ADVANCES IN MANAGEMENT OF COLORECTAL CANCER

DR. RACHEL RAJU

MEDICAL ONCOLOGIST (PASO MEDICAL, PENINSULA HEALTH)

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TOPICS

- Neoadjuvant approach in colorectal cancer
- Approach to treatment of metastatic (stage IV) in colorectal cancer
- Role of immunotherapy in colorectal cancer
- Current and emerging biomarker driven therapies in colorectal cancer

NEOADJUVANT APPROACH IN RECTAL CANCER

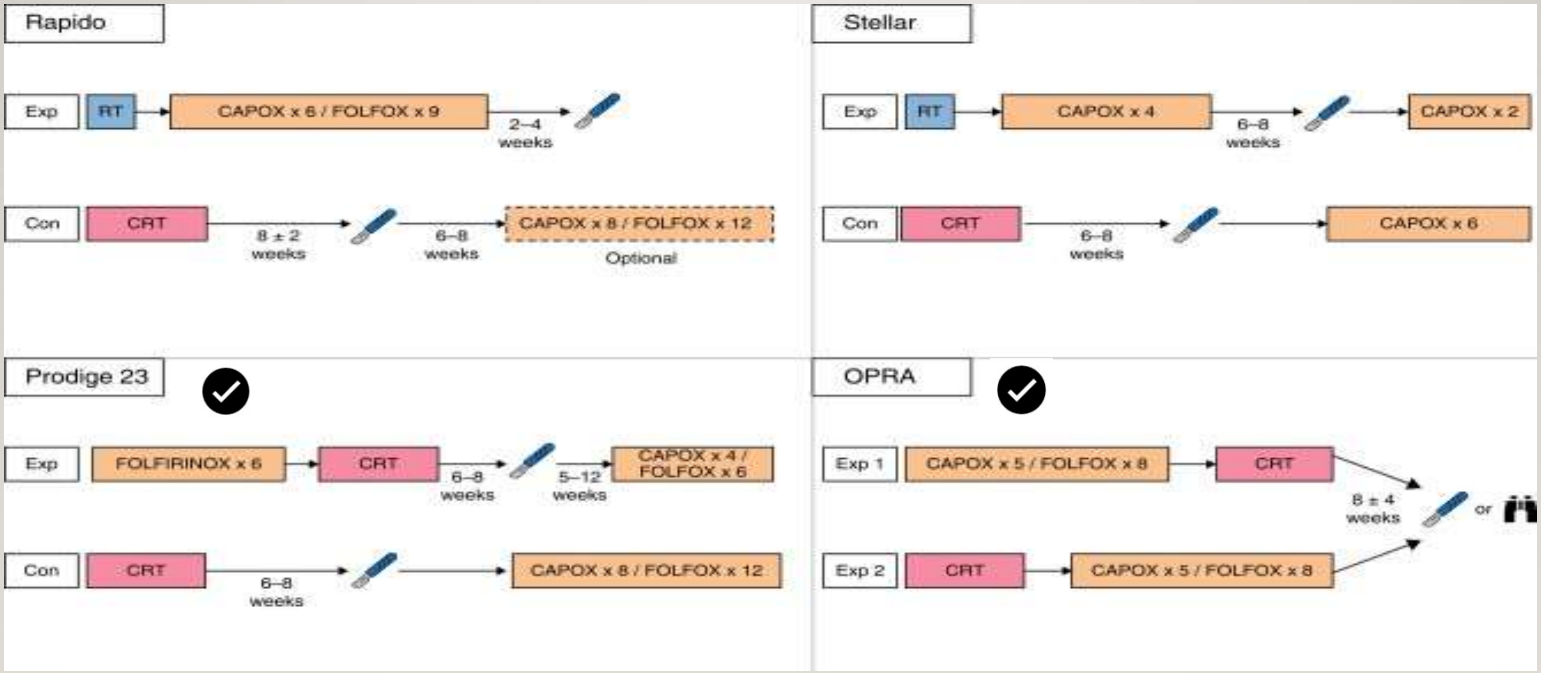
- Rationale for neoadjuvant approach:
  - induce downstaging/downsizing in order to improve R0 resection rates
  - sterilize visible or occult extra-mesorectal pelvic spread
  - reduce surgical complexity and potentially increase the possibility of sphincter preservation

