City of Hope

THIRD ANNUAL
ISSPP Congress 2022
International Society for the Study of Pleura and Peritoneum

APPENDICEAL CANCERS

Updates and Lessons from the BromAc Trial

Ernest Cheng, MD

Surgical Registrar, Department of Surgery
St George Hospital, Sydney
Kogarah NSW 2217

Advancing Innovative Therapies for Cancers That Invade the Peritoneum and the Pleura

Disclosures

- No relevant financial relationships.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

The off-label/investigational use of Bromelain and N-acetylcysteine (BromAc) will be addressed.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:
The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

The following CLC & IB components will be addressed in this presentation:

- Access to new treatment options in non-English speaking background patients.

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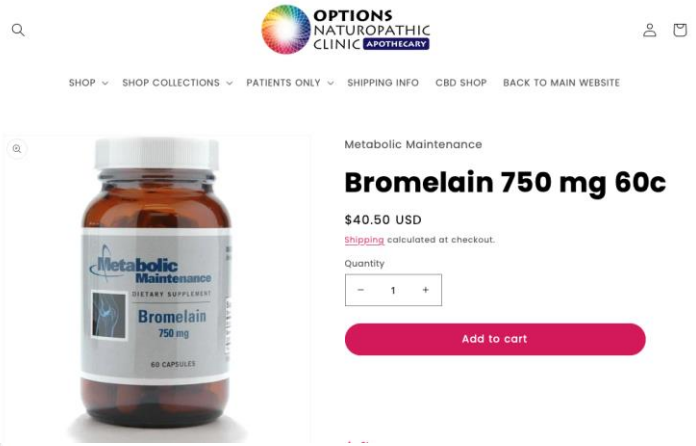
Contents

1. Background of the BromAc
    - Bromelain
    - Acetylcysteine
    - Oncological use of BromAc
2. Phase I Trial – Safety and efficacy
3. Phase II Trial – Current progress

Bromelain

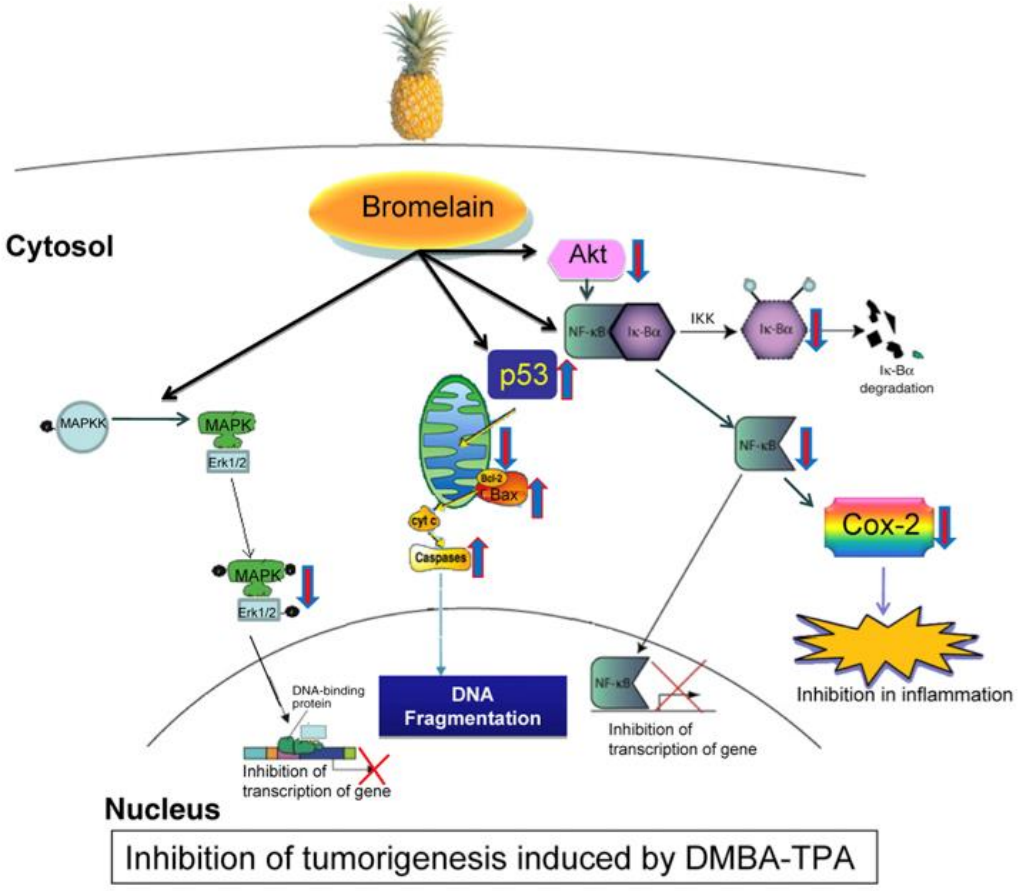
- Bromelain is a combination of proteolytic enzymes and non-enzymatic substances from the *Ananas comosus* pineapple stem
- Anti-inflammatory, anti-thrombotic, fibrinolytic and proteolytic function
- Widely used drug in
  - Digestive aid
  - Surgical debridement
  - Topical treatment for 3rd degree burns



