arterial Pressure – Pt 33



# Hypotension

- Loss of cerebral autoregulation at MAP < 50 mmHg
  - Lower limit of cerebral autoregulation higher in patients with existing hypertension
- Loss of cerebral autoregulation leads to imbalance of oxygen supply and demand
- End result is ischemia
- Loss of cardiac and renal autoregulation at less defined levels

# Cerebral Autoregulation



# Cerebro- , Cardio- , Renovascular Outcomes

<b>Toxicity</b>	<b>Study 1 N=70</b>	<b>Integrated Safety Population n=122</b>
Mean Arterial Pressure < 50 mmHg	47%	45%
Cerebral Infarction	4%	4%
Myocardial Infarction	3%	2%
Troponin Elevation*	10%	6%
Acute Renal Failure	3%	2%

# Troponins

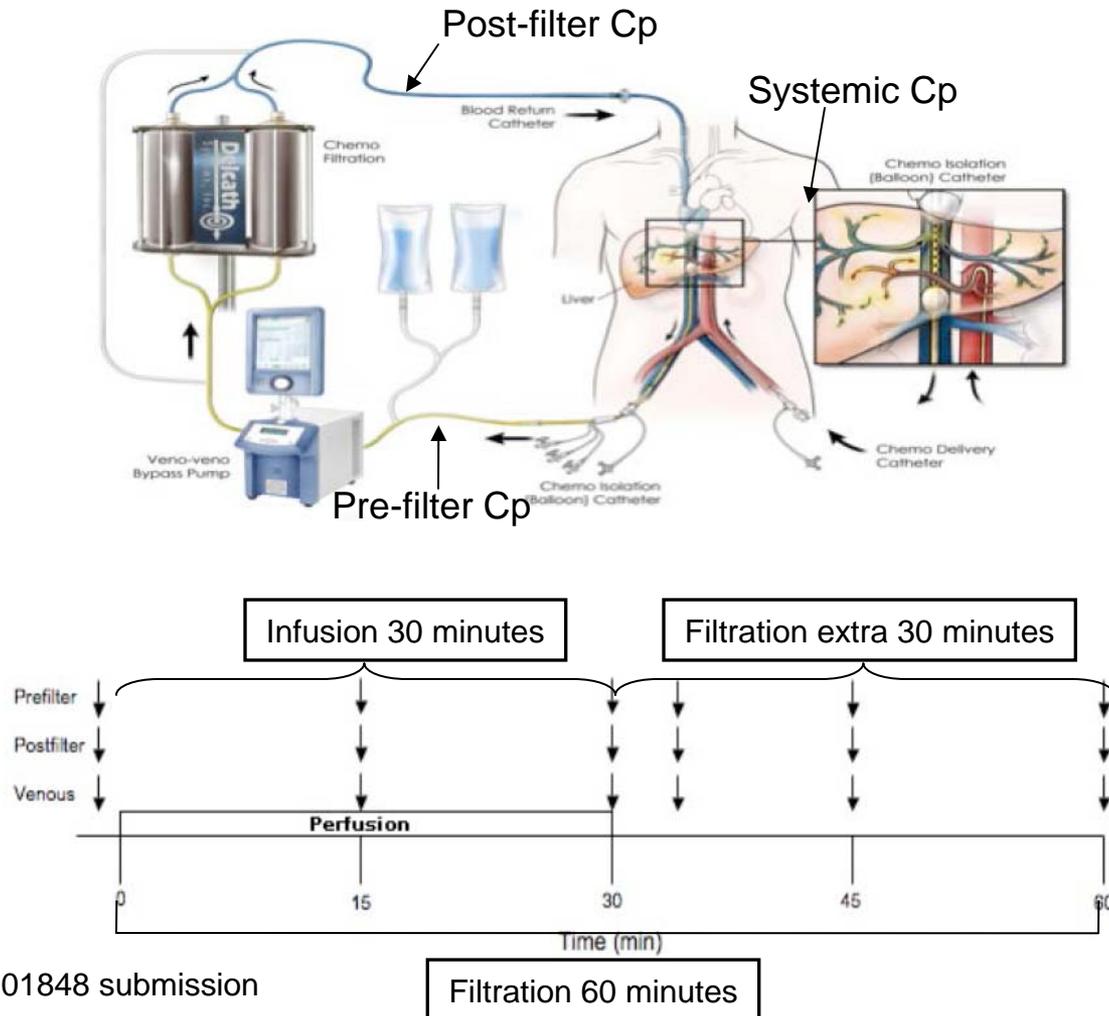
- Only 2 sites measured troponins
- At these sites, all patients undergoing Melblez Kit treatment had positive troponins (n=7, 100%)
- Overall incidence of troponin elevation may be higher but was not routinely monitored
- Clinical significance of silent myocardial infarction in this patient population is unknown

