TROP-2 and AXL as Targets in NSCLC

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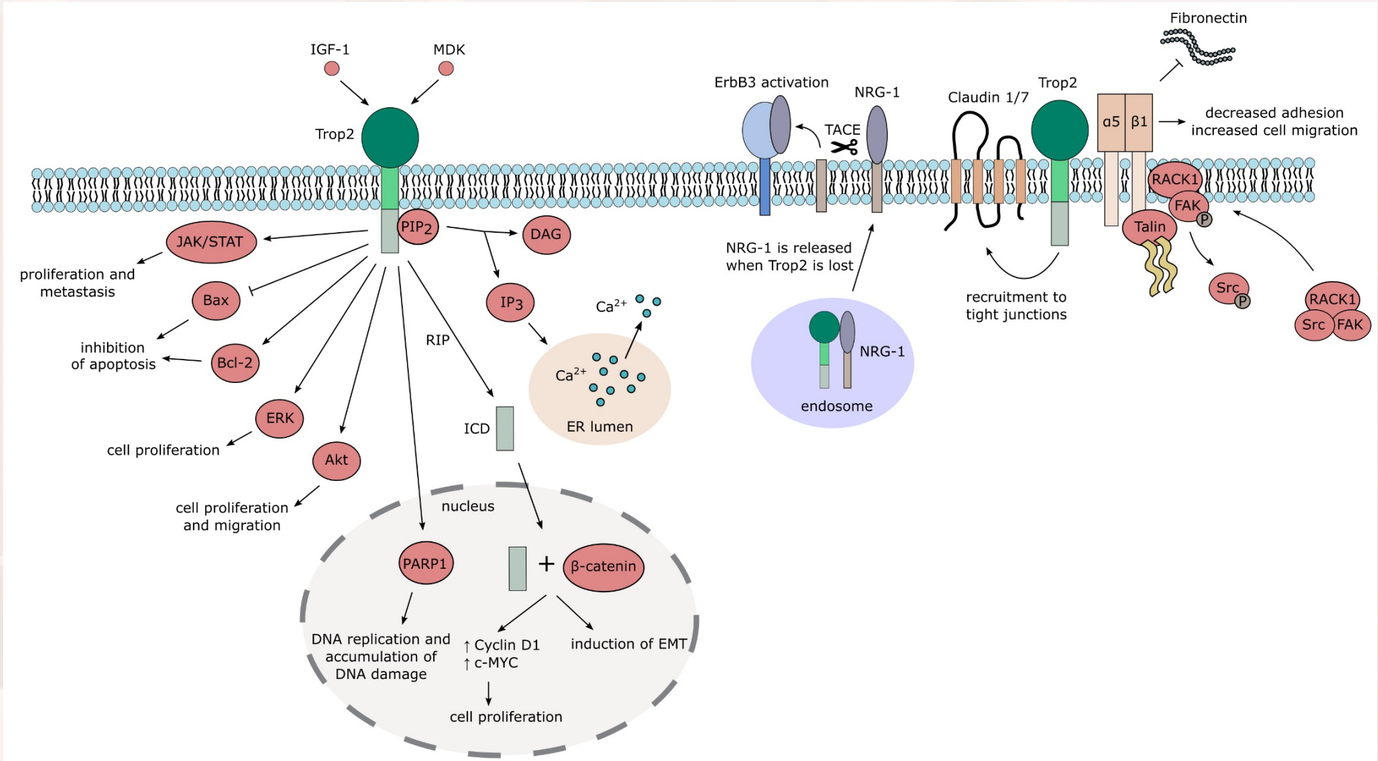
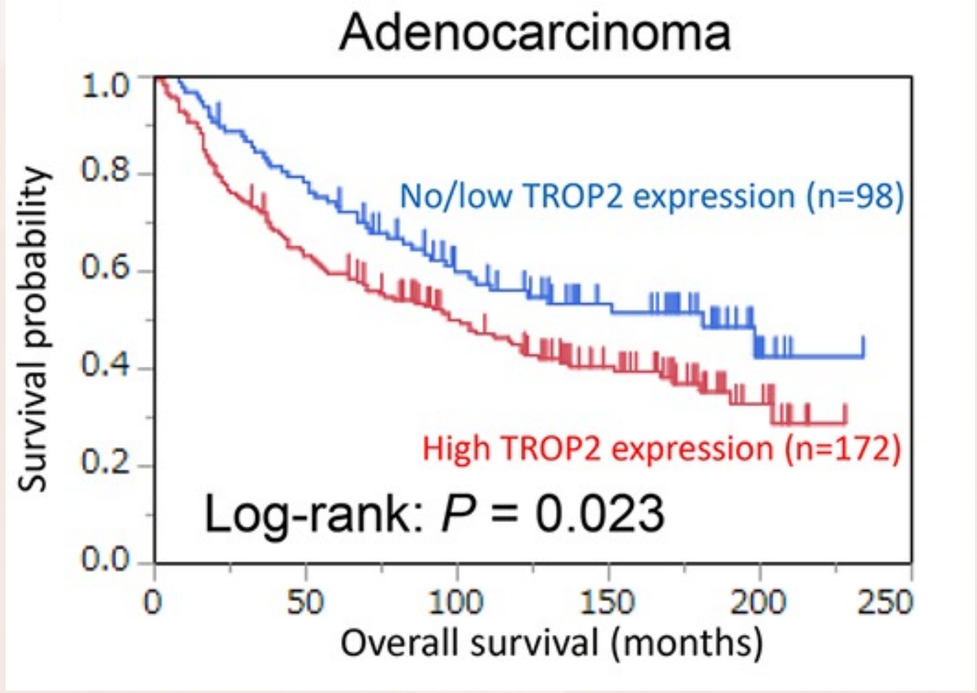
TROP-2 and NSCLC

- Trophoblast cell surface antigen 2 (TROP-2)
  - Highly expressed on epithelial cancers (including NSCLC)