- Tumour factors that may benefit from neoadjuvant therapy:
  - tumour height
  - cT-stage
  - any enlarged suspicious lateral lymph nodes are present
  - cN-stage
  - presence or absence of extramural venous invasion (EMVI)

TOTAL NEOADJUVANT THERAPY (TNT) IN RECTAL CANCER

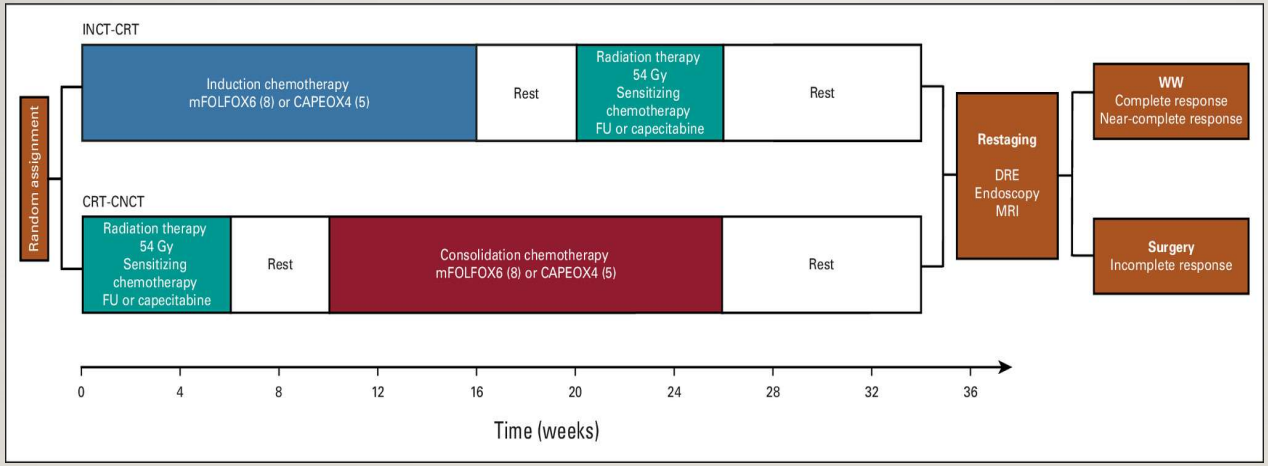
- Neoadjuvant approach usually involves combination of chemotherapy and radiotherapy
- Until recently, neoadjuvant therapy for rectal cancer consisted of two main strategies—short-course radiotherapy or long-course chemoradiotherapy with concurrent low- dose 5-FU based chemotherapy as radiosensitizer
- Adjuvant chemotherapy following rectal cancer surgery has been used in many countries with the aim of reducing the risk of systemic recurrence – but modest compliance due to postoperative recovery/ complications

