New Advances in the Medical Management of Head and Neck Squamous Cell Carcinoma

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11/11/23

Objectives

- Review current state of recurrent of metastatic head and neck squamous cell carcinoma (HNSCC)
- Review updated results of Phase III KEYNOTE-048
- Review treatment approach to recurrent of metastatic HNSCC
- Discuss novel strategies to treat HNSCC that are clinically relevant
  - Targeting Indoleamine 2,3 dioxygenase producing cells
  - Antibody drug conjugate targeting PD-L1

Head and Neck Squamous Cell Carcinoma

- Groups of malignancies that arise from squamous cells lining tissues
  - Oral Cavity
  - Oropharynx
  - Hypopharynx
  - Larynx
  - Nasal Cavity/Paranasal Sinuses
- Seventh most common cancer globally[1]
  - 660,000 new cases annually
  - 350,000 deaths annually
- Risk Factors
  - Smoking
  - Alcohol consumption
  - Human Papilloma Virus (HPV) in oropharyngeal HNSCC
  - Immunosuppression
- Incidence appears to be increasing
  - Young nonsmokers with HPV associated oropharyngeal HNSCC

(Sung et al., CA Cancer J Clin 2021; 71: 209-249)[1]

Recurrent and Metastatic HNSCC

- About half of the patients will have recurrent or metastatic disease[2]
  - Median overall survival of about 12 months
- Majority of patients will be without locoregional treatment options
- Symptom-directed care is appropriate

(Ionna et al., Cancers (Basel). 2021)[2]

Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study

*Barbara Burtness, Kevin J Harrington, Richard Greil, Denis Soulières, Makoto Tahara, Gilberto de Castro Jr, Amanda Psyrri, Neus Basté, Prakash Neupane, Åse Bratland, Thorsten Fuereder, Brett G M Hughes, Ricard Mesía, Nuttapong Ngamphaiboon, Tamara Rordorf, Wan Zamaniah Wan Ishak, Ruey-Long Hong, René González Mendoza, Ananya Roy, Yayan Zhang, Burak Gumuscu, Jonathan D Cheng, Fan Jin, Danny Rischin, on behalf of the KEYNOTE-048 Investigators**

- Pembrolizumab ALONE improves overall survival (OS) compared to cetuximab with a platinum and fluorouracil combination as a first-line regimen in PD-L1 CPS positive population.
  - Total population, median OS 11.6 months vs 10.7 months, HR 0.85 [95% CI 0.71-1.03]
  - CPS > or = 20, median OS 14.9 months vs 10.7 months, HR 0.61 [95% CI 0.45-0.83], p=0.0007
  - CPS > or = 1, median OS 12.3 months vs 10.3 months, HR 0.78 [95% CI 0.64-0.96], p=0.0086

(Burtness et al, Lancet, 2019)[3]

Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study

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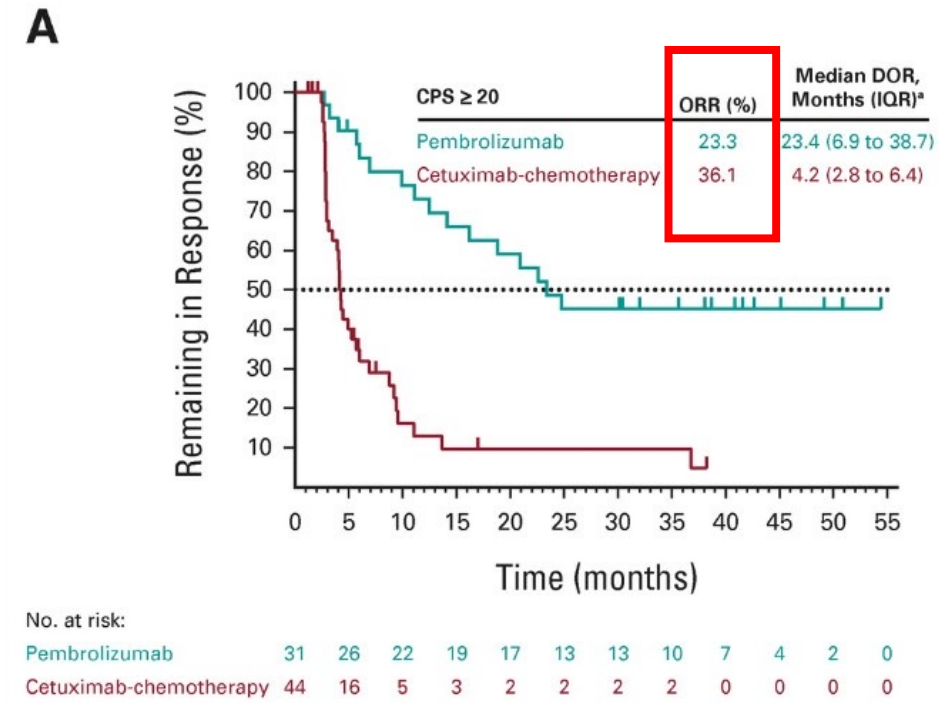
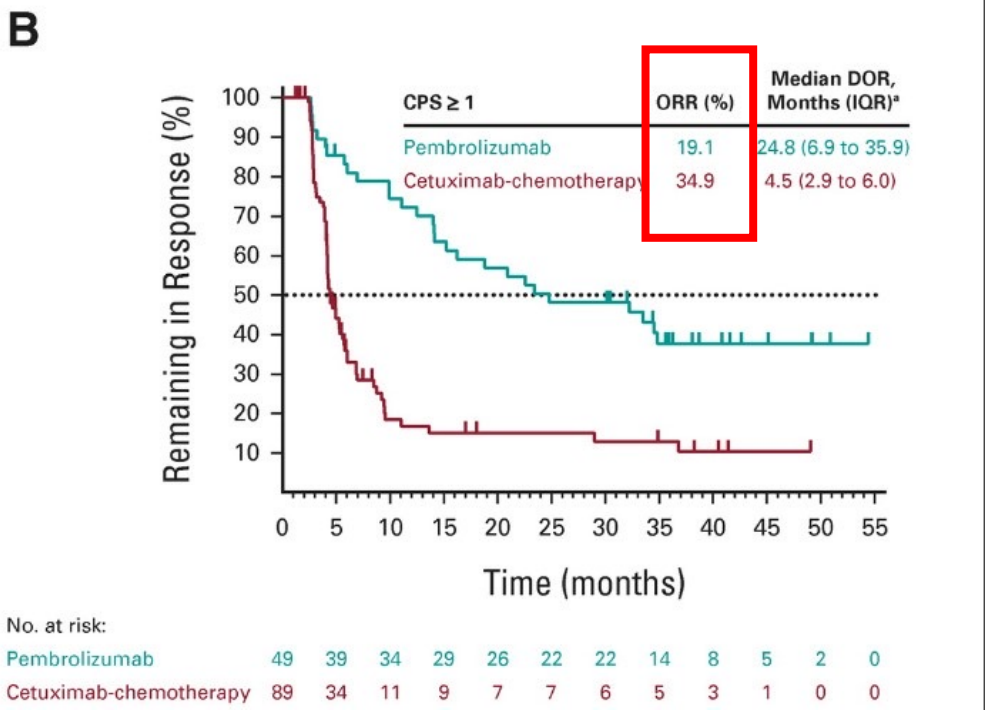
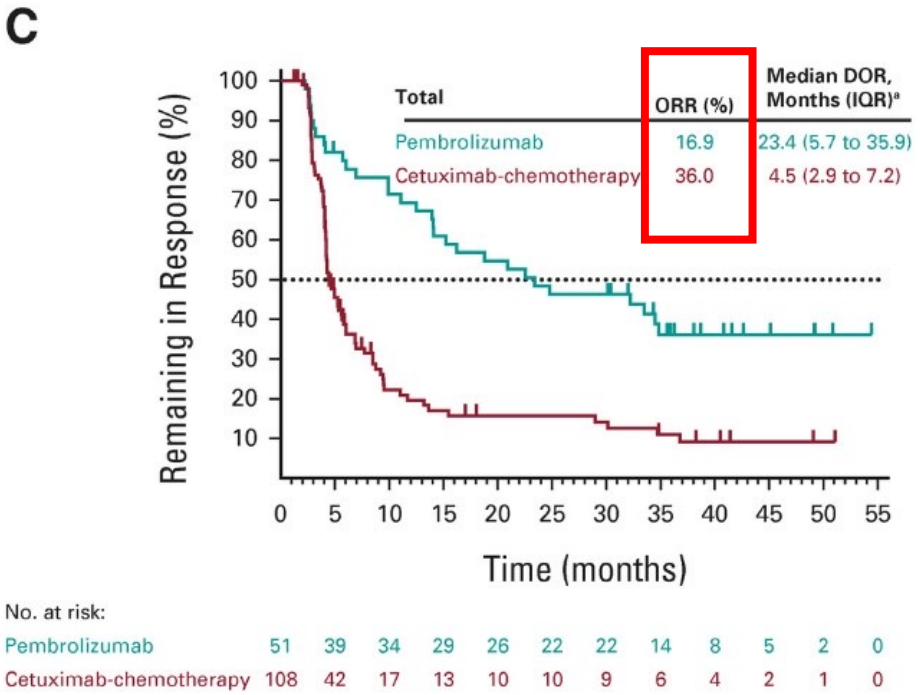
- Pembrolizumab with a platinum and fluorouracil combination improves overall survival (OS) compared to cetuximab with a platinum and fluorouracil combination as a first-line regimen.
  - Total population, median OS 13 months vs 10.7 months, HR 0.77 [95% CI 0.63-0.93], p=0.0034
  - CPS > or = 20, median OS 14.7 months vs 11 months, HR 0.60 [95% CI 0.45-0.82], p=0.0004
  - CPS > or = 1, median OS 13.6 months vs 10.4 months, HR 0.65 [95% CI 0.53-0.80], p<0.0001