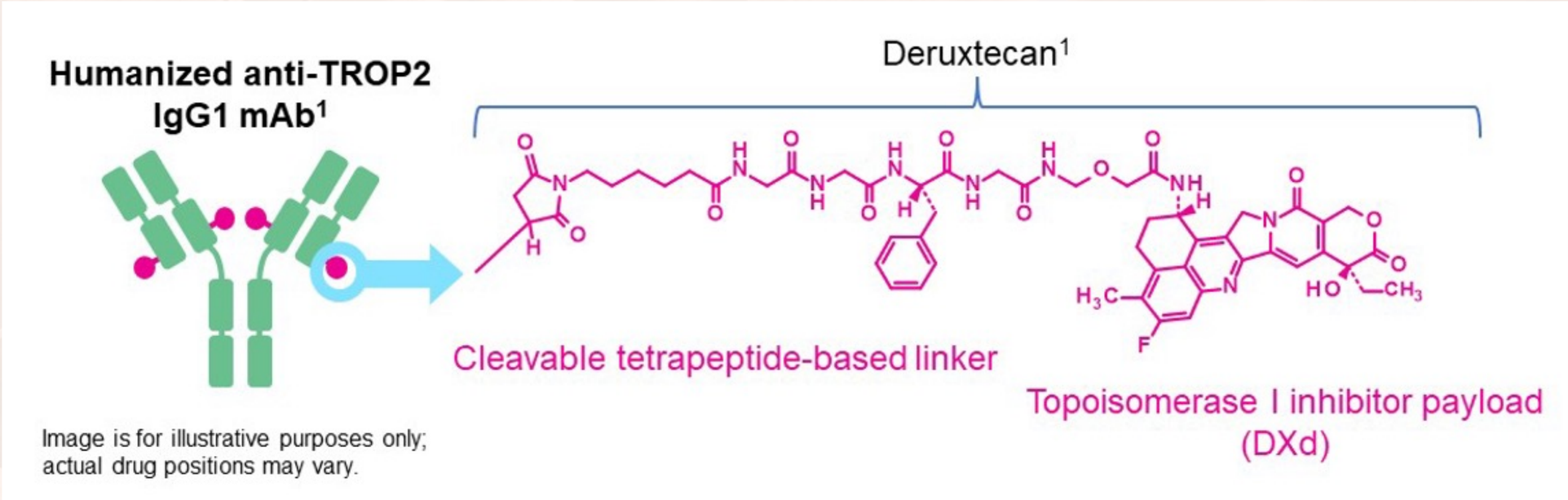




Lenart, Cancers 2020; Inamura, Oncotarget 2017

Datopotamab Deruxtecan

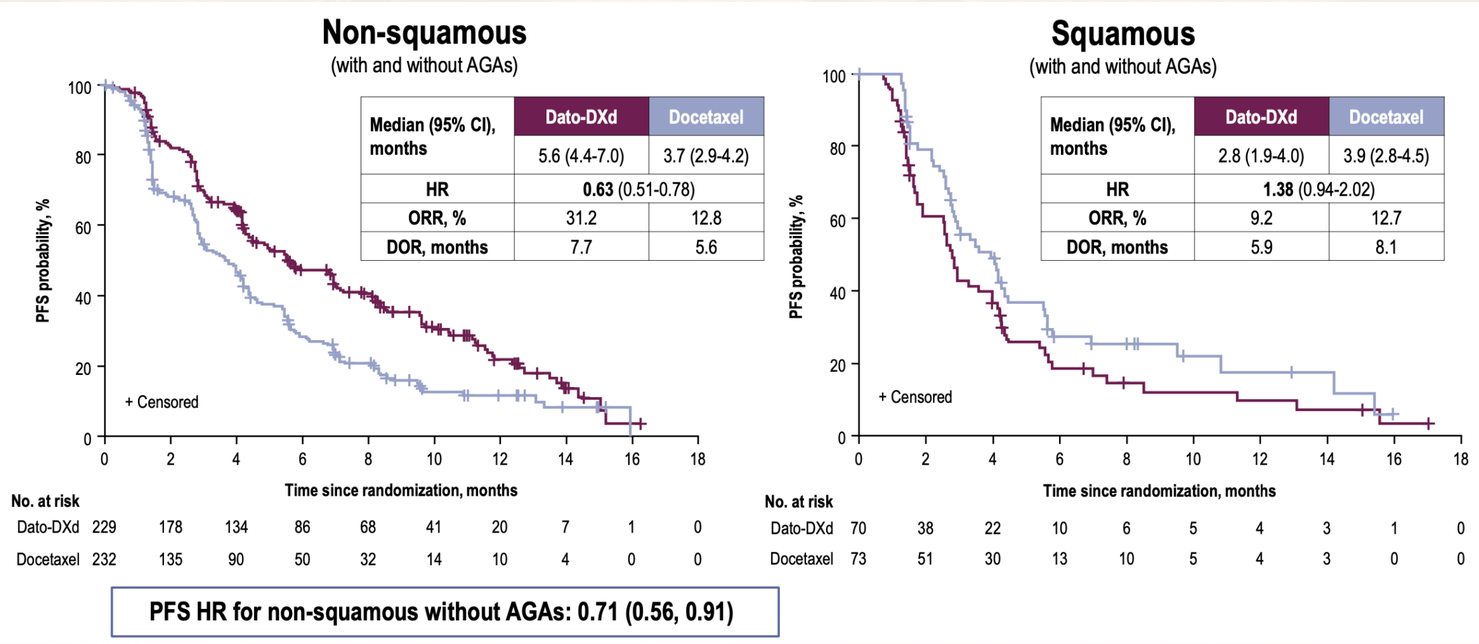
- TROP-2 antibody drug conjugate (Dato-DXd)
  - TROP-2 antibody, cleavable linker, topoisomerase I payload
    - DAR 4:1



Levy, WCLC 2022

Datopotamab Deruxtecan

- TROPION-Lung01 (n=604)
  - Phase III study of datopotamab deruxtecan vs docetaxel
    - PFS HR 0.75 (mPFS 4.4m vs 3.7m)
    - Non-squamous PFS HR 0.63, squamous PFS HR 1.38