…more than just natural therapy and wound care

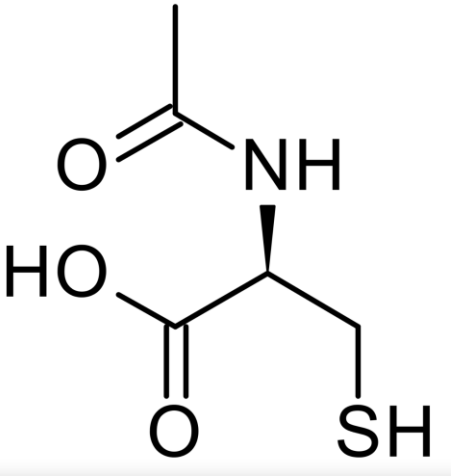
Significant effect on malignancy and cancer growth

- Inhibits tumorigenesis through p53 and caspase signaling pathways
- Regulates several key cellular pathways responsible for cancer invasions
- Immunomodulation e.g. inhibition of CD44 and TGF-B on cancer cells

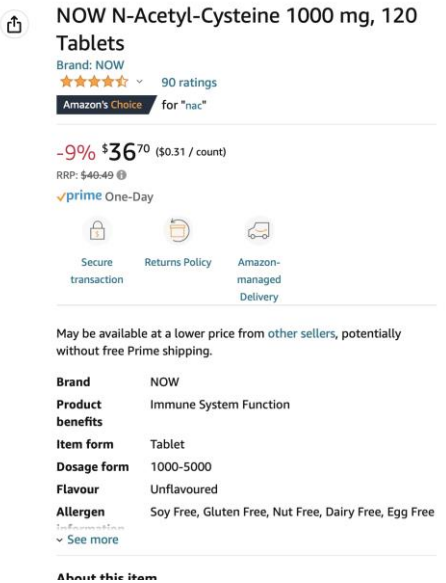


Kalra, N., Bhui, K., Roy, P., Srivastava, S., George, J., Prasad, S. and Shukla, Y., 2008. Regulation of p53, nuclear factor κB and cyclooxygenase-2 expression by bromelain through targeting mitogen-activated protein kinase pathway in mouse skin. *Toxicology and Applied Pharmacology*, 226(1), pp.30-37.

N-Acetylcysteine



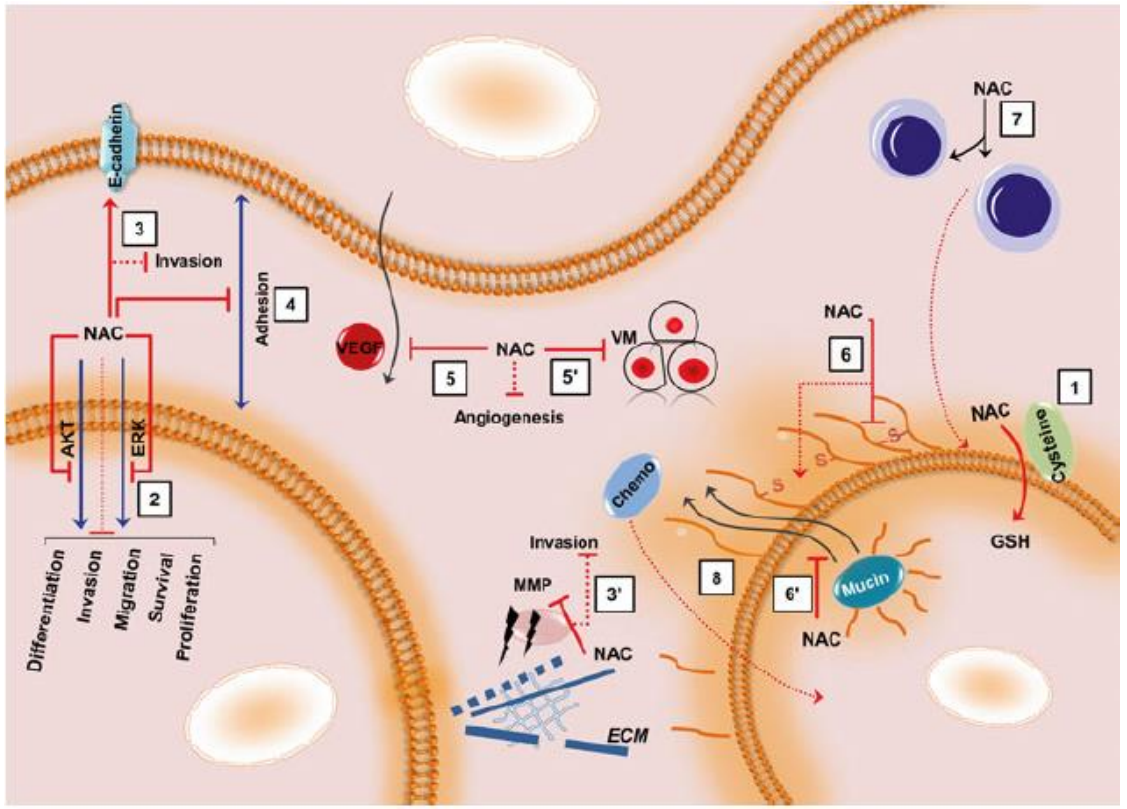
- N-Acetyl derivative of the amino acid L-cysteine
- Widely use ”anti-oxidant” in reducing disulfide bonds, scavenger for reactive oxygen species and precursor for glutathione biosynthesis
- Again, widely used in clinical practice
  - Paracetamol / acetaminophen overdose
  - Mucolytic for chronic bronchopulmonary disorders
  - Dissolve food bezoars
  - Dietary supplement



