Contact Information:
xulu2@msu.edu

Future Directions in Alpha-Emitter Therapy for Metastatic Ovarian Cancer

Lu Lucy Xu [1,2,3], Satyendra Kumar Singh [1.2], Nelli Gaspar [2], Jinda Fan [2,4,5,6], Benjamin L. Viglianti [7], and Kurt R. Zinn [1-6, 8]

Institute for Quantitative Health Science & Engineering
MICHIGAN STATE UNIVERSITY

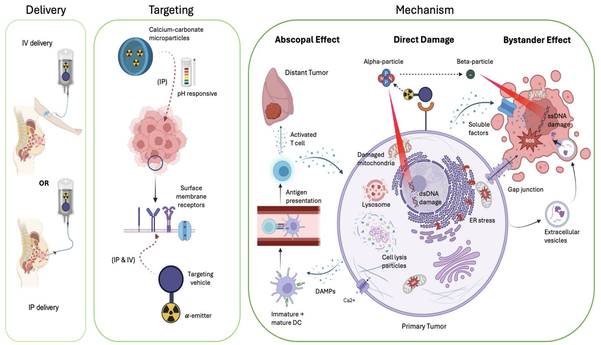
[1] Department of Biomedical Engineering, Michigan State University, East Lansing, MI, United States, [2] Institute for Quantitative Health Science and Engineering, Michigan State University, East Lansing, MI, United States, [3] College of Human Medicine, Michigan State University, East Lansing, MI, United States, [4] Departments of Pharmacology & Toxicology, and Radiology, Michigan State University, East Lansing, MI, United States, [5] Department of Radiology, Michigan State University, East Lansing, MI, United States, [6] Department of Chemistry, Michigan State University, East Lansing, MI, United States, [7]Department of Radiology, University of Michigan, Ann Arbor, Michigan, [8] Department of Small Animal Clinical Sciences, College of Veterinary Medicine, Michigan State University, East Lansing, MI, United States

Scan for abstract

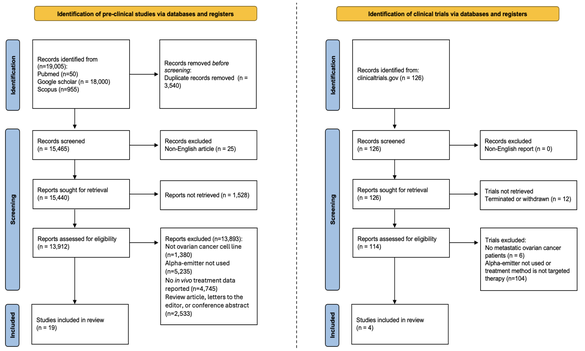
What is Targeted Alpha-Particle Therapy (TAT)?

- Ovarian cancer (OC) is difficult to treat due to the **high rates of recurrence and delayed diagnosis** leading to metastasis spreading throughout the peritoneal cavity (>70%) [1]
- TAT is an emerging cancer treatment that uses an **alpha-particle-emitting radionuclide linked to antibodies or other targeting molecules** to specifically target and destroy cancer cells [2]

Alpha-emitter	Half-life	Range (μm)	Emissions per decay	Max Energy (MeV)
^{224}Ra [28]	3.6 d	50-80	4 alpha [3]	5.79
^{225}Ac [29]	9.92 d	50-90	4 alpha, 2 be [4]	5.83
^{212}Pb* [30]	10.64 h	600	1 alpha, 2 be [5]	8.375
^{211}At [31]	7.21 h	55-80	1 alpha, 1 E [6]	5.982
^{212}Bi [30]	60.6 mins	40-100	1 alpha, 1 be [5]	6.090
^{213}Bi [29]	45.6 mins	40-100	1 alpha, 2 be [4]	5.869



Methodology (PRIMSA 2020 Flow Diagram)