- RR 26.4% vs 12.8%
- mDOR 7.1m vs 5.6m
- OS HR 0.90 (0.72-1.13)
  - Sq OS HR 1.32
  - Non-sq OS HR 0.77

Lisberg, ESMO 2023

Datopotamab Deruxtecan

- TROPION-Lung01 safety
  - G3+ TRAEs in 25% vs 41%
  - Dose reduction 20% vs 29%
  - Discontinuation 8% vs 12%
  - AEs of special interest
    - Stomatitis / mucositis
    - Ocular events
    - Interstitial lung disease

AESI, n (%)	Dato-DXd N=297	Docetaxel N=290
Stomatitis/oral mucositis[a]		
All grades	160 (54)	59 (20)
Grade ≥3	19 (6)	4 (1)
Ocular events[b]		
All grades	57 (19)	27 (9)
Grade ≥3	5 (2)[c]	0
Adjudicated drug-related ILD[d]		
All grades	25 (8)	12 (4)
Grade ≥3	10 (3)	4 (1)
Grade 5	7 (2)	1 (0.3)

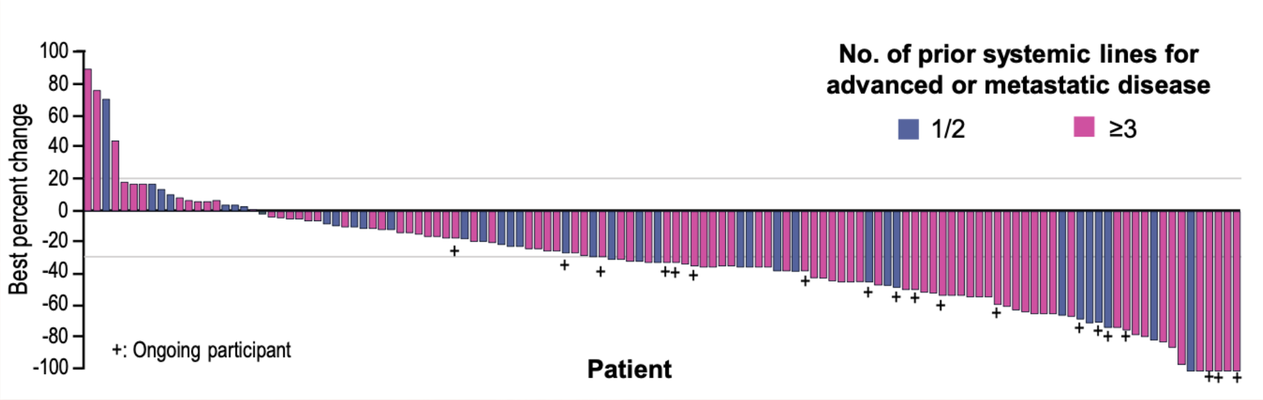
Lisberg, ESMO 2023

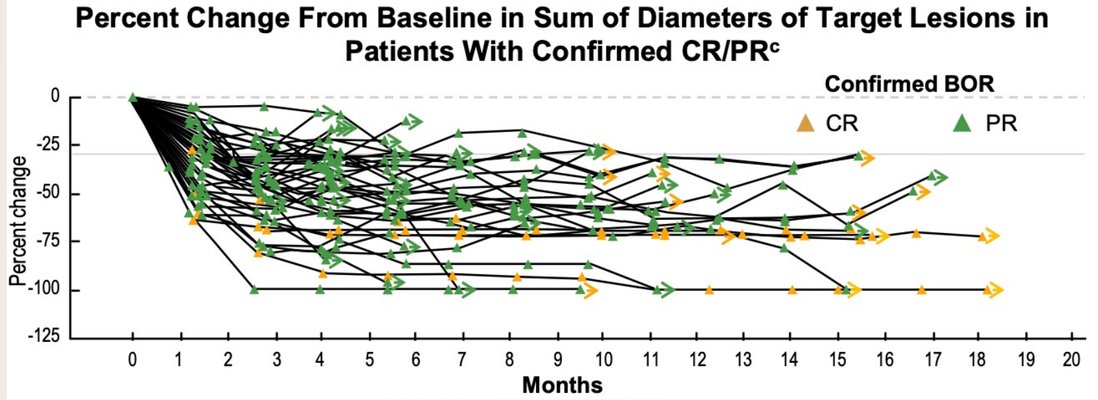
Datopotamab Deruxtecan

- TROPION-Lung01
  - Positive trial that met its primary endpoint
  - Modest absolute benefit in PFS
  - Poor outcomes in squamous NSCLC
  - More promising activity in non-squamous
- May play a role as monotherapy
  - Is this the best use of this tool?

Datopotamab Deruxtecan

- TROPION-Lung05 (n=137), TROP-2 and EGFR co-expression
  - Phase II study of datopotamab deruxtecan in NSCLC with AGA
    - 57% EGFR, 25% ALK, 7% ROS1, 6% RET, 4% METex14
    - Overall cohort: RR 35.8%, mDOR 7m, mPFS 5.4m
    - EGFR cohort: RR 43.6%, mDOR 7m, mPFS 5.8m