Effect on cancer

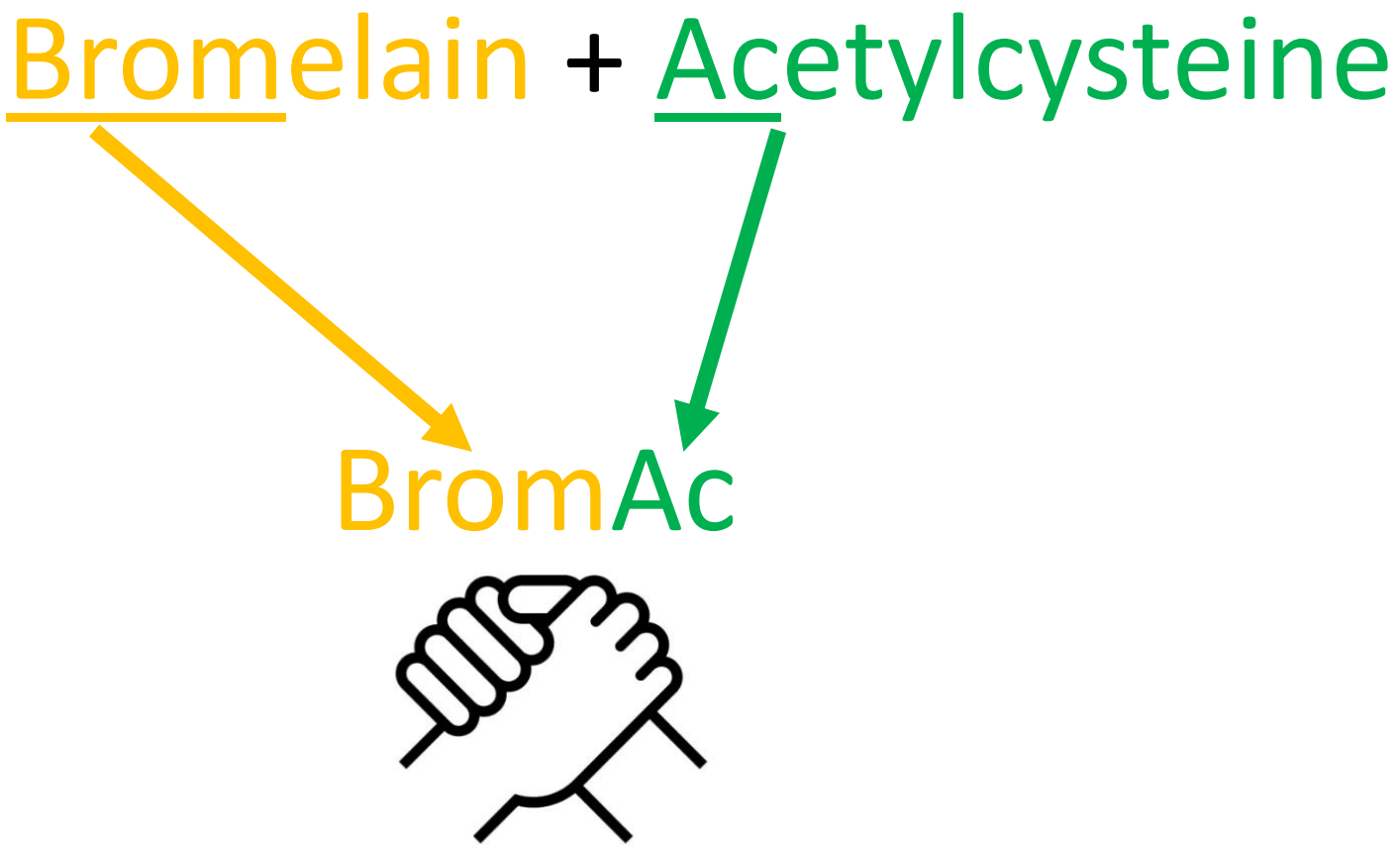
N-acetylcysteine

- Inhibits chemotactic and invasive activities of cancer cells
  - Matrix metalloproteinase (MMPs)
  - Vascular endothelial growth factors (VEGF)
- Immunomodulatory effect
  - Increase TNF-a expression
  - Enhance T-cell cytotoxicity against tumor cells in vivo and in vitro