(Burtness et al, Lancet, 2019)[3]







(Harrington et al, J Clin Oncol, 2023)[4]

(Harrington et al, J Clin Oncol, 2023)[4]

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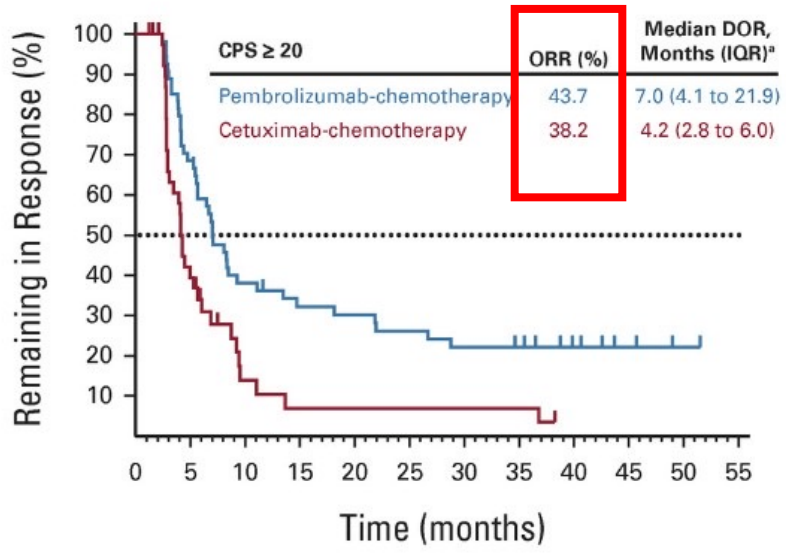

No. at risk:

Pembrolizumab-chemotherapy	55	37	20	16	15	13	11	10	6	3	1	0
Cetuximab-chemotherapy	42	15	4	2	2	2	2	2	0	0	0	0

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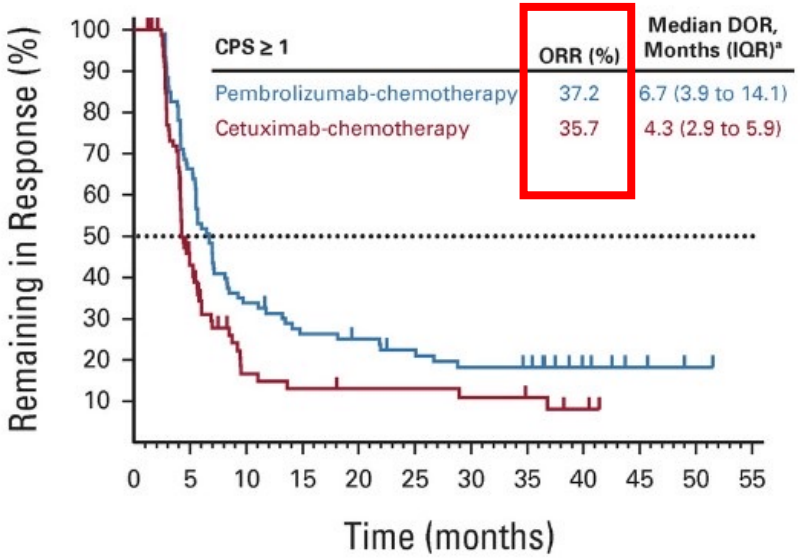