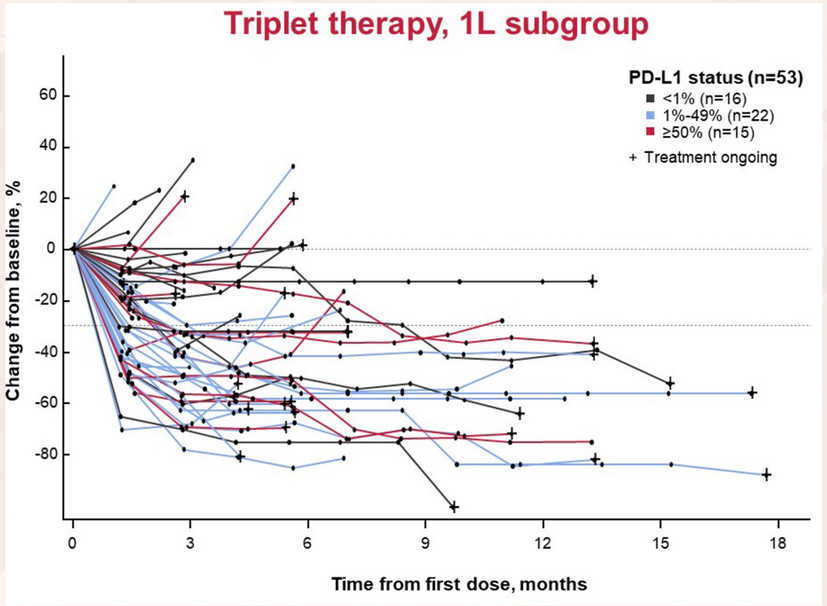


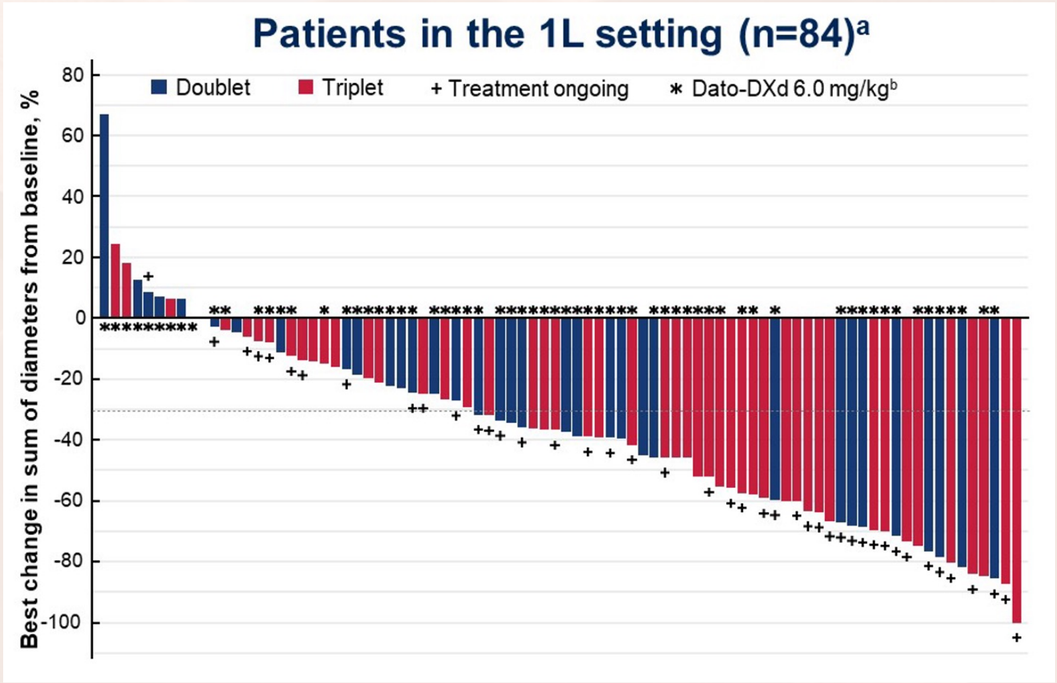


Paz-Ares, ESMO 2023

Datopotamab Deruxtecan

- TROPION-Lung02 (n=87)
  - First-line datopotamab + pembrolizumab +/- chemotherapy
    - RR dato + chemo/pembro: 57%; RR dato + pembro: 50%
  - Phase III ongoing

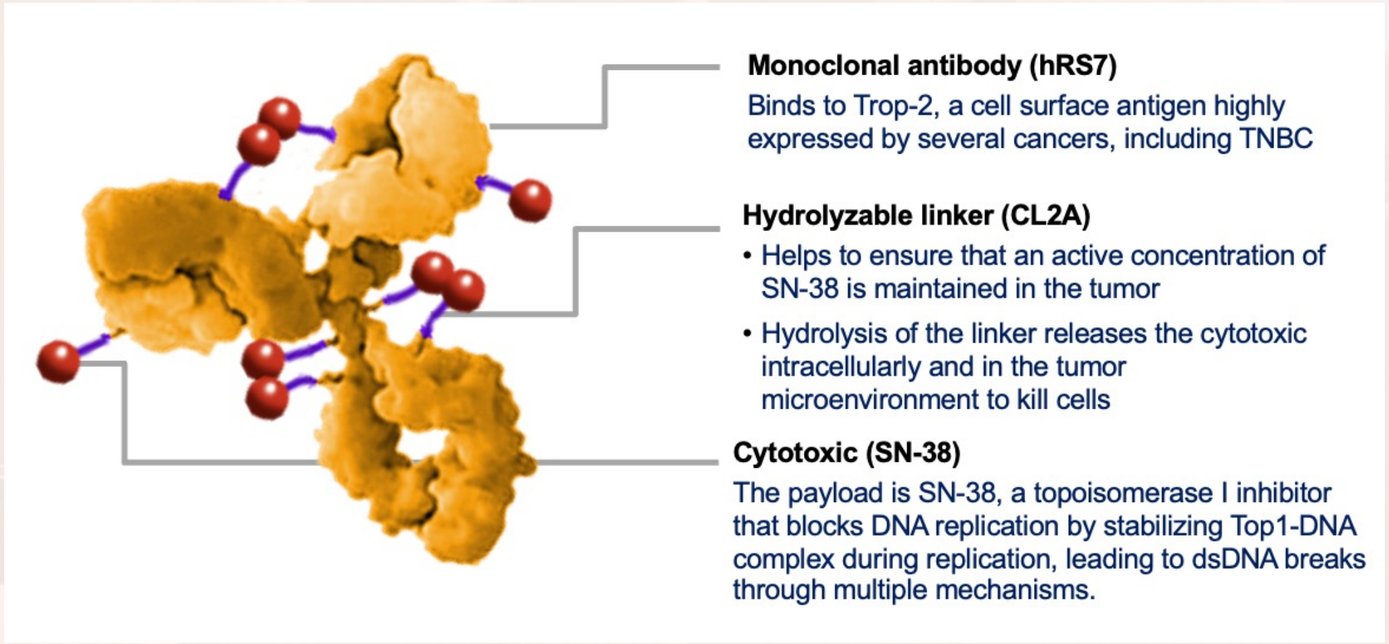




Goto, ASCO 2023

Sacituzumab Govitecan

- TROP-2 antibody drug conjugate
  - Trop2 antibody, hydrolyzable linker, SN-38 payload
    - DAR 7.6