Pre-clinical Evidence of TAT in Ovarian Cancer

Target	Vector (α-emitter /route)	Model	Dosing/Timing	Reported Toxicity	Primary Outcomes
FR-α	MOv18 (^{211}At/I.P.)	Nude mice, IP inoculation with OVCAR-3 using microscopic model or macroscopic with ascites model	Microscopic disease cohort: single ~450–555 kBq. Macroscopic/ascites cohort: single ~377–389 kBq. Controls: untreated	No specific toxicity or treatment-related deaths reported in microscopic-disease and advanced-disease/ascites cohort	Microscopic disease: median survival 213 days with ^{211}At -MOv18 vs. 138 days in untreated controls; tumor-free fraction (TFF)=33% of treated mice at 7 months
	Farletuzumab (^{211}At/I.P.)	Nude mice bearing IP disseminated OVCAR-3 ovarian cancer.	Single IP injection: ~170 kBq/mL. Controls: ^{211}At rituximab (unspecific) ~170 kBq/mL, unlabeled farletuzumab, and PBS.	Thyroid uptake observed when no blocking agent was used	TFF at endpoint: ^{211}At-farletuzumab ~91%, PBS 12%, unlabeled farletuzumab 9%, and unspecific ^{211}At-rituximab 14%; 6-10× higher antitumor effect for ^{211}At-farletuzumab compared with controls
	MOv18 (^{211}At/I.P.)	Female Balb/c nu/nu nude mice inoculation with OVCAR-3 cells IP. Therapy initiated 2 weeks post-inoculation (microscopic disease stage).	Single IP injection: ~300–400 kBq per mouse (2 weeks after tumor inoculation). Controls: PBS, unlabeled MOv18, or ^{211}At-unspecific mAb (C242).	No obvious side effects reported at therapeutic dosing (~300–400 kBq); WBC depression was insignificant	TFF: IP ^{211}At -MOv18 at ~400 kBq 93%, IP unlabeled MOv18 10%, non-specific control 25%, and PBS 0%; all surviving animals were free from macroscopic tumors; durable complete responses in ~1/3 of mice at 7 months; ascites prevented in almost all treated animals
MUC1	C595 (^{213}Bi /I.P.)	Nude mice bearing OVCAR-3 ovarian cancer cells as an intraperitoneal ascites model.	Single IP injection: 355, 710, or 1065 MBq/kg (9 days post-inoculation). Controls: not specified in the dosing/timing cell.	Minimal toxicity observed, no leukocyte depression at 90 days, mild renal tubular changes/mild radiation nephropathy at 1065 MBq/kg	Single 355 MBq/kg IP prolonged survival by ~25 days vs control in the ascites model
CD138	B-B4 (^{213}Bi /I.P.)	Nu/nu nude mice, inoculated IP with SHIN-3-Luc cells. Therapy administered 3 days post-inoculation to mimic postoperative minimal residual disease.	Single IP injection: 7.4 MBq or 11.1 MBq (3 days post-inoculation). Controls: HIPEC (oxaliplatin 5 mg/kg, 42° C, 90 min) and HIPEC + alpha-RIT.	Transient, mild hematologic effects with insignificant decreases in WBC and platelets; no acute blood toxicity at 7.4–11.1 MBq ^{213}; transient weight loss recovered by day 7	Median survival: control 68 d; HIPEC 37.5 d; HIPEC + α-RIT 75.5 d; ^{213}Bi-B-B4 7.4 MBq >90 d (7/11 alive at 90 d); ^{213}Bi-B-B4 11.1 MBq >90 d (5/7 alive); ascites & tumor burden markedly reduced in α-RIT groups compared with controls/HIPEC
B7-H3	376.96 (^{212}Bi&^{212}Pb)	ES-2 (ascites) IP xenografts (athymic mice), A2780cp20 (nodular) IP xenografts (athymic mice)	Single IP injection: 0.17, 0.35, 0.51 MBq for ES-2 (day 4 tumors) and 0.35, 0.53, 0.70 MBq ± weekly carboplatin 50 mg/kg (carboplatin given 1 day before ^{212}Pb-376.96) for A2780cp20 (day 10 tumors). Controls: ^{212}Pb-F3-C25 and untreated.	Transient weight loss recovered by 2–4 weeks; no blood/organ pathology	Treated groups with ^{212}Pb -376.96 (alone or with carboplatin) survived 2-3× longer than those treated with ^{212}Pb-F3-C25 or untreated controls