No. at risk:

Pembrolizumab-chemotherapy	90	56	28	21	19	16	13	12	6	3	1	0
Cetuximab-chemotherapy	84	31	9	7	6	6	5	4	2	0	0	0

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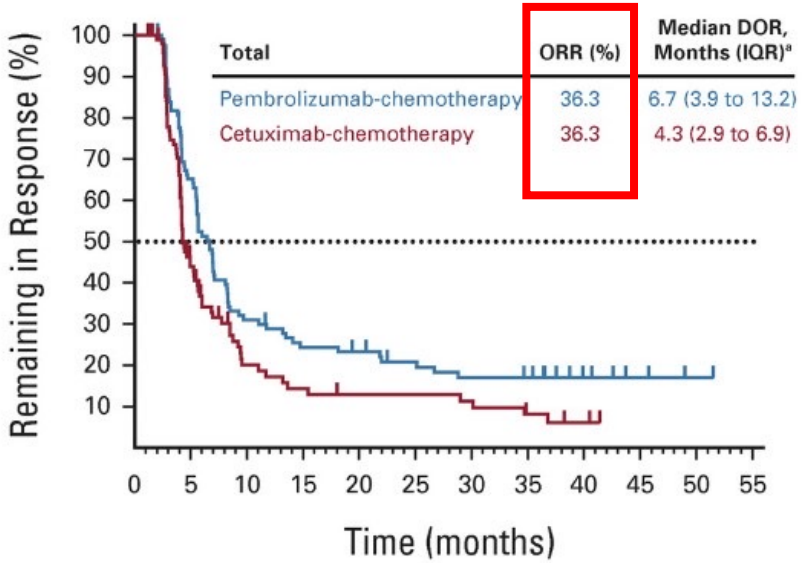
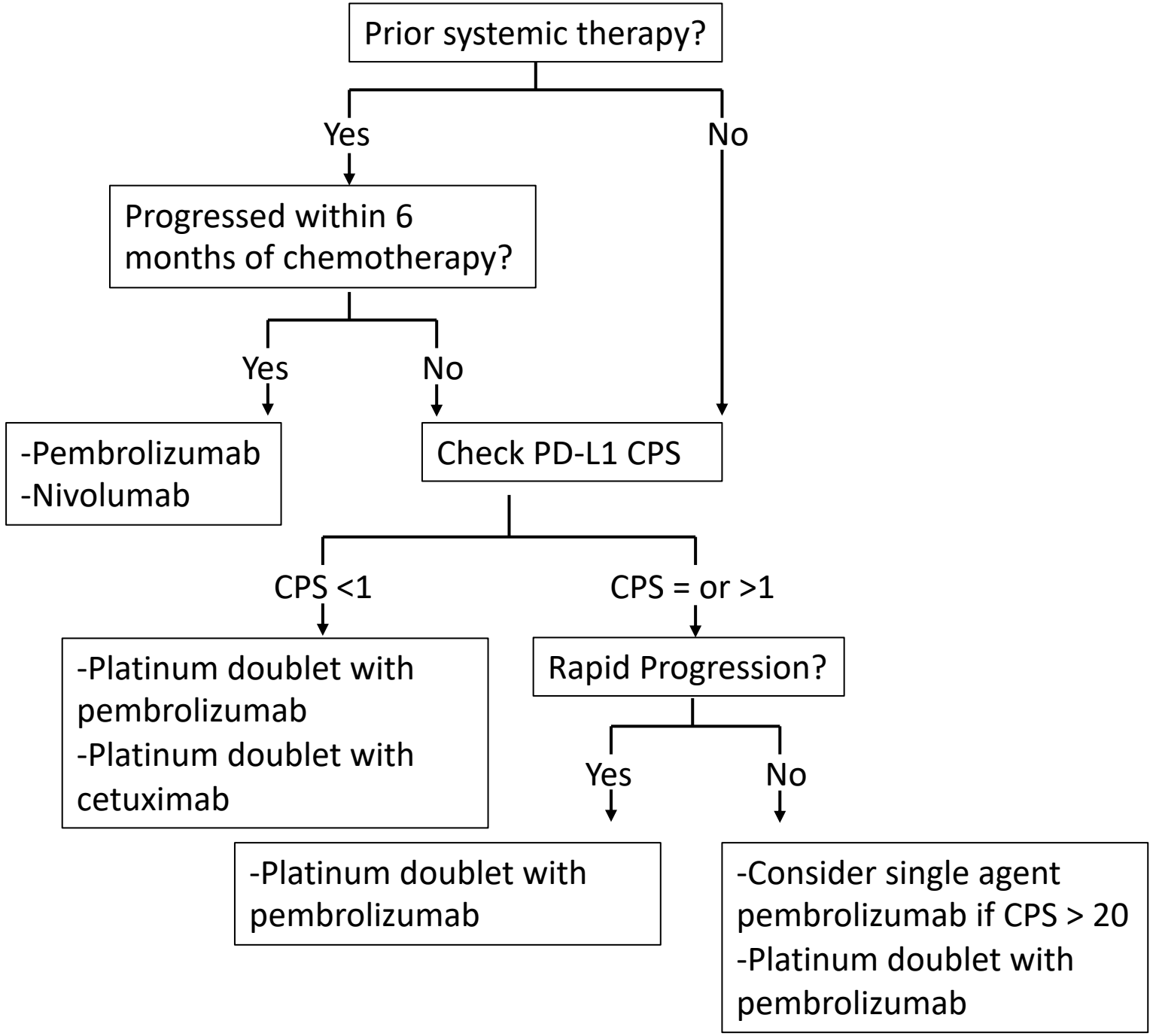


No. at risk:

Pembrolizumab-chemotherapy	102	62	29	22	20	16	13	12	6	3	1	0
Cetuximab-chemotherapy	101	38	14	10	8	8	7	4	2	0	0	0


Prior systemic therapy?
Yes
No
Progressed within 6 months of chemotherapy?
Yes
No
-Pembrolizumab
-Nivolumab
Check PD-L1 CPS
CPS <1
CPS = or >1
-Platinum doublet with pembrolizumab
-Platinum doublet with cetuximab
Rapid Progression?
Yes
No
-Platinum doublet with pembrolizumab
-Consider single agent pembrolizumab if CPS > 20
-Platinum doublet with pembrolizumab

Summary

- Single agent pembrolizumab demonstrated improved overall survival when compared to cetuximab with chemotherapy in PD-L1 CPS positive patients.
- Pembrolizumab with chemotherapy demonstrated improved overall survival when compared to cetuximab with chemotherapy.
- Improved survival appears to be driven by duration of response.

