Antibody Drug Conjugate Adverse Events and Toxicities

SGO Winter meeting: GOG Partners Symposium

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Disclosures

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Steering Committees: GSK, Mersana, Incyte

Outline

- General Toxicities with ADC’s
- Tisotumab Vedotin AE’s
- Mirvetuximab Soravtasine AE’s
- Upifitimab Rilsodotin (UpRi)
- STRO-002

What can lead to toxicity

- Drug is toxic even when linked to antibody
- Suboptimal monoclonal antibody specificity
- Drug releases in circulation
- Drug leaches out of target cell

G Wiener, ASCO 2013

Estimates of the incidence of G3/4 response by toxicity and payload class

Endpoint	DM1	DM4	MMAE	MMAF	# Studies	# Patients
Anemia	2.6 (1.9, 3.6)	6.4 (3.3, 12.0)	6.8 (5.0, 9.3)	NR	18	1389
Neutropenia	3.5 (2.0, 6.0)	11.7 (6.9, 19.0)	16.4 (12.7, 21.0)	NR	25	1519
Thrombocytopenia	9.3 (7.3, 11.9)	7.3 (4.1,12.6)	9.7 (6.3, 14.8)	15.3 (7.8, 27.8)	20	1536
Leukopenia	0.6 (0.1, 3.1)	9.5 (4.3, 20.0)	10.3 (5.8, 17.4)	NR	8	284
Hepatic toxicity	7.2 (5.1, 10.2)	0.7 (0.1, 4.2)	1.5 (0.4, 5.6)	NR	16	1196
Peripheral neuropathy	0.3 (0.1 1.7)	2.1 (0.9, 5.0)	6.5 (4.4, 9.4)	0.0 (NA, NA)	27	1116
Ocular toxicity	3.3 (0.8, 12.0)	5.3 (2.4, 11.0)	NR	16.0 (6.9, 33.0)	8	272

Masters et al. Investigational New Drugs, 36(1): 121-135 2018

Ocular AEs in ADC clinical trials

- **Ocular AEs are** : Common with other ADCs having a maytansinoid payload (DM1, DM4, etc..)

- IMGN853: Clearly an **off-target mechanism** since cornea/limbal stem cells lacks FRα receptor expression.

- Across all ADC trials:
  - **Blurred vision** and **keratopathy** are the commonest reported ocular AEs.
  - **Reversible**.

Tisotumab Vedotin: FDA Approved

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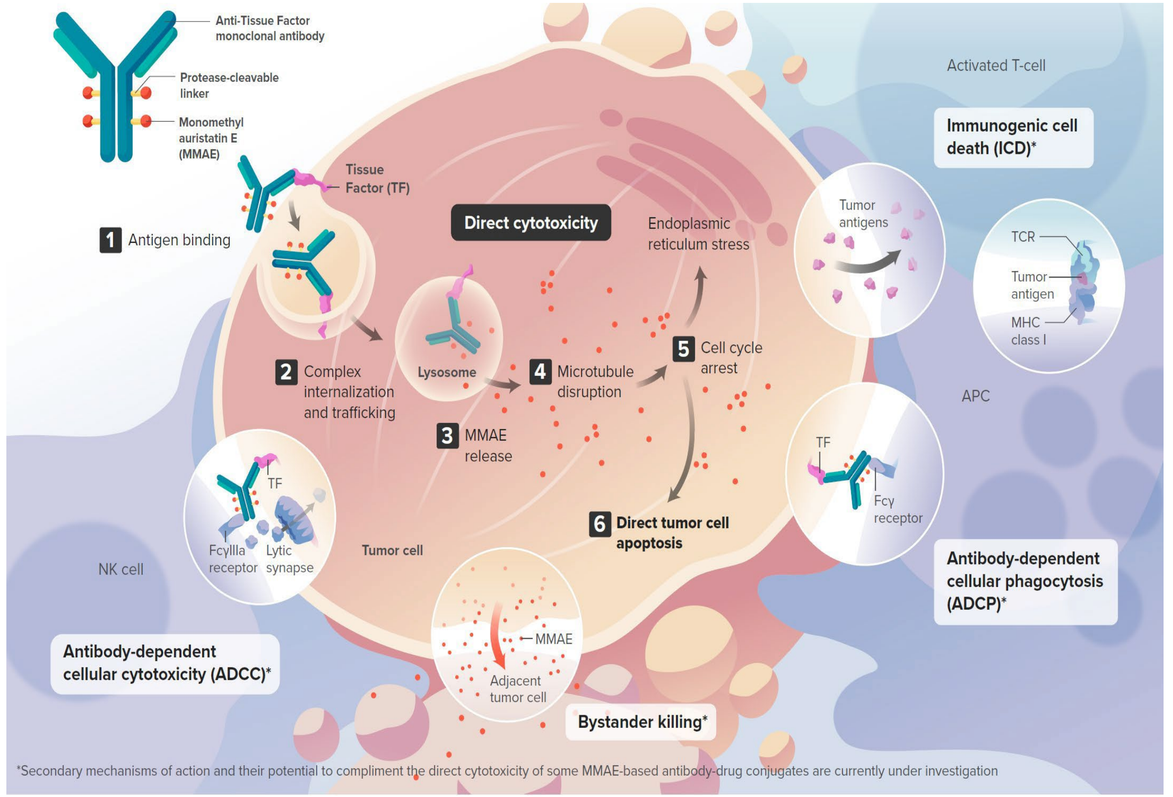
Tisotumab vedotin is an investigational antibody–drug conjugate directed to TF and covalently linked to the microtubule-disrupting agent MMAE via a protease-cleavable linker[1,2]