# Bone Marrow Suppression

Limited pharmacokinetic studies “predict” systemic exposure of melphalan post filtration consistent with low to intermediate intravenous dosing of melphalan

Observed pharmacodynamic effects on platelets and neutrophils consistent with high dose melphalan despite filtration

# Pharmacokinetic Sampling





# Bone Marrow Suppression

<b>Toxicity</b>	<b>Low Dose 16 mg/m<sup>2</sup></b>	<b>Melblez Kit 3.0 mg/kg IBW</b>	<b>High Dose (BMT) 200 mg/m<sup>2</sup></b>
<b>Dose (70 kg male)</b>	29 mg	Dose administered 210 mg Predicted systemic dose 63 mg	358 mg
<b>Grade 4 Neutropenia</b>	6%	71%	100%
<b>Recovery Neutrophils</b>	N/A	8 days	8 days with stem cell support
<b>Grade 4 Platelets</b>	5%	78%	100%
<b>Recovery Platelets</b>	N/A	16 days	7 days with stem cell support

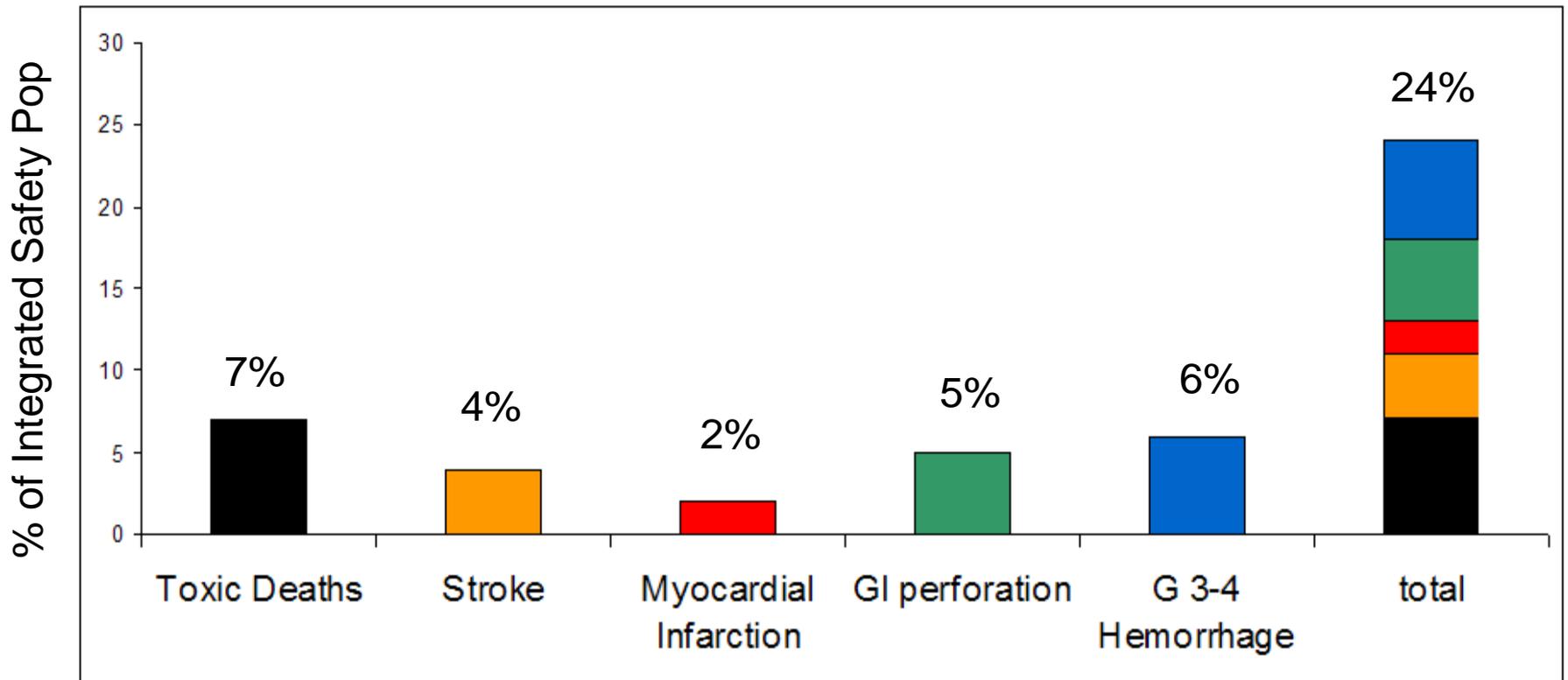
% Filter efficiency = [(Prefilter AUClast) - (Postfilter AUClast)]/(Prefilter AUClast) 40

# Key Grade 3-5 Adverse Reactions

<b>Hepatic Investigations</b>	
AST increased	32%
ALT increased	20%
Hyperbilirubinemia	21%
Blood alkaline phosphatase increased	14%
<b>Gastrointestinal Disorders</b>	
Gastrointestinal ulceration and perforation*	6%
<b>Hemorrhage</b>	
Hemorrhagic adverse reactions*	6%