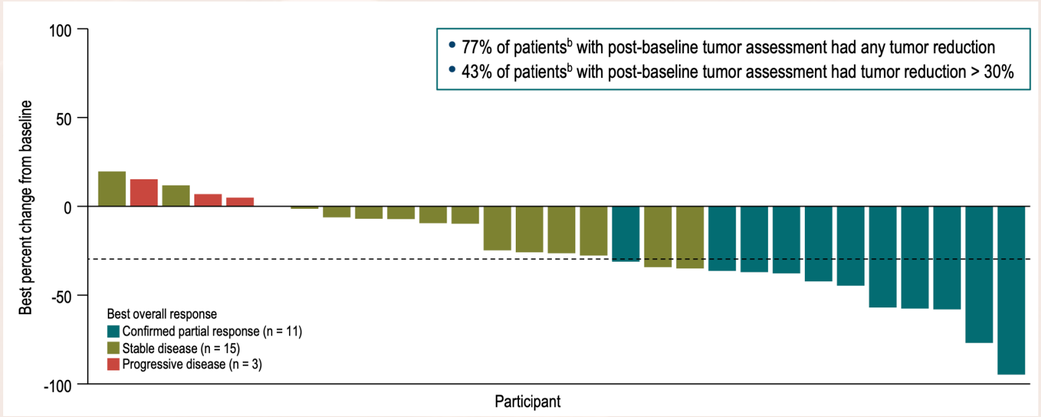


- FDA approved
  - TNBC 4/22/20
  - Bladder cancer 4/13/21
  - HR+ breast cancer 2/3/23

Bardia, Ann Oncol 2021

Sacituzumab Govitecan: SCLC

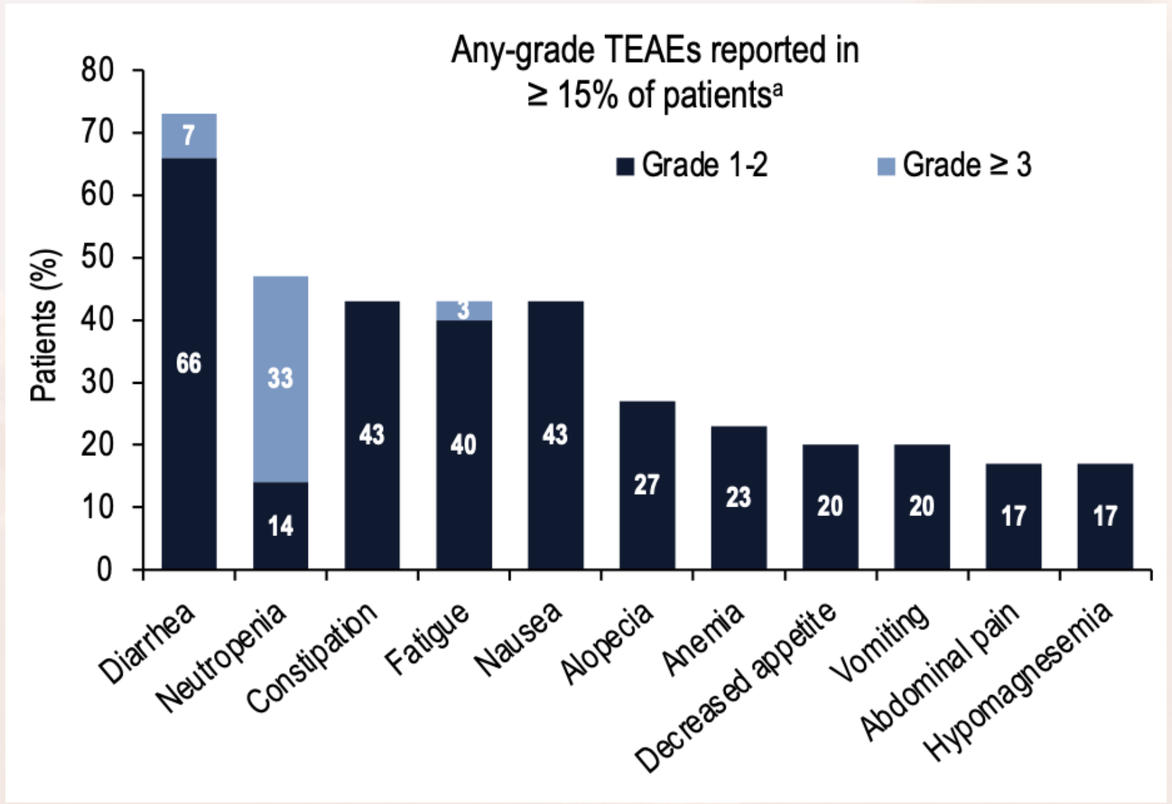
- Early efficacy explored in multiple basket trials
- IMMU-132 basket trial
  - SCLC expansion (n=62)
    - RR 17.7%, mDOR 5.7m, mPFS 3.7, mOS 7.1m
- Phase 2 TROPiCS-03 basket trial
  - SCLC expansion (n=30)
    - RR 37%, DCR 87%, mDOR 6.3m
    - mPFS 3.7m, mOS 7.1m



Gray, CCR 2017; Dowlati, ESMO 2023

Sacituzumab Govitecan: SCLC

- Safety largely reflects payload
- Phase 2 TROPiCS-03 basket trial
  - SCLC expansion (n=30)
    - 60% G3+ TEAEs
    - 27% dose reduction for TEAEs
    - 0% discontinuation for TEAEs