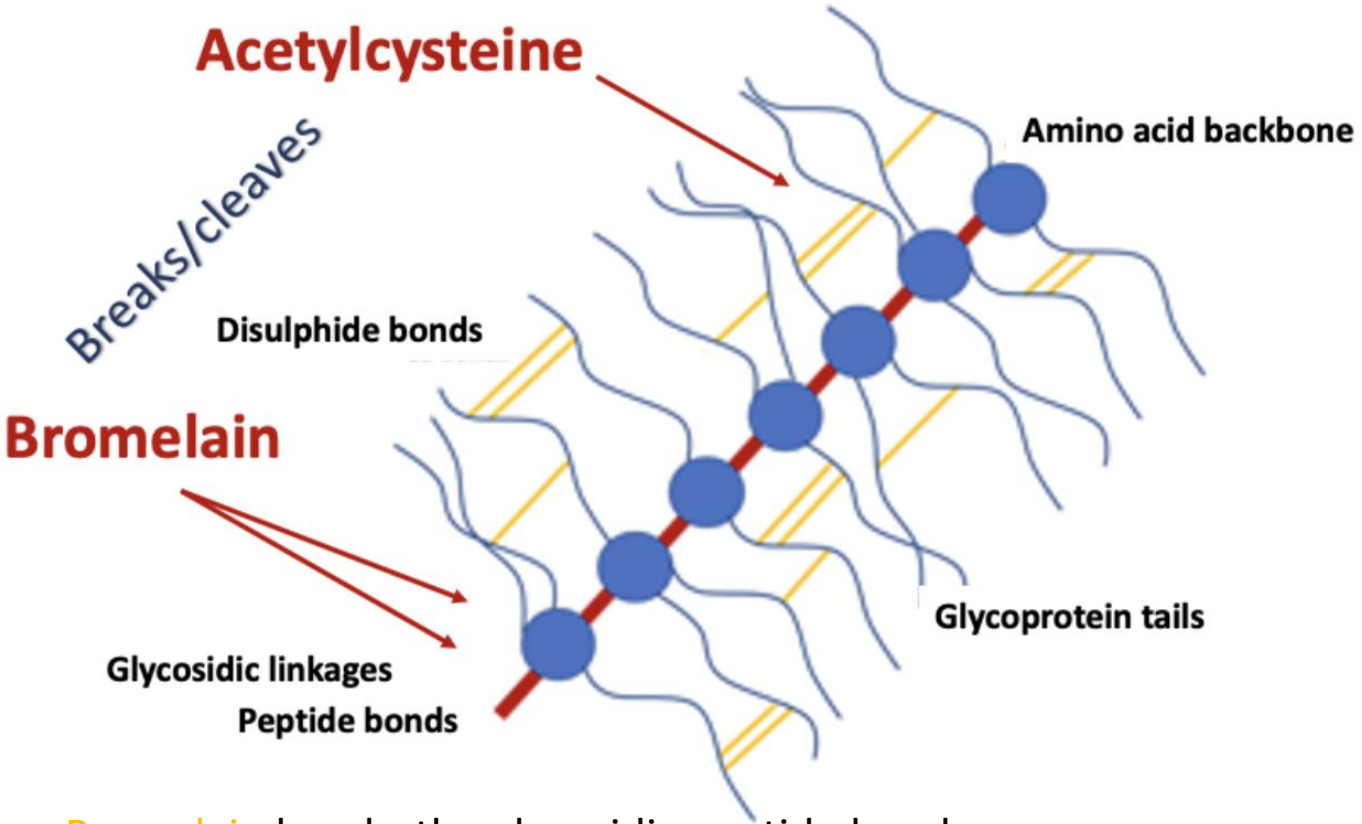


Amini, A., Morris, D. and Masoumi-Moghaddam, S., 2016. *Utility of Bromelain and N-Acetylcysteine in Treatment of Peritoneal Dissemination of Gastrointestinal Mucin-Producing Malignancies*. 1st ed. Australia: Springer International Publishing.

Bromelain + Acetylcysteine



BromAc and Mucinous cancers



Bromelain breaks the glycosidic peptide bonds
Acetylcysteine breaks the disulphide bonds

- Mucin are a set of proteins that form a physical barrier to protect the epithelial layer
- Mucin is aberrantly expressed in malignancy to allow for invasion, growth and survival

BromAc and Mucinous cancers

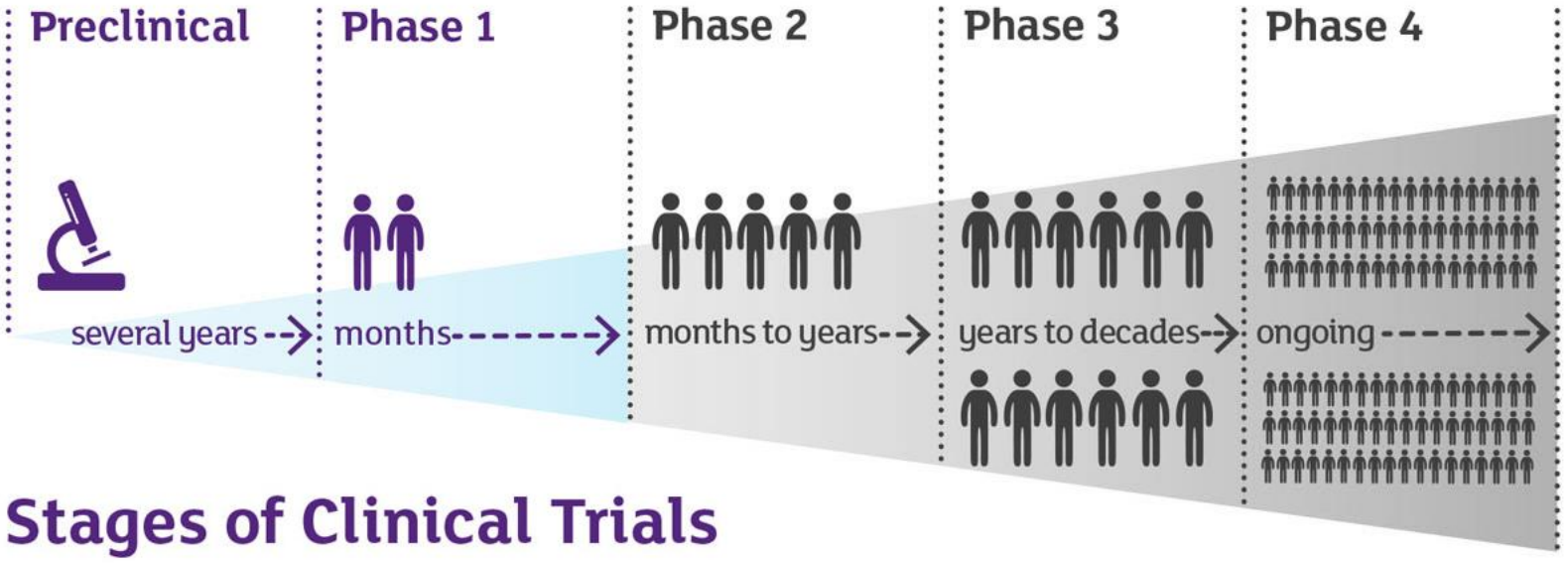
- Mucinous cancers and pseudomyxoma peritonei (PMP)
  - Standard of care is CRS + HIPEC (Maximally invasive surgical procedure)
  - Half of these patients reoccur
  - **There is no pharmacological treatment for recurrent PMP with mucin**