TOTAL NEOADJUVANT THERAPY (TNT) IN RECTAL CANCER



ORGAN PRESERVATION IN LOCALLY ADVANCED RECTAL CANCER

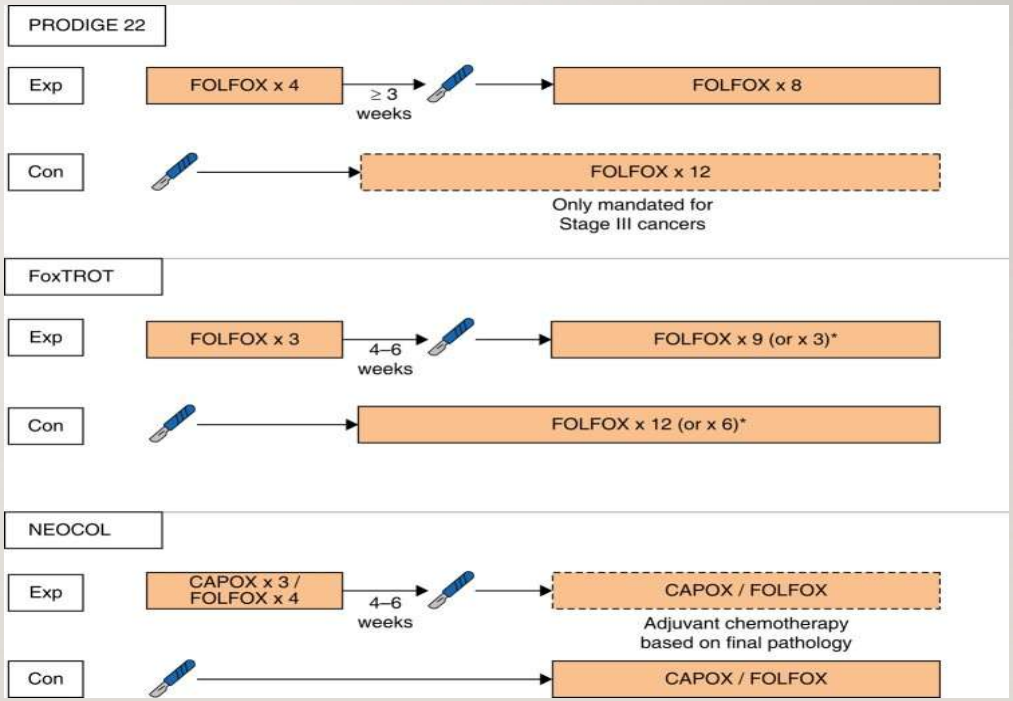
"Watch and wait" approach not only has the potential to spare patients from unnecessary surgery but also to improve their quality of life, as it is associated with fewer risks of morbidity, mortality and functional impairment



- ✓ Lower rates of tumour regrowth in consolidation chemo arm
- ✓ No difference in disease-free survival both at 3-year and 5-year follow-up between patients undergoing TME after initial restaging and those undergoing TME after tumour regrowth

NEOADJUVANT THERAPY IN COLON CANCER

- Less established role in colon cancer
- Upfront surgical resection for stage III and high risk stage II followed by adjuvant chemotherapy
- Could be considered in oligometastatic (or very bulky nodal) disease
- Disease free survival benefit in mismatch repair (MMR) proficient disease



METASTATIC COLORECTAL CANCER: SIDEDNESS MATTERS

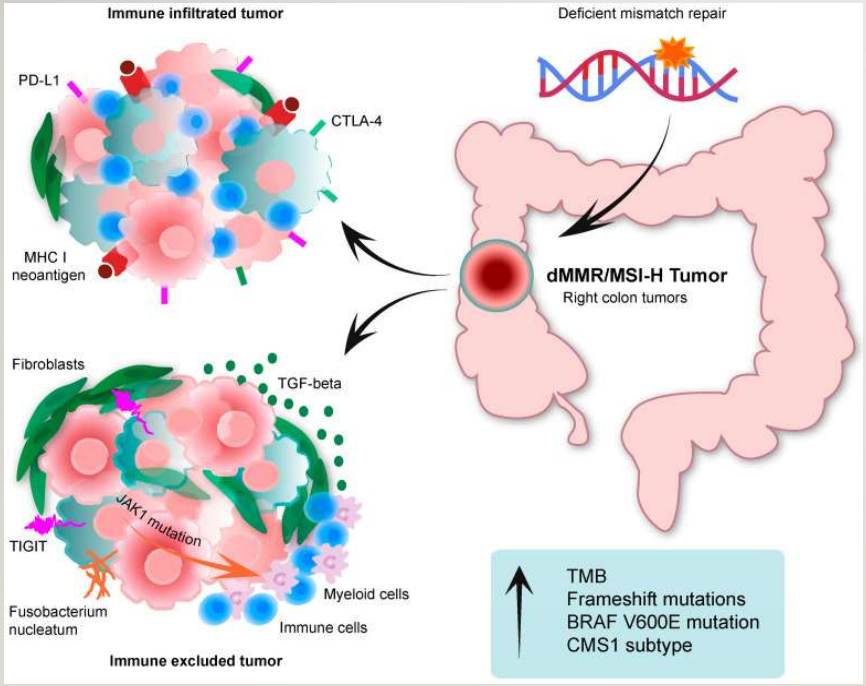
Right sided/ proximal	Left- sided/ distal
More common in women	More common in men
More common in older patients	More common in younger patients
More likely in patients with Lynch syndrome	More likely in patients with familial adenomatous polyposis (FAP)
More likely to have dMMR or MSI-high, KRAS and BRAF mutations	More likely to have HER2 amplification
More likely to metastasize to peritoneum	More likely to metastasize to liver and lung