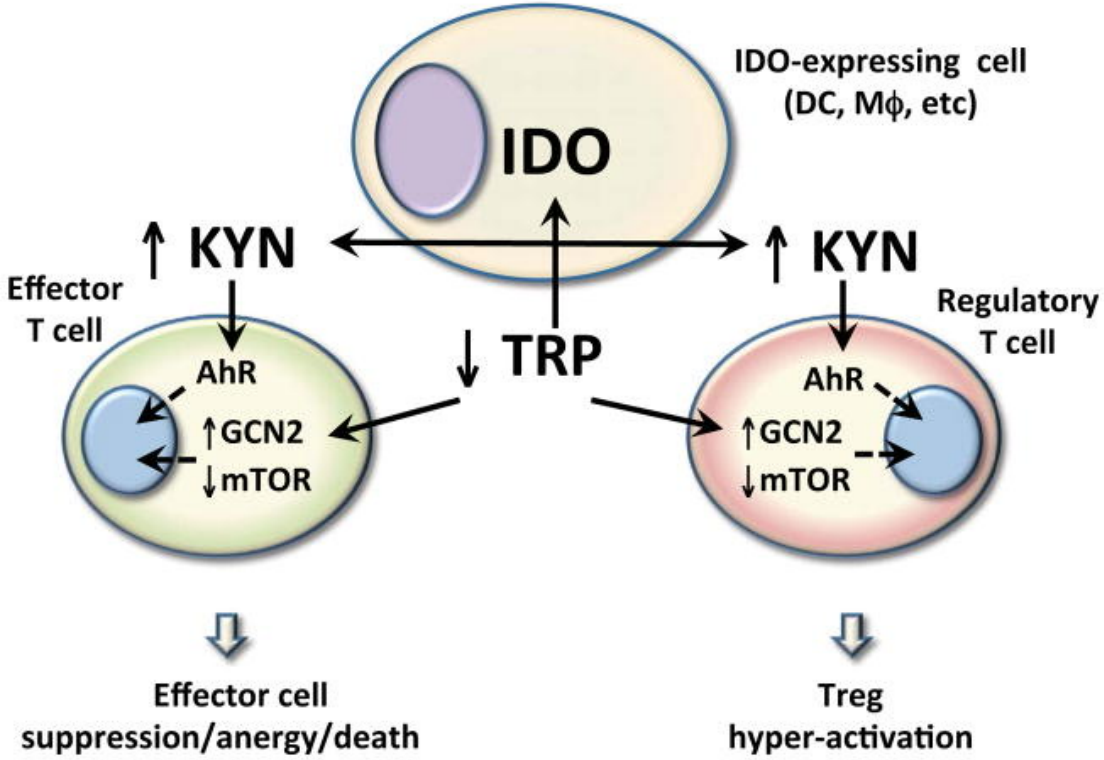
Summary

- Majority of patients with recurrent or metastatic HNSCC do not respond to first-line standard of care palliative systemic therapy.
- Majority of patients with recurrent or metastatic HNSCC who respond to therapy will ultimately progress.
- There is a critical need to improve treatment for patients with recurrent or metastatic HNSCC.

Targeting Indoleamine 2,3 dioxygenase producing cells in cancer

- Indoleamine 2,3 dioxygenase (IDO)
  - Secreted by tumor cells, antigen presenting cells, immunosuppressive cells
  - Catalyzes oxidative catabolism of tryptophan in the kynurenine pathway
  - Results in increase in kynurenine
    - Aryl hydrocarbon receptor ligand
      - Enhances Treg differentiation
      - Suppresses Effector T cell responses

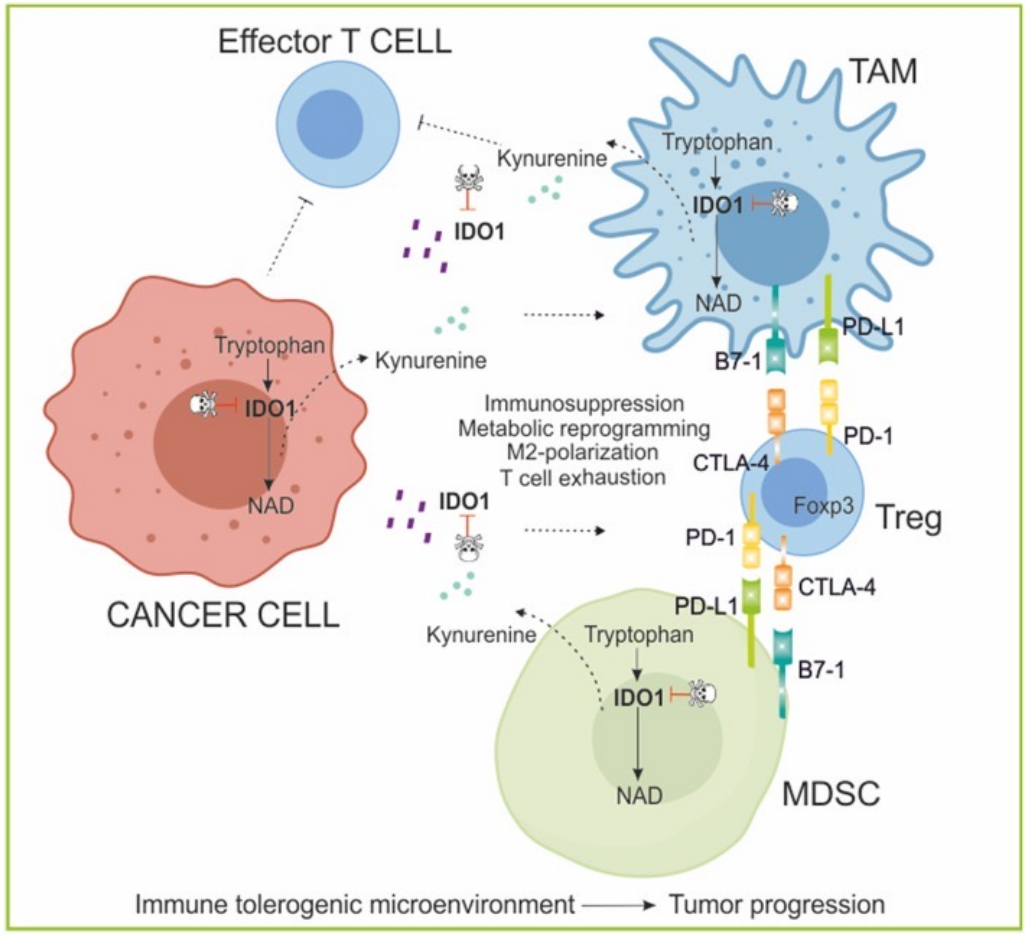
(Munn and Mellor, Trends Immunol, 2013)[5]