- BromAc can remove MUC1, MUC2, MUC4, MUC5AC and MUC5B
  - Inhibit cellular invasiveness, metastasis, proliferation and chemoresistance of appendix tumors

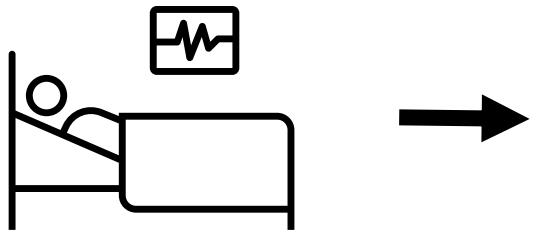
Synergy with chemotherapy agents (Gemcitabine and Doxorubicin) identified in vitro

Phase I study - Aim

- Determine the safety profile and efficacy of Bromelain and Acetylcysteine (BromAc) in treatment of mucinous peritoneal tumors

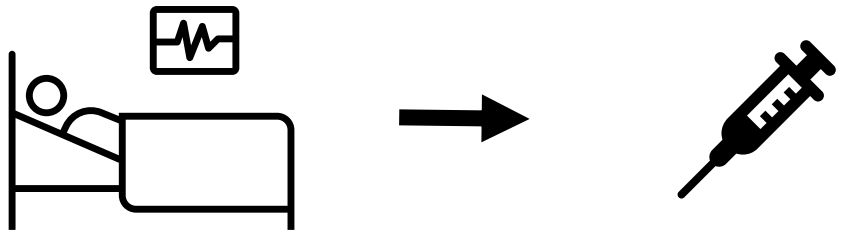


Phase I study - Methods



- Peritoneal spread of mucinous tumors
  - Inoperable
  - Declined surgery
- Computed Tomography (CT) scan to assess tumor burden and accessibility

Phase I study - Methods



- Gastrointestinal mucinous tumors
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  - Declined surgery
- Computed Tomography (CT) scan to assess tumor burden and accessibility

- Radiologically guided drain placement either intratumoral or intraperitoneal
- Administration of BromAc

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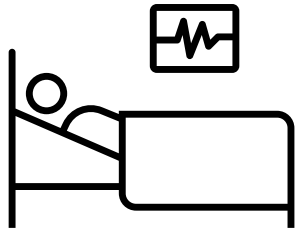
- Routine post procedural monitoring
- Repeat treatment with drain aspiration and re-administration of BromAc if indicated

Phase I study - Methods



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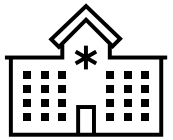
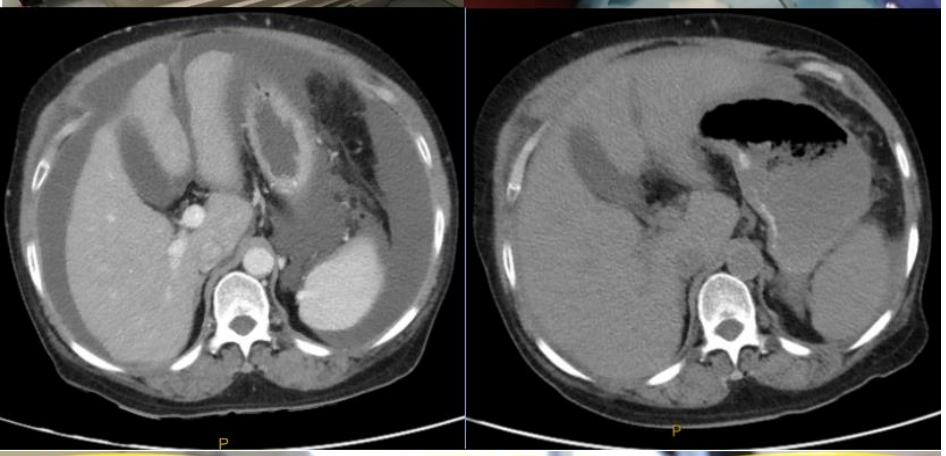


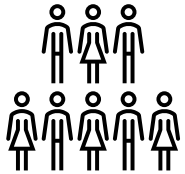
- Routine post procedural monitoring
- Discharged home after drain insertion
- Repeat treatment with drain aspiration and re-administration of BromAc if indicated

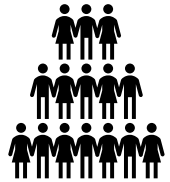
- Follow up blood tests and CT scans

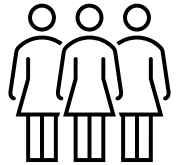


- Radiological guided drain insertion
  - If <u>unable</u> to aspirate, then for treatment to proceed
- Before (left) and after (right) treatment peritoneal mucinous tumor
- Aspirated contents of mucinous tumors