Dowlati, ESMO 2023

Sacituzumab Govitecan: NSCLC

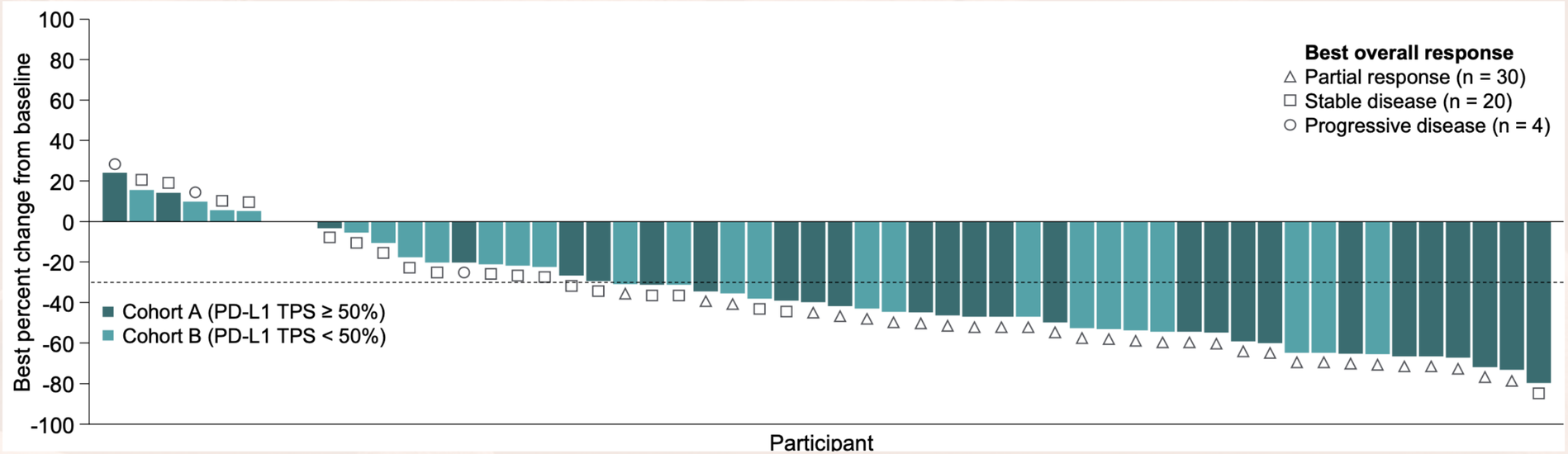
- Early efficacy explored in multiple basket trials
- IMMU-132 basket trial
  - NSCLC expansion (n=54; median 4th line)
    - RR 17%, mDOR 6m, CBR 43%, mPFS 5.2m, mOS 9.5m

	All Grades, No. (%)			Grade ≥ 3, No. (%)		
Adverse Event	All Patients	8 mg/kg Dose	10 mg/kg Dose	All Patients	8 mg/kg Dose	10 mg/kg Dose
No. of patients	54	8	46	54	8	46
Nausea	43 (80)	7 (88)	36 (78)	4 (7)	0 (0)	4 (9)
Diarrhea	33 (61)	5 (63)	28 (61)	4 (7)	1 (13)	3 (7)
Fatigue	25 (46)	3 (38)	22 (48)	3 (6)	0 (0)	3 (7)
Alopecia	21 (39)	3 (38)	18 (39)	NA	NA	NA
Neutropenia	20 (37)	2 (25)	18 (39)	15 (28)	1 (13)	14 (30)
Vomiting	19 (35)	4 (50)	15 (33)	2 (4)	1 (13)	1 (2)
Anemia	17 (31)	1 (13)	16 (35)	2 (4)	0 (0)	2 (4)
Constipation	17 (31)	3 (38)	14 (30)	0 (0)	0 (0)	0 (0)
Anorexia	13 (28)	0 (0)	13 (28)	1 (2)	0 (0)	1 (2)
Hypophosphatemia	12 (22)	1 (13)	11 (24)	1 (2)	0 (0)	1 (2)
Dehydration	10 (19)	0 (0)	10 (22)	2 (4)	0 (0)	2 (4)

Heist, JCO 2017

Sacituzumab Govitecan: NSCLC

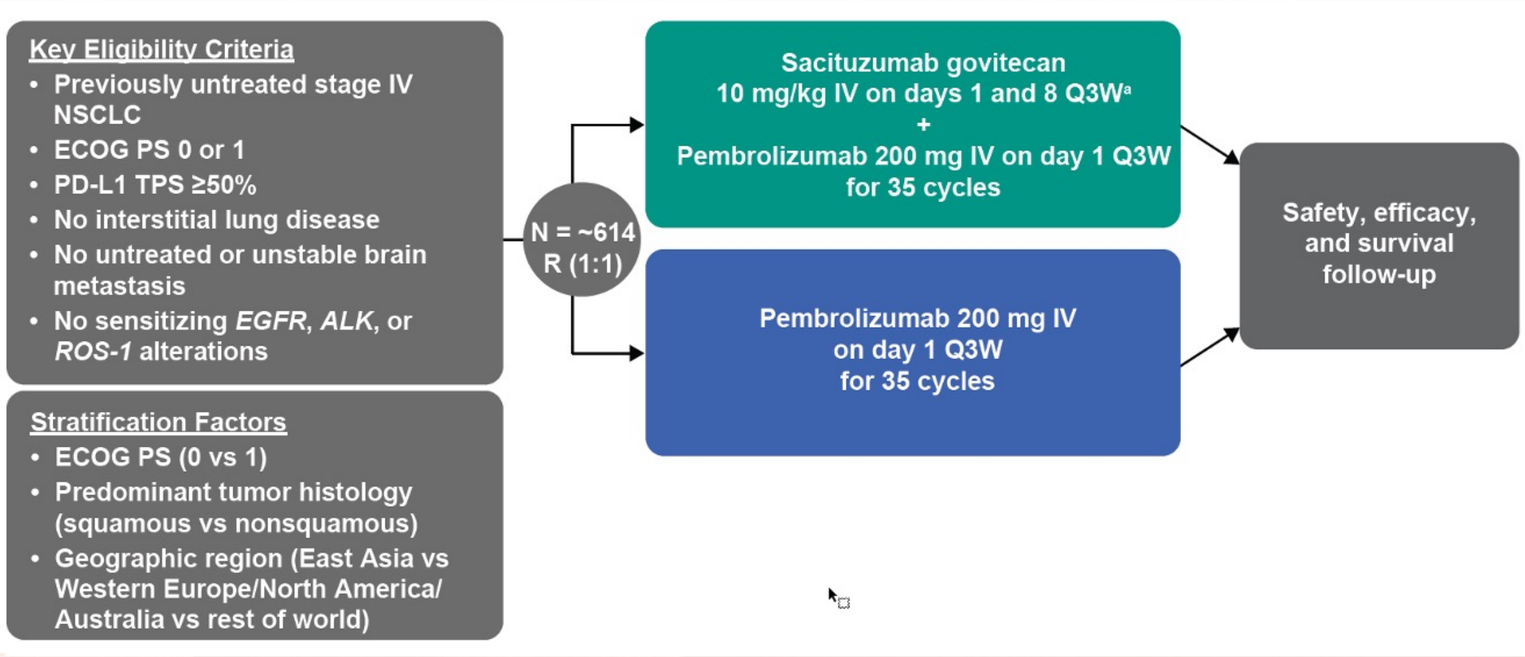
- EVOKE-02
  - Sacituzumab govitecan + pembrolizumab (1L)
    - PD-L1 ≥ 50%: RR 69%, 88% ongoing at 6m
    - PD-L1 < 50%: RR 44%, 88% ongoing at 6m