HER2	2Rs15d single-domain antibody fragment (^{213}Bi/ I.V.)	Female athymic nude mice, SKOV-3 IP (luciferase+)	Study 1 (fractionated I.V. injection on days 7.8. and 24): 1.01 ± 0.05 MBq x3 or 2.12 ± 0.11 MBq x3; vehicle control. Study #2 (fractions on days 7, 9, 11): 1.03 ± 0.03 MBq x3 or 0.5 ± 0.08 MBq x3; same two regimens + trastuzumab (loading 7.5 mg/kg, then 3.5 mg/kg maintenance); trastuzumab alone; vehicle.	Dose-limiting renal toxicity (≥2 MBq) caused kidney histopathology (tubular dilatation/degeneration/necrosis and medullary interstitial fibrosis + mononuclear infiltrates); >20% weight loss in high dose and repeat-dose group; spleen hemosiderin in red pulp with increasing activity	Study 1: 1 MBq×3 median survival 68 d vs 56 d control; 2 MBq×3 not significantly better than control Study 2: 0.5 MBq×3 mean overall survival 80 d vs control 53 d, 1 MBq×3 median 67 d vs 53 d control, 1 MBq×3 + trastuzumab median 145 d vs 109 d trastuzumab alone, and 0.5 MBq×3 + trastuzumab median 140.5 d (increased 28% vs trastuzumab alone) BLI showed delayed tumor growth in all treated groups.
	Pre-targeted 1: Bispecific antibody (anti-HER2) 2: 225Ac-Proteus-DOTA (^{225}Ac/I.P.)	Female athymic nude mice, injected IP with SKOV3-luc cells	One or two cycles of PRIT. 5 mg/kg bsAb (day 0) per cycle→ 24 h later 37 kBq ^{225}Ac-Proteus-DOTA (day 1). Day 15 repeat for 2nd cycle group. Control: irrelevant bispecific antibody and radiohapten	Well tolerated, no significant weight loss, minimal–mild renal tubular changes, and hematology within reference limits.	2-cycle PRIT group: 85% (17/20) alive at day 133 vs 37% (10/27) in control; 15/15 PRIT-treated mice had no viable carcinoma
TAG-72	TAG-72 CC49 (^{225}Ac /I.P.)	Female athymic nude mice with subcutaneous OVCAR-3 xenografts (~100 mm^3 at therapy start)	Single-dose cohorts: 1.85, 3.7, or 7.4 kBq per mouse. Fractionated regimen: 1.85 kBq initial dose + 0.74 kBq weekly x5 (total 5.55 kBq). Controls: vehicle, unlabeled huCC49, or ^{225}Ac-IgG.	Dose-dependent weight loss <20%; fractionated was better tolerated than a single 7.4 kBq dose (less weight loss, reduced acute toxicity); targeted 7.4 kBq had better tolerability than untargeted	Single-dose efficacy (7.4 kBq): tumor regression in most mice; median survival >120 days vs ~30–40 d in controls
MUC16	AR9.6 (^{225}Ac /IV)	Female athymic nude (Nu/Nu) mice subcutaneous OVCAR3 xenografts; Initial injection of 10 × 10^6 cells, followed by 5 × 10^6 cells one week later; Tumors allowed to reach ~200–600 mm^3 before treatment.	RIT: Single dose 0.037 MBq PRIT: AR9.6-TCO followed by 0.148 MBq 72 h later. Controls: saline; IgG RIT control: 0.037 MBq, single dose; IgG PRIT control: IgG-TCO followed by 0.148 MBq AR9.6 72 h later	Transient hematologic toxicity (WBC/RBC/platelets recovered by 2–4 weeks); early weight loss (~5–10% with recovery by day 14) with 1 PRIT mouse euthanized for >20% loss); mild-moderate renal tubulonephropathy; moderate ovarian cortical atrophy/follicular loss	Median survival: AR9.6 RIT ~80 days, AR9.6 PRIT ~80 days IgG ~ 60 days, and saline controls ~25 days; complete tumor responses without recurrence in surviving mice from both treatment groups
PTK7	chOI-1 (^{212}Pb/I.P.)	Female BALB/cOlaHsd-Foxn1^{nu}/^{nu} nude mice, 6–8 weeks old, IP xenograft model A2780 cells. Treatment initiated at day 18 post-inoculation.	Single IP injection: 458 kBq ^{212}Pb –TCMC–chOI-1 (~50 MBq/mg) on day 18 post-tumor inoculation Controls: free ^{212}Pb (470 kBq), unlabeled chOI-1 (10 μg), and vehicle formulation buffer.	Mild transient weight loss stabilized by day 5; no comprehensive toxicity assessment performed (no hematology/organ pathology)	Median survival: 42 days for ^{212}Pb-TCMC-chOI-1 and 22–25.5 days for all control groups; reduced abdominal distension and tumor burden compared with controls.
	chOI-1 (^{212}Pb/I.P. and I.V.)	Female athymic nude mice IP xenograft model: SKOV-3-luc cells. Treatment initiated 3 days post-inoculation to model early peritoneal disease.	Single IP injection: 180 kBq and 405 kBq ^{212}Pb –TCMC–chOI-1 (3 days post-inoculation). Controls: saline, unlabeled chOI-1, ^{212}Pb –TCMC–hIgG (211 or 384 kBq).	Toxicity not comprehensively assessed; need blood counts and histopathology in future studies	TFF: 180 kBq ^{212}Pb –TCMC–chOI-1 100%. 405 kBq ^{212}Pb –TCMC–chOI-1 87.5% (7/8), ^{212}Pb –TCMC–hIgG controls 25%, non-radioactive controls 0%. TFF= total IP tumor weight ≤ 0.020 g at endpoint.