Targeting Indoleamine 2,3 dioxygenase producing cells in cancer

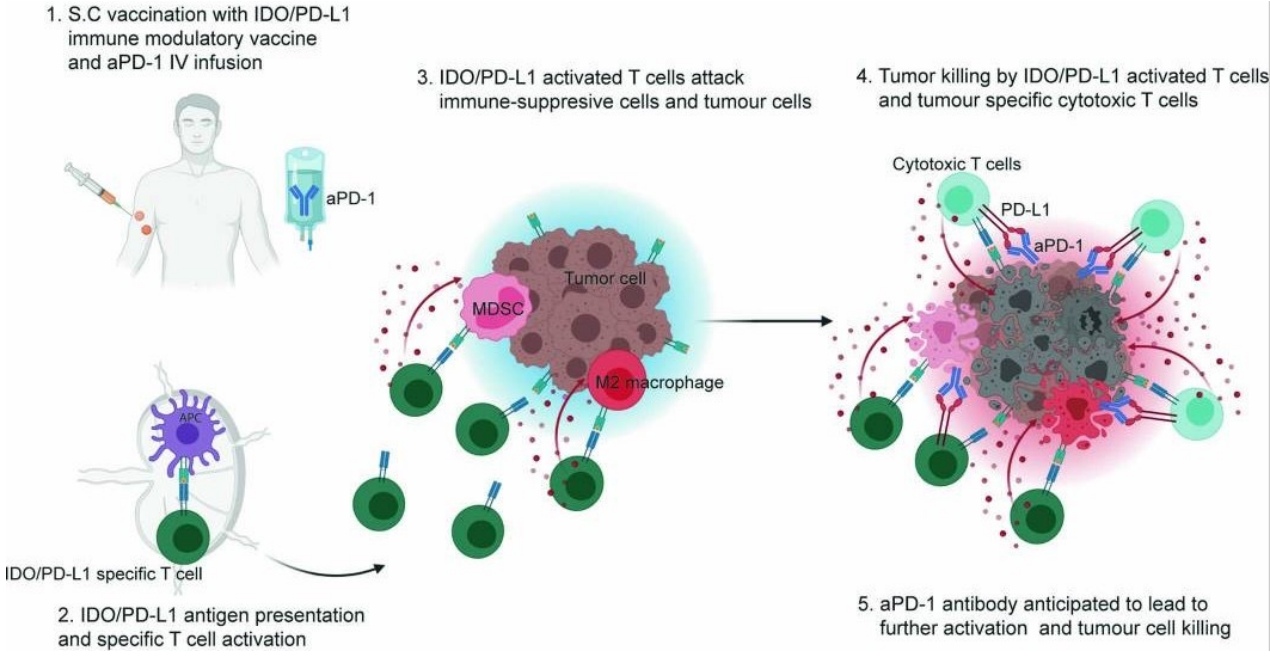
- IDO induced kynurenine can be secreted by tolerenic immune cells and create an immunologic “cold” microenvironment.
  - Polarizing myeloid cells to M2 phenotype
    - Tumor Associated Macrophages
    - Myeloid derived suppressor cells
  - Activate and expand Tregs
  - Allow for additional immune escape mechanisms (PD-1/PD-L1)

(Audrito et al., Front Immunol, 2019)[6]



Targeting Indoleamine 2,3 dioxygenase producing cells in cancer

- IDO/PD-L1 peptide
  - Activate IDO and PD-L1 specific T cells
  - Results in eradication of immunosuppressive cells
  - Create an immunologic “hot” microenvironment
  - In conjunction with anti-PD-1 mAb, could enhance tumor killing by tumor specific T cells due to PD-1 blockage



(Kjeldsen et al., Nat Med, 2021)[7]

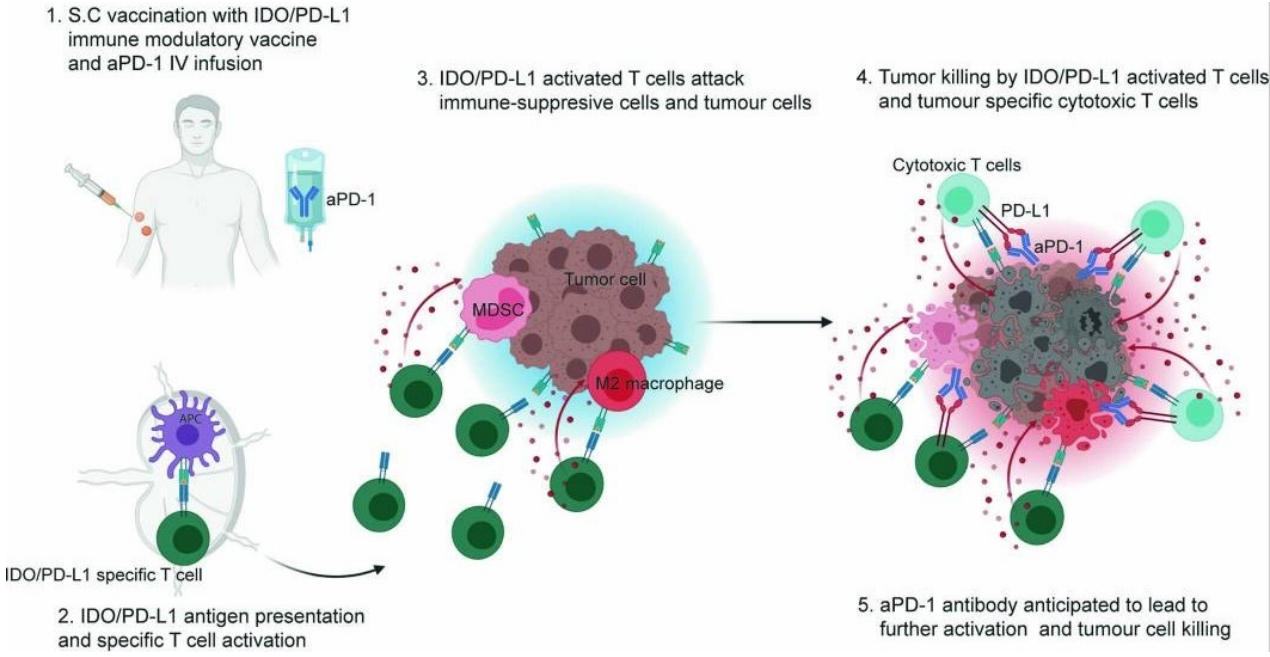
ARTICLES
https://doi.org/10.1038/s41591-021-01544-x
nature medicine
Check for updates