Cho, WCLC 2023

Sacituzumab Govitecan: NSCLC

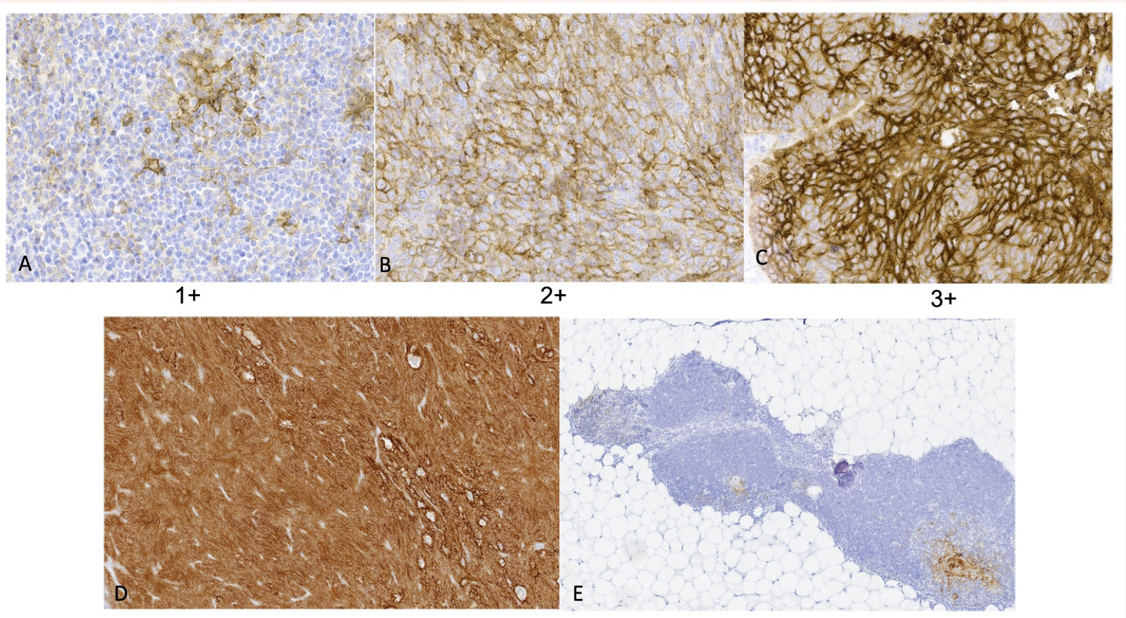
- EVOKE-01
  - Sacituzumab govitecan vs docetaxel
- EVOKE-05
  - Sacituzumab + pembro vs pembro



Garassino, ASCO 2022; Moskovitz, AACR 2023

TROP-2 and Thymic Cancers

- TROP-2 expression explored in thymic samples
  - In normal thymus tissue, 38% with TROP-2 IHC 1+, 62% negative
  - In thymoma, 76% TROP-2 IHC 2+/3+ and 24% negative or 1+
  - In thymic carcinoma, 23% TROP2 3+, 54% TROP2 2+, 23% 1+

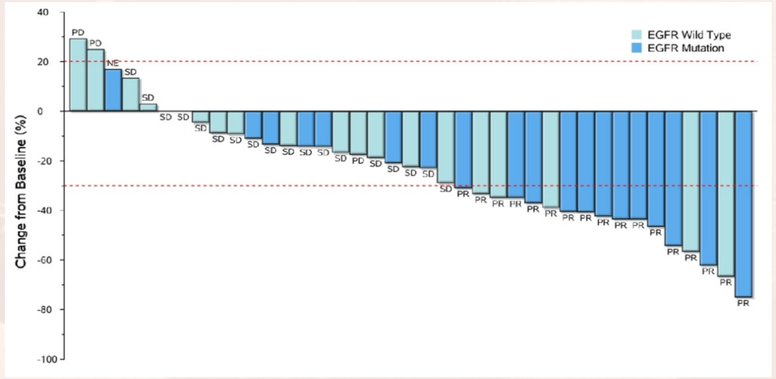


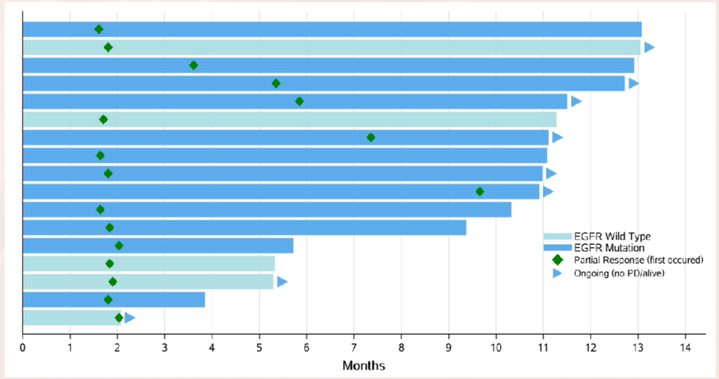
- Single-arm phase II IIT of sacituzumab govitecan in thymoma and thymic carcinoma opening soon