METASTATIC COLORECTAL CANCER- GENERAL APPROACH

- Doublet chemotherapy in combination with targeted therapy usually used (FOLFOX or CAPOX usual first line chemotherapy choice)
- Targeted therapy choice;
- Left sided RAS wild type-> anti- EFGR (eg. Cetuximab, Panitumumab)
- Right sided RAS mutant-> anti- VEGF - Bevacizumab
- BRAF mutant-> BRAF inhibitor- Encorafenib (in combination with Cetuximab)
- Triplet chemotherapy (FOLFIRINOX) may be considered in younger patients, or referral to clinical trial for targeted therapies

IMMUNOTHERAPY IN MSI-HIGH METASTATIC CRC



- Between 5% and 15% of colorectal cancers show deficiencies in the mismatch repair machinery and high microsatellite instability (dMMR/MSI-H)
- dMMR/MSI-H CRC is characterized by a dysfunctional DNA repair system, which renders the tumor immune microenvironment more susceptible to immunotherapy
- Frameshift mutations are one of the hallmarks of dMMR/MSI-H

IMMUNOTHERAPY IN MSI-HIGH METASTATIC CRC

Clinical outcome in pivotal trials involving dMMR/MSI-H mCRC patients.

	KEYNOTE-177		Checkmate 142			Keynote 164		Keynote 016
Treatment	1st	1st	1st	>2nd	>2nd	>2nd	>3rd	>3rd
Phase	III	III	II	II	II	II	II	II
N patients	153	154	45	74	119	63	61	10
Schedule	Pembro	Chemo	Nivo + Ipi	Nivo	Nivo + Ipi	Pembro	Pembro	Pembro
ORR	44%	33%	60%	31%	55%	33%	33%	40%
DCR	65%	75%	84%	69%	80%	57%	51%	90%
mPFS	16.5 m	8.2 m	NR	14.3	NR	4.1 m	2.3 m	NR
12 m PFS	55%	37%	77%	50	71%	41%		78%
mOS			NR	NR	NR	NR	31.4 m	NR
12 m OS			83%	73	85%	76%	72%	NR

- Pembrolizumab used as first line treatment for MSI- high, dMMR metastatic CRC
- Immunotherapy has better side effect profile than chemotherapy – QOL
- Rates of Grade 3–5 treatment-related adverse events were 22% for Pembrolizumab (colitis, hepatitis) and 66% for chemotherapy (neutropenia, diarrhea, fatigue)

NEOADJUVANT IMMUNOTHERAPY IN MSI-HIGH CRC

- NICHE study - 40 patients with localized dMMR or pMMR colon cancers-> single dose of the CTLA-4 inhibitor ipilimumab and two doses of the PD-1 inhibitor pembrolizumab → standard surgical resection performed within 6 weeks of inclusion
- All 20 of the patients with dMMR cancers responded to treatment, with major pathological responses (defined as ≤10% residual viable tumour) seen in 19 patients and a pCR seen in 12 patients (60%)
- Another phase II study- clinical stages II or III rectal cancer-> received nine cycles of the PD-1 inhibitor dostarlimab
- A cCR was noted in every single patient -> none underwent CRT or surgery
- Not yet standard practice- need larger studies and not on PBS.. But certainly promising