OPEN

A phase 1/2 trial of an immune-modulatory vaccine against IDO/PD-L1 in combination with nivolumab in metastatic melanoma

- 30 patients with metastatic melanoma where treated with (IO102/IO103) combined with nivolumab
- Toxicity profile was comparable to that of nivolumab monotherapy
  - 77% injection site reactions
    - Granulomas (63%)
    - Redness (20%)
    - Pain (13%)
    - Pruritus (13%)
- OR (80%)
  - CR (43%)
- PFS 26 months
- Vaccine reactive T cells were detected in >93% of patients
  - CD4+ and CD8+ T cells with activity against IDO+ and PD-L1+ cells in vitro.

(Kjeldsen et al., Nat Med, 2021)[7]



RECRUITING

IO102-IO103 in Combination With Pembrolizumab as First-line Treatment for Patients With Metastatic NSCLC, SCCHN, or mUBC

ClinicalTrials.gov ID NCT05077709

Sponsor

Information provided by

Last Update Posted 2023-06-12

Description

Inclusion Criteria:

1. Patients with histologically or cytologically confirmed:

   Metastatic NSCLC (Arm A), who have not received prior systemic treatment for their metastatic disease and who have:

   • no known sensitizing EGFR or ALK mutations.

   or

   Metastatic SCCHN (Arm B) with no prior therapy and who have:

   • Histologically- or cytologically-confirmed recurrent or metastatic SCCHN considered incurable by local therapies. Tumors of nasopharyngeal origin (any histology) are excluded

   • Documented results of HPV status for oropharyngeal cancer.

   or

   Metastatic UBC (Arm C) with no prior therapy and not eligible for any cisplatin therapy:

   • Advanced/unresectable (inoperable) or metastatic urothelial cancer of the renal pelvis, ureter, bladder or urethra (transitional cell and mixed transitional/non transitional cell histologies permitted but transitional cell histology must be the dominant histology)

   All solitary metastases must be biopsied to confirm diagnosis of metastases from primary indication
2. PD-L1 tumor expression or PD-L1 CPS (as confirmed prior to enrolment using the DAKO 22C3 assay, using local/central services):

   • Arm A (NSCLC): PD-L1 TPS ≥ 50%

   • Arm B (SCCHN): PD-L1 CPS ≥ 20; HPV +/-

   • Arm C (mUBC): PD-L1 CPS ≥ 10

Experimental: Arm B (SCCHN) SCCHN patients (metastatic stage IV) treated with IO102-IO103 SC Q3W in combination with pembrolizumab IV 200mg Q3W	Drug: IO102-IO103 in combination with pembrolizumab • The experimental drug IO102-IO103 is for SC injection and consist of IDO and PD-L1 peptides

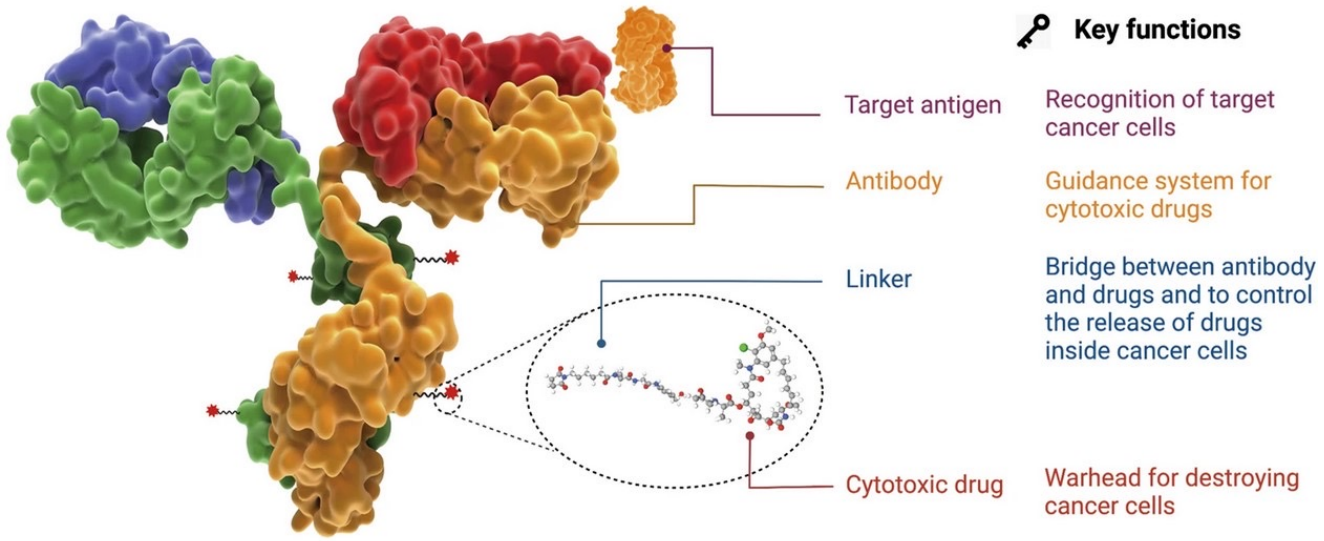
Outcome Measure	Measure Description	Time Frame
ORR or PFS	Target ORR according to RECIST v1.1 or PFS Rate at 6 months as per investigator assessments.	6 months

https://clinicaltrials.gov/study/NCT05077709#eligibility

Antibody Drug Conjugates

- Monoclonal antibodies (mAb)s allow precise targeting of tumor surface antigens
  - Antibody-dependent cellular cytotoxicity
- Treatment with single agent mAbs are often insufficient
- Antibody drug conjugates (ADC)s were developed to improve the therapeutic window
  - Tumor targeting mAb conjugated to a cytotoxic payload