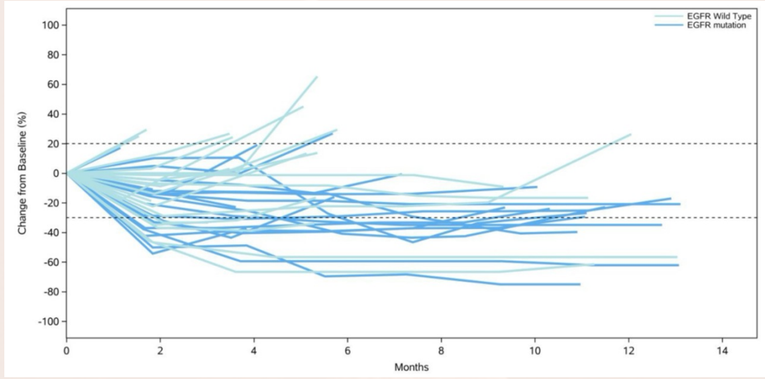
Yeung, Lung Cancer 2023

Other TROP-2 ADCs

- SKB264 (MK-2870, topoisomerase I payload, DAR 7.4)
  - Phase I/II study, 43 pts with NSCLC (22 EGFR mutant)
  - EGFR mutant: cRR 55%, DCR 100%, mDOR 9.3m, mPFS 11.1m
  - EGFR wild type: cRR 21.1%, DCR 89.5%, mDOR 9.6, mPFS 5.3m
- TRAE w/reduction 23.3% (none discontinued)
- Anemia 72% (30%≥G3), NTP 54% (33%≥G3), stomatitis 49% (9%≥G3)







Fang, ASCO 2023

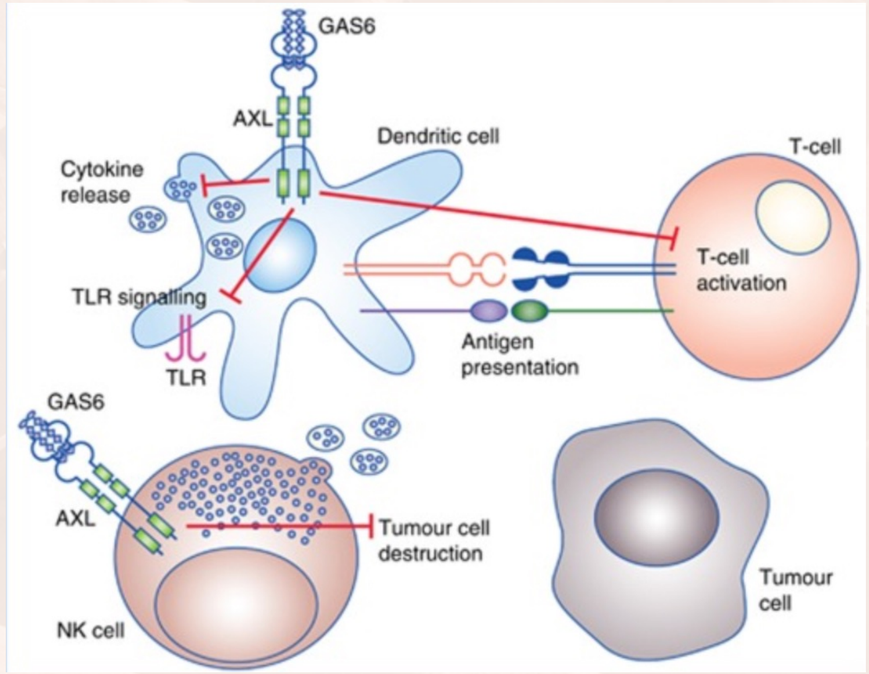
Future for TROP-2 ADCs?

- Monotherapy as a substitution for cytotoxics?
  - For which patients?
- Combination with immunotherapy with potential synergy?
  - What are the best partners?
- High TROP-2 expression as a predictive biomarker?
  - Trend seen in OS for high vs low in breast cancer (ASCENT)
  - Trend seen in PFS for high vs low in breast cancer
  - Warrants further study

Shastry, The Breast 2022; Bardia, Ann Oncol 2021; Bardia, JCO 2017;

AXL and NSCLC

- AXL is a receptor tyrosine kinase
  - Overexpressed in NSCLC
  - Implicated in EMT and angiogenesis



- Contributes to resistance
  - Chemotherapy
  - Targeted therapy
  - Immunotherapy

Gay, Br J Cancer 2017

AXL and NSCLC

- Targeting AXL signaling with small molecules
- Cabozantinib
  - Inhibits AXL… and MET, RET, VEGFR-2, KIT, TIE2
    - Phase II study of erlotinib + cabozantinib in EGFR+ NSCLC
      - Post-EGFR TKI, n=37, RR 10.8%, mPFS 3.6m
      - 32% with grade 3+ diarrhea
- Glesatinib
  - Oral MET and AXL inhibitor

Reckamp, Front Oncol 2019

AXL and NSCLC

- Enapotamab vedotin (AXL ADC) - development discontinued

- Conditionally active biologic (CAB) ADC
  - Mecbotamab vedotin (BA3011)
    - ADC preferentially binds to AXL on cancer cells
    - Enrolled 20 evaluable pts with NSCLC
      - Monotherapy, 4/10 with response in nonsquamous
      - Combination with nivolumab, 1/8 responses in nonsquamous
    - Ongoing studies with monotherapy or with nivolumab

Dy, WCLC 2023

TROP-2 and AXL in NSCLC

- Encouraging activity with agents targeting TROP-2 and AXL
- Need to further develop therapeutic strategies
  - How can we best integrate these agents?
  - Monotherapy vs combinations?
  - Biomarker vs empiric?
  - Unique agents offer different options