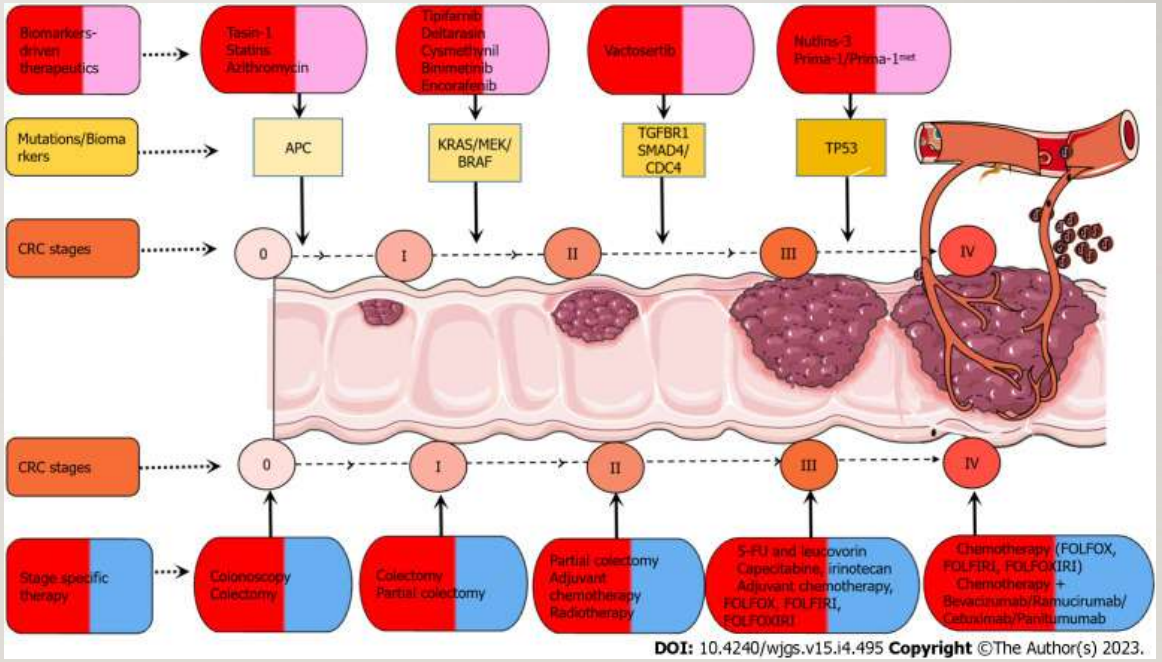
IMMUNOTHERAPY – TOXICITY PROFILE AND MANAGEMENT

- ✓ Commonly mild and reversible/ treatable– rash, diarrhoea, hepatitis, thyroiditis/ hypothyroidism
- ✓ Some toxicities can be permanent- thyroid dysfunction, hypopituitarism, pancreatic insufficiency and need life long replacement therapy
- ✓ Some toxicities (although less common) can be life threatening- pneumonitis, cardiac toxicity, neurological toxicity
- ✓ Treatment of immunotherapy related toxicity – steroids (oral Prednislone or IV Methylprednisolone), replacement (hormone) therapy