Phase I study – Summary of results







Demographics

20 patients

- 13 intra-tumoral
- 7 intraperitoneal

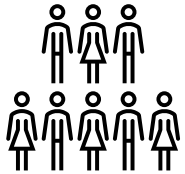
Primary tumor

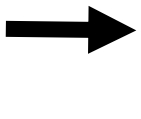
- 6 Low grade appendiceal tumors
- 10 Appendiceal adenocarcinoma
- 3 Mucinous ovarian carcinoma
- 1 Mucinous colon adenocarcinoma

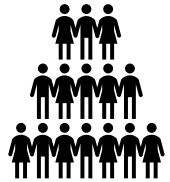
Adverse events

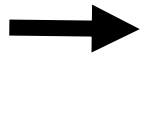
Efficacy

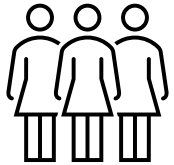
Phase I study – Summary of results











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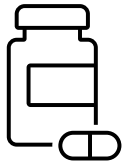
Adverse events

- 85% patients experienced an adverse event
- 12.5% serious treatment-related events
- 3 unplanned hospital admissions

Efficacy

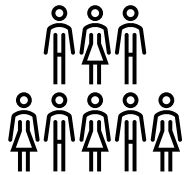
Phase 1 Study – Safety

- 3 patients required unplanned hospital admission
  - Liver hematoma due transhepatic drain placement, hypovolemia post procedure, peritoneal inflammation
- 5 site related technical failures
  - 2 drain dislodgements and 3 sites with hard tumors with no response
- Small bowel fistula and bladder leak both secondary to tumor invasion and removal of tumor mass
  - “tumor plugging”: contrast injection during drain insertion to assess cavity communication
- 1 patient underwent washout for intraabdominal sepsis



No drug-related deaths due to treatment-related adverse events

Phase I study – Summary of results



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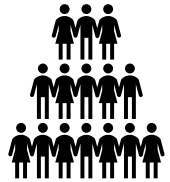

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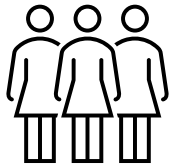


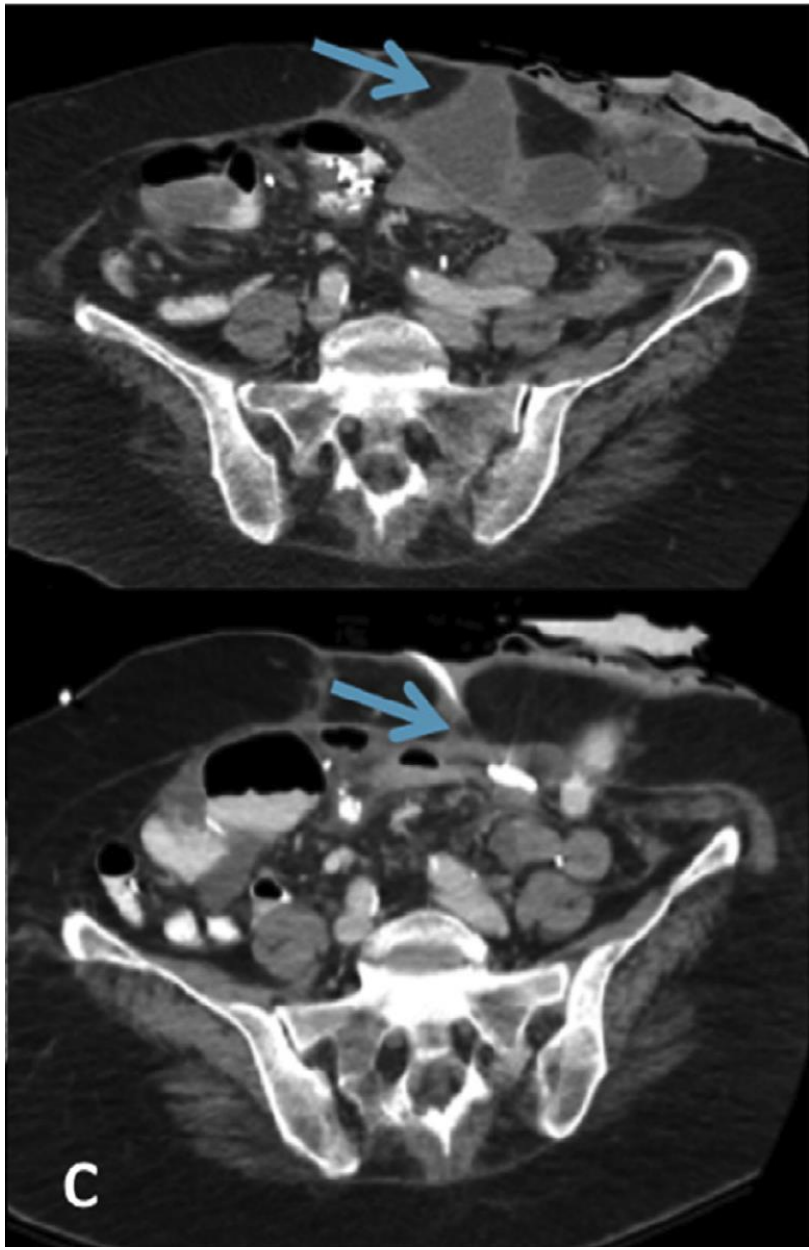
Efficacy

- 75% patients reported reduction in tumor related symptoms
- 85% patients and 73.2% of treated sites demonstrated an objective response
- 50% patients did not progress at 15.5 months