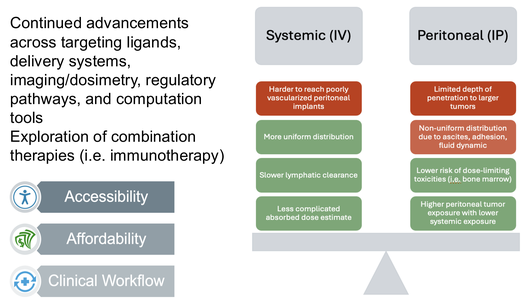
*studies using ^{211}At and ^{213}Bi targeting NaPi2b (SLC34A2) using MX35 F(ab')$_2$ with single, fractionated, and pre-targeted dosing were not included in the table above, treatment was relatively well-tolerated with sufficient anti-tumor efficacy and ascites elimination

Clinical Evidence of TAT in Ovarian Cancer

Agent (Target)	α-emitter	Route	Phase /Status	Patient Population	Dosing Schema	Primary Outcomes
MX35 F(ab')$_2$ (NaPi2b/SLC34A2)	^{211}At	I.P.	Phase I completed, long-term follow-up	Ovarian cancer patients in clinical remission, microscopic residual	Escalating doses 20-215 MBq/L range	Toxicity limited to transient, low-grade procedural symptoms; hematologic, renal, and late radiation-induced toxicities were not observed
Trastuzumab (HER2)	^{212}Pb	I.P.	Phase I completed	Patients with HER2+ ovarian and other peritoneal carcinomatosis	Escalating doses up to 27 MBq/m^2	Minimal toxicity across the initial dose cohorts and no late toxicity observed in most patients with >1 year follow-up
Radspherin CaCO$_3$ microparticles	^{224}Ra	I.P.	Phase 1/2a completed; Phase 2 randomized ongoing	Ovarian cancer patients undergoing cytoreductive surgery ± HIPEC with residual microscopic peritoneal disease	Escalating doses at 1-2-4-7 MBq, not reported for ongoing trial	No dose limiting toxicities across the 1–2–4–7 MBq dose levels, with one serious adverse event related to administration. The ongoing trial is intended to track safety/toxicity (adverse events) alongside efficacy.

Challenges and Future Opportunities

- Continued advancements across targeting ligands, delivery systems, imaging/dosimetry, regulatory pathways, and computation tools
- Exploration of combination therapies (i.e. immunotherapy)



Acknowledgements

- **Funding:** This work was supported with funding available to Kurt R. Zinn as the Hickman Family Endowed Chair in Oncology at Michigan State University. Travel funding was provided by Michigan Radiology Society.
- Images were made using BioRender

References: [1] Garzon, S.; Laganà, A.S.; Casarin, J.; Raffaelli, R.; Cromi, A.; Franchi, M.; Barra, F.; Alkatout, I.; Ferrero, S.; Ghezzi, F. Secondary and Tertiary Ovarian Cancer Recurrence: What Is the Best Management? Gland Surg. 2020, 9, 1118–1129. [2] Tafreshi, N.K.; Doligalski, M.L.; Tichacek, C.J.; Pandya, D.N.; Budzevich, M.M.; El-Haddad, G.; Khushalani, N.I.; Moros, E.G.; McLaughlin, M.L.; Wadas, T.J.; et al. Development of Targeted Alpha Particle Therapy for Solid Tumors. Molecules 2019, 24. [3] Bergeron, D.E.; Collins, S.M.; Pibida, L.; Cessna, J.T.; Fitzgerald, R.; Zimmerman, B.E.; Ivanov, P.; Keightley, J.D.; Napoli, E. Ra-224 Activity, Half-Life, and 241 keV Gamma Ray Absolute Emission Intensity: A NIST-NPL Bilateral Comparison. Applied Radiation and Isotopes 2021, 170, doi:10.1016/j.apradiso.2020.109572. [4] Pommé, S.; Marouli, M.; Suliman, G.; Dikmen, H.; Van Ammel, R.; Jobbágy, V.; Dirican, A.; Stroh, H.; Paepen, J.; Bruchertseifer, F.; et al. Measurement of the 225Ac Half-Life. Applied Radiation and Isotopes 2012, 70, 2608–2614, doi:10.1016/j.apradiso.2012.07.014. [5] Azure, M.T.; Archer, R.D.; Sastry, K.S.R.; Rao, D. V; Howell, R.W. Biological Effect of Lead-212 Localized in the Nucleus of Mammalian Cells: Role of Recoil Energy in the Radiotoxicity of Internal Alpha-Particle Emitters 1. Radiat. Res. 1994. [6] Feng, Y.; Zalutsky, M.R. Production, Purification and Availability of 211At: Near Term Steps towards Global Access. Nucl. Med. Biol. 2021, 100–101, 12–23.

Scan for full list of references