➢ NCCN guidelines, eVIQ

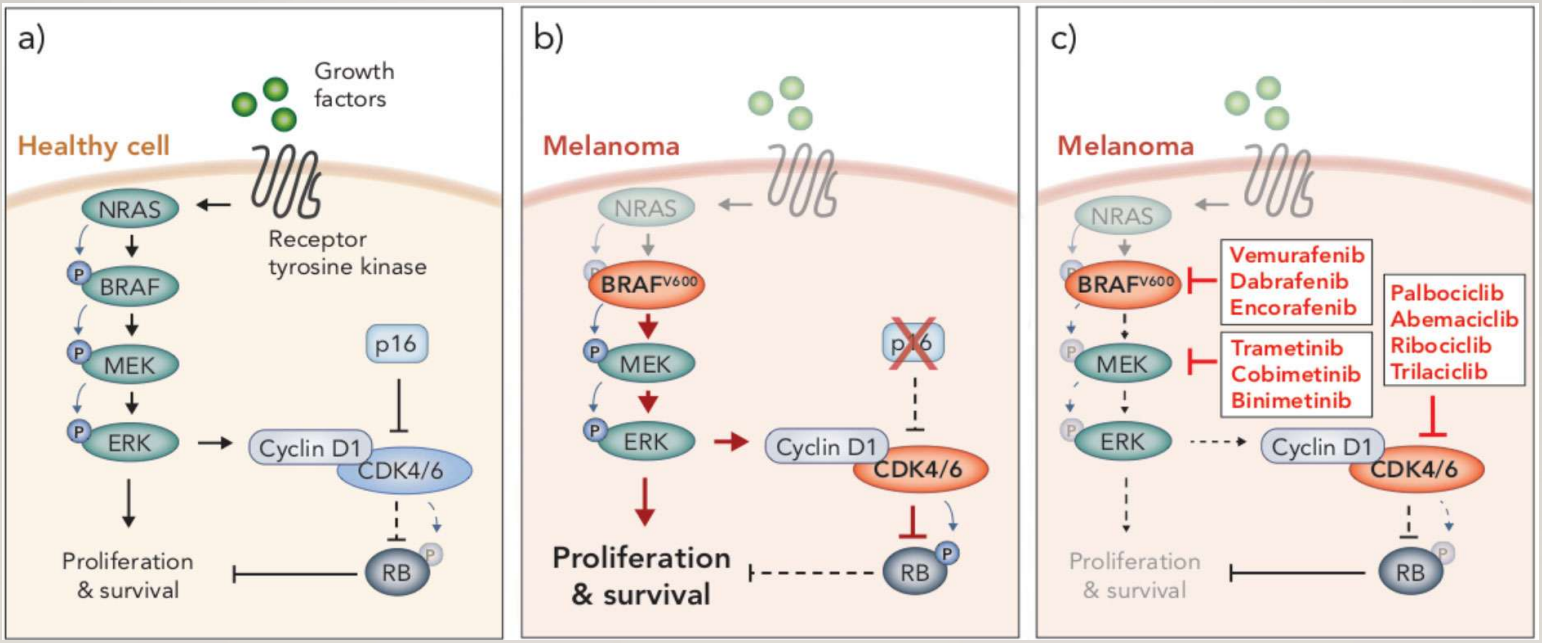
CURRENT AND FUTURE BIOMARKER SPECIFIC THERAPIES

- BRAF and MEK inhibitors (in combination with anti EGFR) – BRAF mutant colorectal cancer
- KRAS G12C inhibitors- adagrasib/ sotarasib combined with anti- EGFR
- Anti- HER2 antibody/ drug conjugates (Herceptin)- HER2 positive colorectal cancer



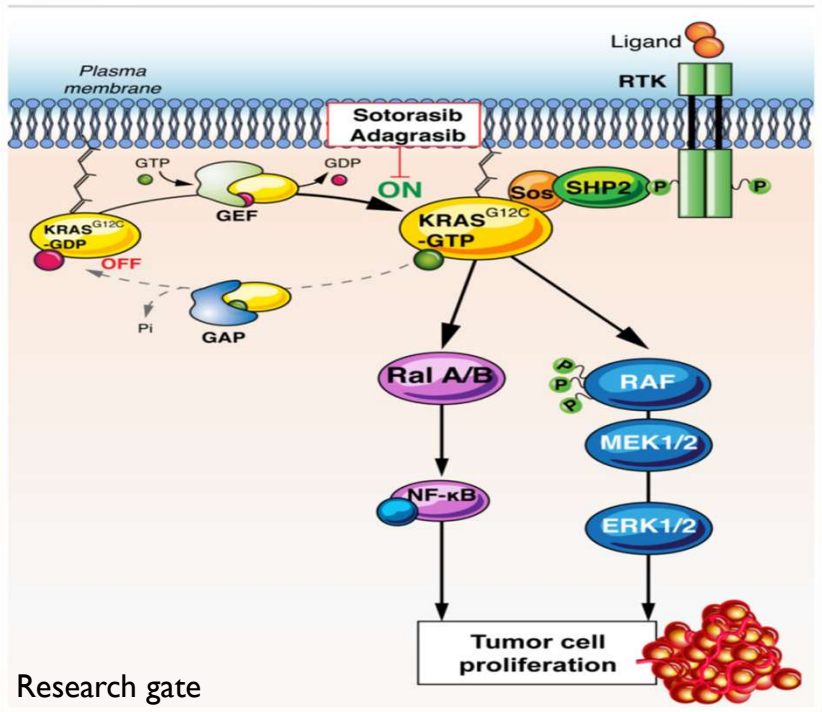
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CURRENT AND FUTURE BIOMARKER SPECIFIC THERAPIES