Phase 1 – Efficacy

Case example of 60M with low grade appendiceal tumor

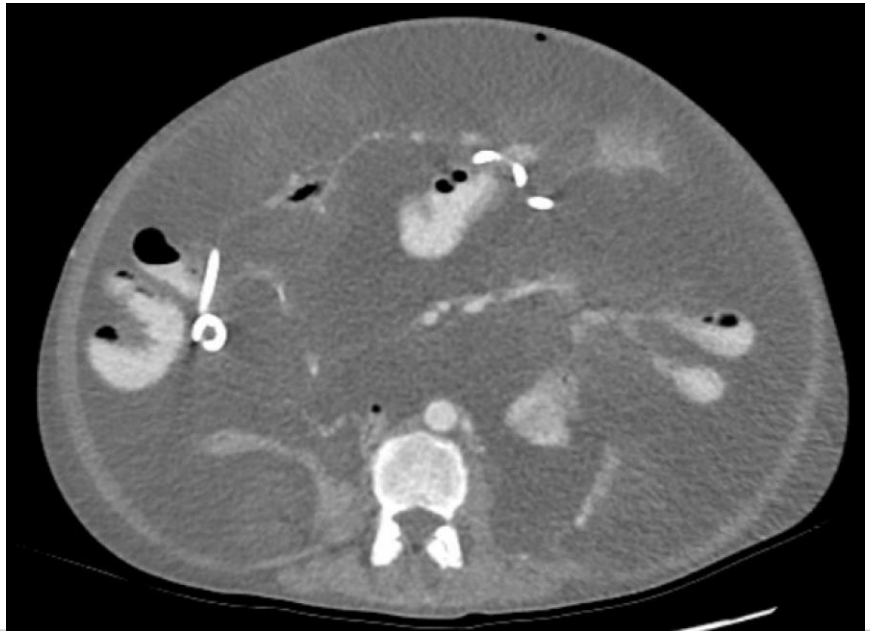
- Abdominal wall involved appendix tumor recurrence causing parastomal obstruction
- Treatment with BromAc resulted with non-operative relief of obstruction



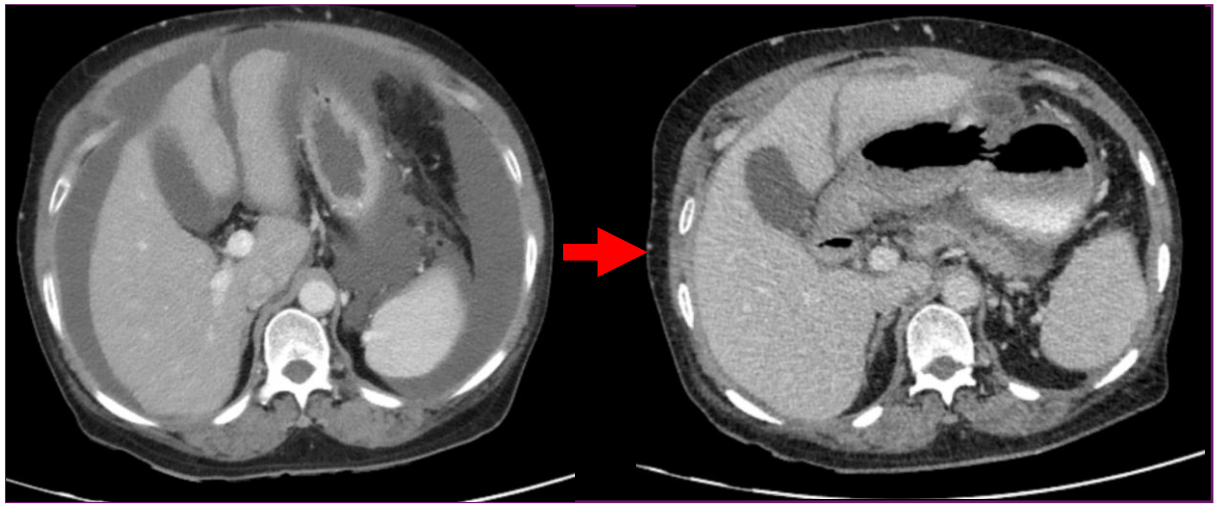
Phase 1 - Efficacy

61 year old female with mucinous ovarian cancer

- Intraperitoneal drain placement
- 23L of mucinous tumor aspirated – complete response



Phase 1 - Efficacy



63 year old female with ovarian cancer

- Significant disease with abdominal distention and pain
- Intraperitoneal treatment with BromAc (4 treatments) with a total of > 15L of mucinous tumor aspirated