\*Includes fatal adverse reactions

# Toxic Deaths and Major Non-Hematologic Adverse Reactions Occurring in Non-overlapping Patients



# Other Issues

- Median initial hospitalization of 4 days
- 50% required readmission lasting another 5 days
- Median cycle transfusion requirements of:
  - 3 units PRBCs
  - 8 units platelets
  - 10 units cryoprecipitate
  - 3 units of fresh frozen plasma
- Other concomitant medications:
  - Vasopressors, nitroglycerin, heparin, protamine, diuretics, growth factors, antibiotics

# Adverse Reaction Summary

- 7% incidence of fatal adverse reactions
- In addition, 4% incidence of stroke and 2% incidence of myocardial infarction
- Incomplete cardiac risk assessment
- Prolonged bone marrow suppression consistent with high dose melphalan in BMT
- Severe and potentially life threatening adverse reactions of hepatic injury, gastrointestinal perforation, and hemorrhage

# Concerns Regarding Device

- Filters are non-selective for melphalan and adsorb drugs, proteins, cytokines, cells, and electrolytes
- Clinical trials began in 2001 with Study 3 at NCI
  - Melphalan starting dose at 2.0 mg/kg IBW
  - Mixed tumor type
  - Asahi Hemosorba as filtration component
- Changed to Clark Cartridge when Asahi filters became unavailable

# Device Comparison

Type of Filter	Asahi Hemosorba	Clark Cartridge	Clark Cartridge
<b>Patient Population</b>	Studies 2 and 3 Mixed Histology	Study 2 Mixed Histology	Study 1 Melanoma
<b>Dose</b>	2.5-3.5 mg/kg IBW	2.5-3.0 mg/kg IBW	2.5-3.0 mg/kg IBW
<b>N</b>	30	41	70
<b>Filter Efficiency</b>	70%	73%	71%
<b>Median Nadir MAP</b>	60 mmHg	49 mmHg	49 mmHg

# Adverse Reaction Profile

Type of Filter	Asahi Hemosorba	Clark Cartridge	Clark Cartridge
<b>Patient Population</b>	Studies 2 and 3 Mixed Histology	Study 2 Mixed Histology	Study 1 Melanoma
<b>N</b>	30	41	70
<b>Toxic Deaths</b>	0	5%	9%
<b>Grade 3 or 4 AR</b>	77%	98%	93%
<b>Serious AR</b>	47%	90%	74%
<b>Toxicity resulting in discontinuation</b>	7%	41%	41%

# Organ Specific Adverse Reactions

Type of Filter	Asahi Hemosorba	Clark Cartridge	Clark Cartridge
<b>Patient Population</b>	Studies 2 and 3 Mixed Histology	Study 2 Mixed Histology	Study 1 Melanoma
<b>N</b>	30	41	70
<b>Febrile Neutropenia</b>	7%	22%	17%
<b>Grade 4 Neutropenia</b>	60%	71%	74%
<b>Grade 4 Platelets</b>	47%	78%	81%
<b>Hemorrhagic AR</b>	5%	13%	14%
<b>Gastrointestinal Ulceration/Perforation</b>	0	5%	7%
<b>Thrombosis</b>	0	5%	7%

# Device Summary

- Change in filter manufacturer during study 2 is associated with an increase of the incidence of toxic deaths and the incidence and severity of adverse reactions
- Increase in incidence and severity was not predicted by battery of in vitro tests or by pharmacokinetic data
- A new iteration of the Delcath Hepatic Delivery System is proposed for marketing
- This new combination drug-device product must undergo validation in adequate and well-controlled clinical trials demonstrating a favorable benefit-risk profile

# REMS

- Sponsor is proposing REMS with elements to assure safe use
- Largely mimics the didactic and experiential training used in pre-marketing testing
- REMS objective is to limit the risk to what was observed in clinical trials
- Additional patient management criteria would need to be validated in clinical trials to determine if toxicity can be improved
  - Without validation, cannot predict improved benefit-risk with REMS

# Efficacy Summary

## Study 1:

- 5.5 month improvement in hPFS (HR=0.42)
- 3 month improvement in overall PFS
- Trend toward overall survival detriment

# Safety Summary

## Integrated safety population

- 7% incidence of toxic death
- 4% incidence of cerebral infarction
- 2% reported incidence of myocardial infarction in the setting of an incomplete cardiac risk assessment
- > 70% grade 4 bone marrow suppression with a median time to recovery of > 1 week
- Hepatic injury, severe hemorrhage, and GI perforation

# Conclusions

- Melblez Kit treatment is associated with anti-tumor activity
- Melblez Kit treatment is associated with fatal and life threatening adverse reactions
- REMS program under review will not improve the observed benefit-risk profile