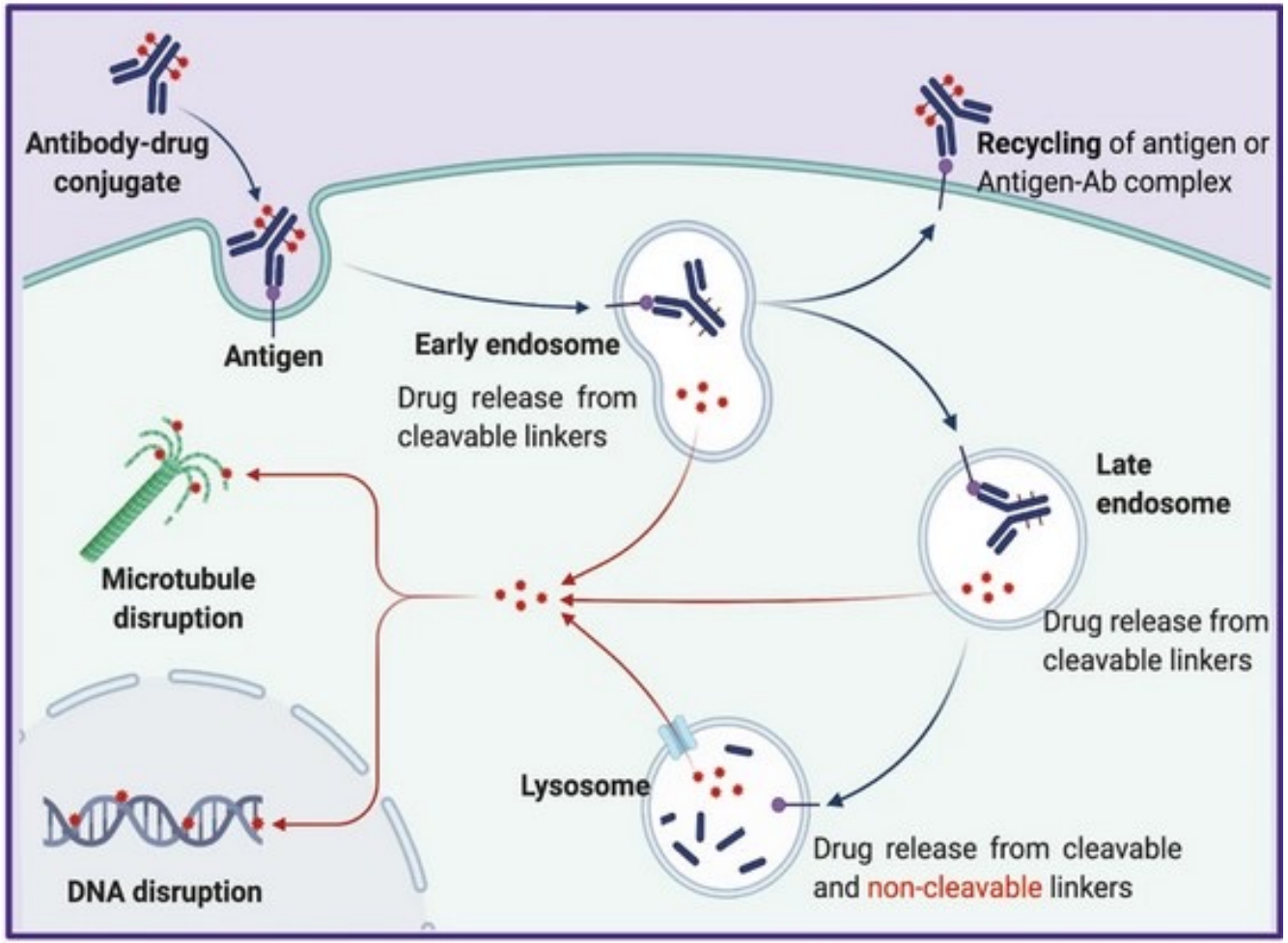
(Fu et al., Sig Transduct Target Ther, 2022)[8]



Antibody Drug Conjugates

- Delivery of cytotoxic payloads
  - ADC binds to target antigen
  - ADC endocytosed by tumor cells
  - Endosomes fuse with lysosomes
  - Release of cytotoxic payload
    - Apoptosis
- Additional mAb functions
  - ADCC
  - CDC
  - PD-L1/PD-1 Blockade
  - Blockage of signaling transduction

(Fu et al., Sig Transduct Target Ther, 2022)[8]