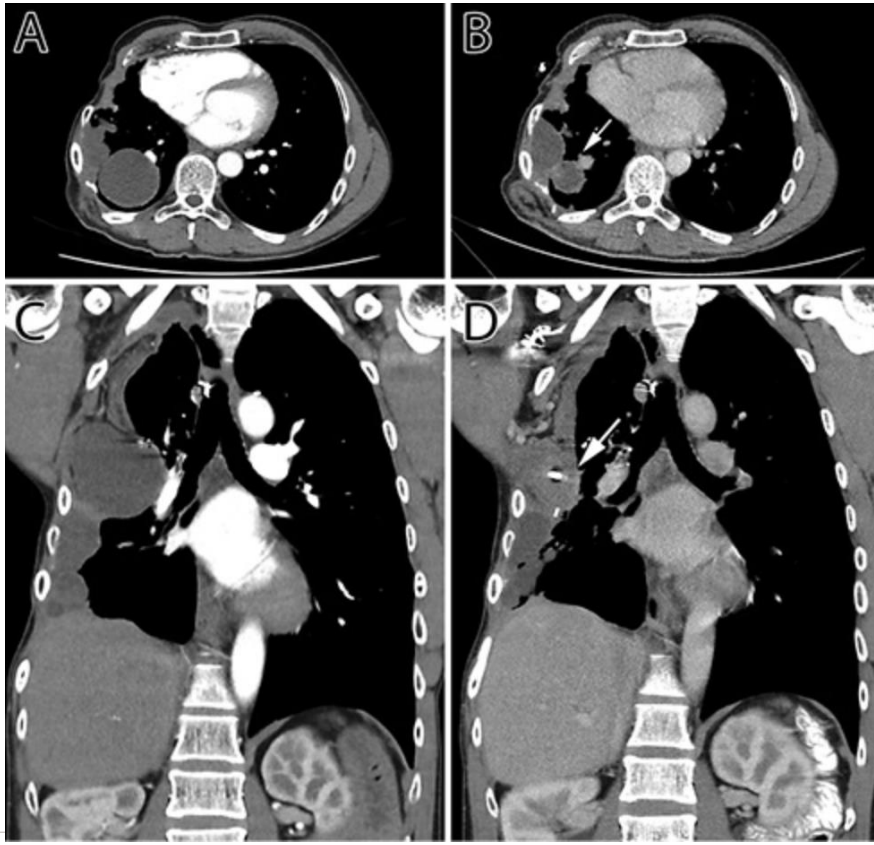
Phase 1 - Limitations

- Mucin hardness and drug penetration
    - Hard tumors require more treatments
- Tumor accessibility – e.g. fibrous loculations
- Advanced interventional radiologists required
- Long term effects of BromAc still unknown
    - Phase 2 aims to assess treatment longevity and further quality of life endpoints

Post-Phase I study

Compassionate use (21 in Australia, 11 overseas)

- Safety: Serious adverse event rate has remained the same
- Efficacy:
  - Quality of life survey (SF36) (n = 35) – significant improvement at 3 months
  - Improvement in tumor related symptoms increased to 86%
  - Median progression free survival of 5.1 months (median follow up 12.7 months)
    - 45% of patients have NOT progressed
- 2 patients with pleural recurrence of PMP treated with BromAc



A Phase 2 Multi-centre study of Bromelain and Acetylcysteine for Recurrent Peritoneal Mucinous Tumour or Pseudomyxoma Peritonei

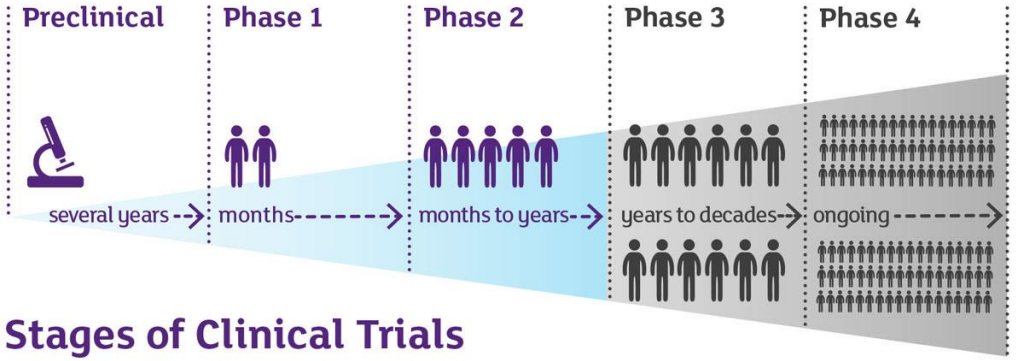
- **Several international centers including 4 in USA and 3 in Europe**
  - Mercy Medical Hospital (Baltimore), University of Pittsburgh Medical Centre (Pittsburgh), Wake Forest University Hospital (North Carolina), UT Southwestern Medical Center (Texas)
  - University of Ghent (Belgium), Eindhoven Cancer Centre (Netherlands)
- Aiming to recruit over 60 patients
- University of Cordoba (Spain) have treated 13 patients as part of the trial

Mercy BALTIMORE, MD
Sponsored by the Sisters of Mercy

UT Southwestern Medical Center

UPMC LIFE CHANGING MEDICINE

Atrium Health Wake Forest Baptist



Stages of Clinical Trials

*The studies recruits patients of all backgrounds including non-English speaking patients

Unanswered questions

- Soft vs hard tumors
- Intra-operative administration of BromAc prior to HIPEC
- Intraperitoneal administration with chemotherapy
- Percutaneous ”debulking” of tumor with BromAc as neoadjuvant therapy

Summary

- Bromelain and Acetylcysteine have anti-tumor properties against gastrointestinal cancer cells in the laboratory and in repeat animal models alone and in combination with some chemotherapy agents
    - Additive and synergistic effect is observed with these two drugs
- Complete: Phase 1 trial in metastatic mucinous cancer with peritoneal spread
    - Safety
    - Efficacy
- In progress: Phase 2 trial

Questions?

Contact information:

Professor David Morris
Peritonectomy and Liver Cancer Unit
St George Hospital
University of New South Wales
Kogarah, NSW
Australia
david.morris@unsw.edu.au

Dr Ernest Cheng
Peritonectomy and Liver Cancer Unit
St George Hospital
University of New South Wales
Kogarah, NSW
Australia
ernest.cheng1@unsw.edu.au