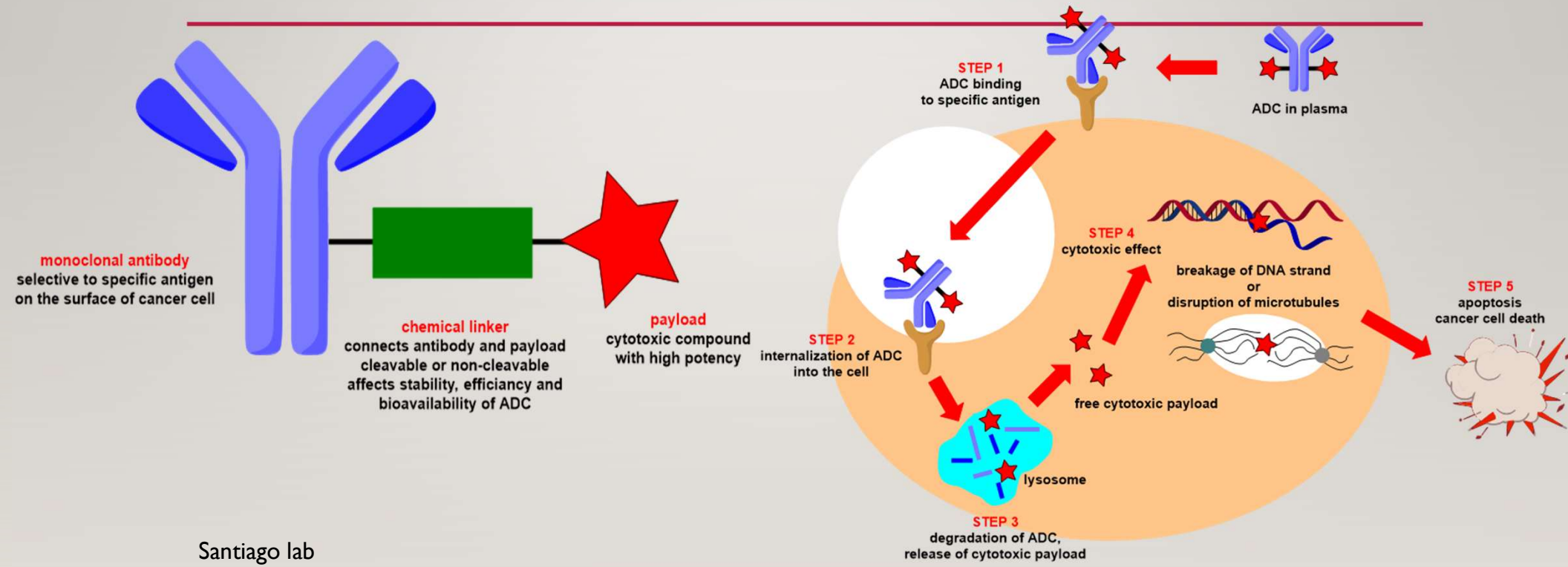
Frontiers immunology

CURRENT AND FUTURE BIOMARKER SPECIFIC THERAPIES



Research gate

CURRENT AND FUTURE BIOMARKER SPECIFIC THERAPIES



Santiago lab

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THANK YOU!

QUESTIONS?