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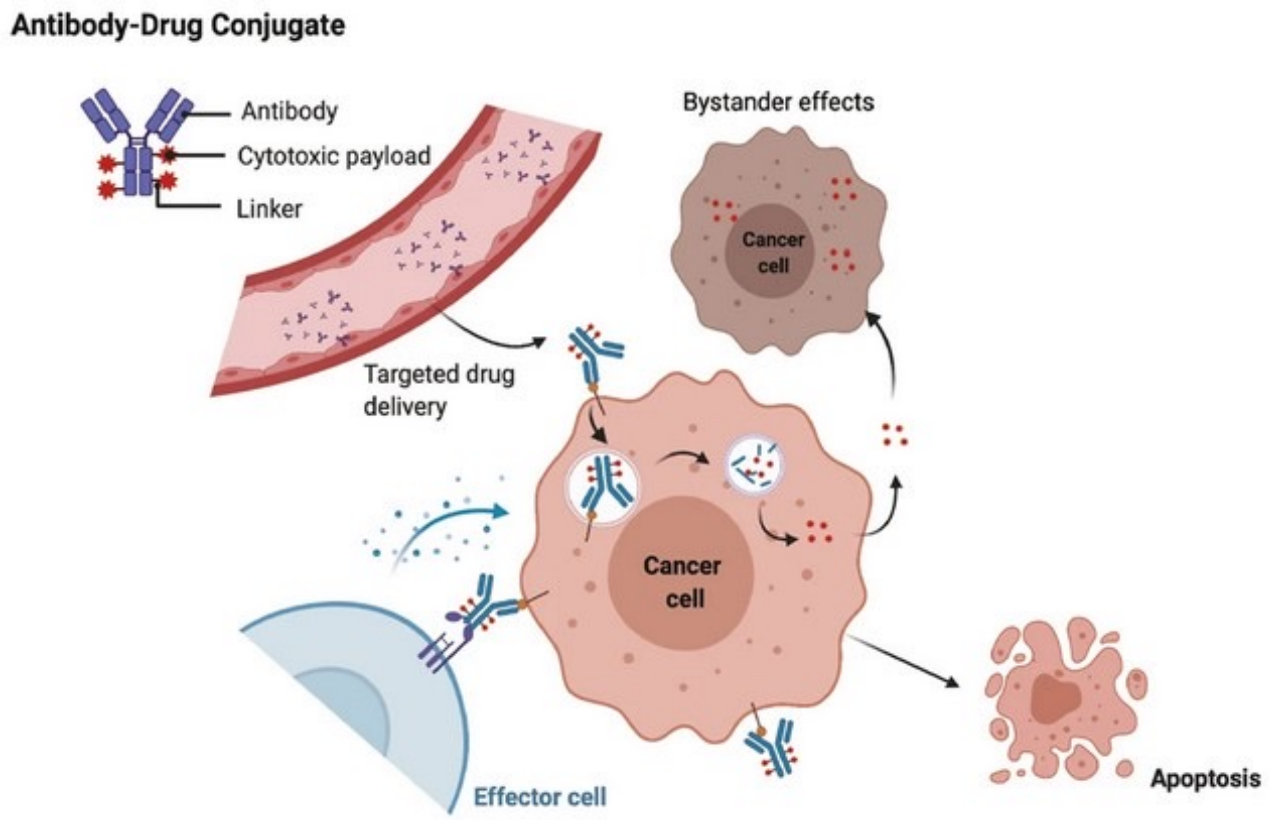
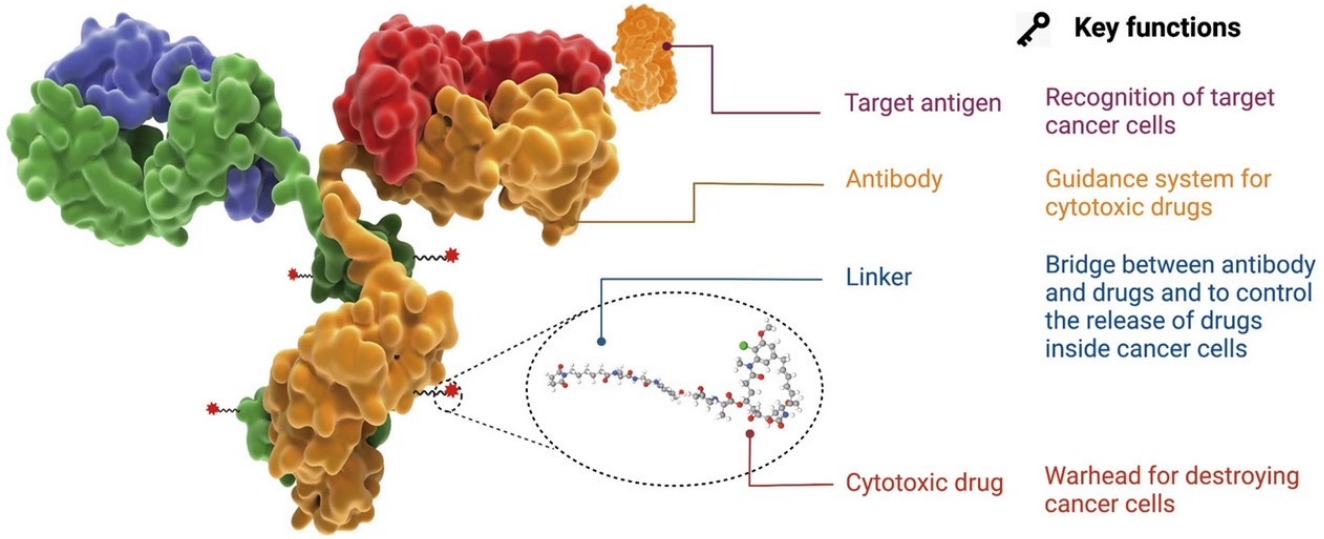


SGN-PDL1V

- Engineered human mAb against PD-L1
- Valine-citrulline linker (cleavable)
- Monomethyl auristatin E (MMAE)
  - Membrane-permeable microtubule disrupting agent
- Potential to treat PD-L1 positive malignancies
  - Cytotoxic payload
  - Immune cell death
  - Checkpoint Blockade



RECRUITING

A Study of SGN-PDL1V in Advanced Solid Tumors

ClinicalTrials.gov ID NCT05208762

Sponsor

Information provided by

Last Update Posted 2023-10-16

Inclusion Criteria:

- Parts A and B:
  - Participants must have one of the following histologically- or cytologically-confirmed metastatic or unresectable solid tumor types
    - Non-small cell lung cancer (NSCLC)
    - Head and neck squamous cell carcinoma (HNSCC)
    - Esophageal squamous cell carcinoma (SCC)
    - Triple negative breast cancer (TNBC)
  - Participants must have disease that is relapsed or refractory, that has progressed on approved therapies, be intolerant to or refused such therapies, or such and therapies are contraindicated and in the judgement of the investigator, should have no appropriate SoC therapeutic option
  - Participants must have PD-L1 expression based on historical testing

- Phase 1 Dose Escation Trial
  - SGN-PDL1V administered IV
    - Day 1, 8 in a 21 day cycles

https://clinicaltrials.gov/study/NCT05208762

Overall Conclusions

- Incorporation of PD-1 blockade into treatment regimens have become standard of care for patients with recurrent or metastatic HNSCC
- Vast majority of patients with recurrent of metastatic HNSCC will progress despite first line palliative systemic therapy
- There is a critical need to improve treatment for patients with recurrent or metastatic HNSCC.
- Clinical trials are important for improving treatment for recurrent of metastatic HNSCC
  - Targeting IDO with pembrolizumab as a first line in patients with PD-L1 = or > 20
  - ADC targeting PD-L1 in patients without standard of care options and PD-L1 positive disease

THANK YOU!!!

- Participants
- Program Directors
  - Helen K. Chew, MD, FACP
  - Primo N. Lara, Jr. MD
- Program Organizers

References

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