TF is a protein highly expressed in cervical cancer and other solid tumors[3-6]

Multimodal MoA of tisotumab vedotin[1,2,7]

- Direct cytotoxicity
- Bystander killing
- Immunogenic cell death
- ADCC
- ADCP



1. Breij. Cancer Res. 2014;74:1214. 2. De Goeij. Mol Cancer Ther. 2015;14:1130. 3. Forster. Clin Chim Acta. 2006;364:12.
4. Pan. Mol Med Rep. 2019;19:2077. 5. Cocco. BMC Cancer. 2011;11:263. 6. Zhao. Exp Ther Med. 2018;16:4075. 7. Alley. AACR 2019. Abstr 221.

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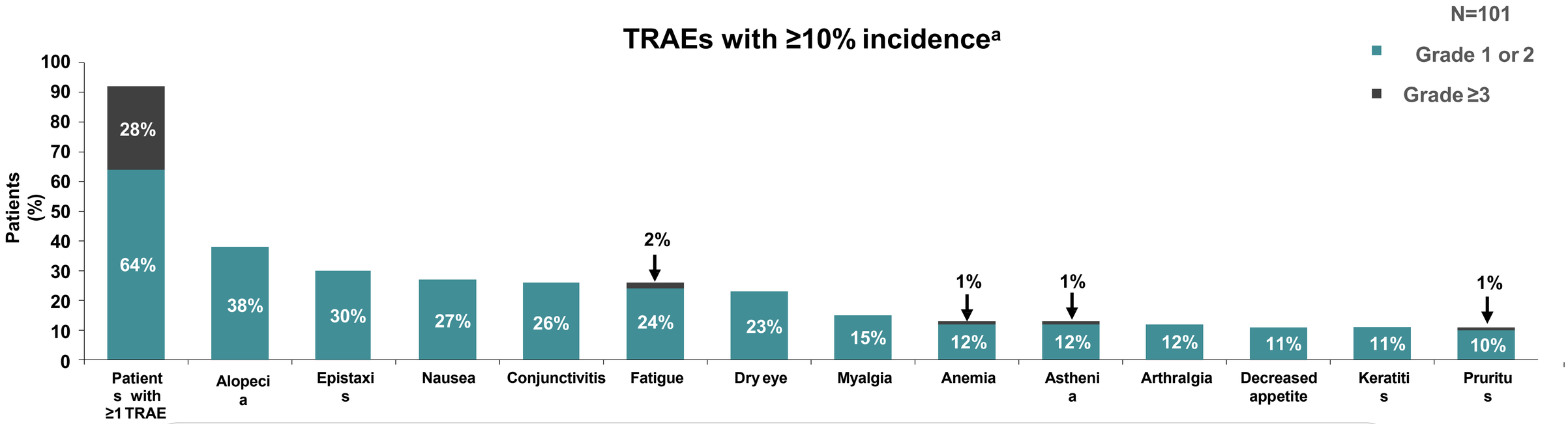
Phase 2: Innova TV/GOG 3023/ENGOT cx6 Most Common TRAEs with Tisotumab Vedotin

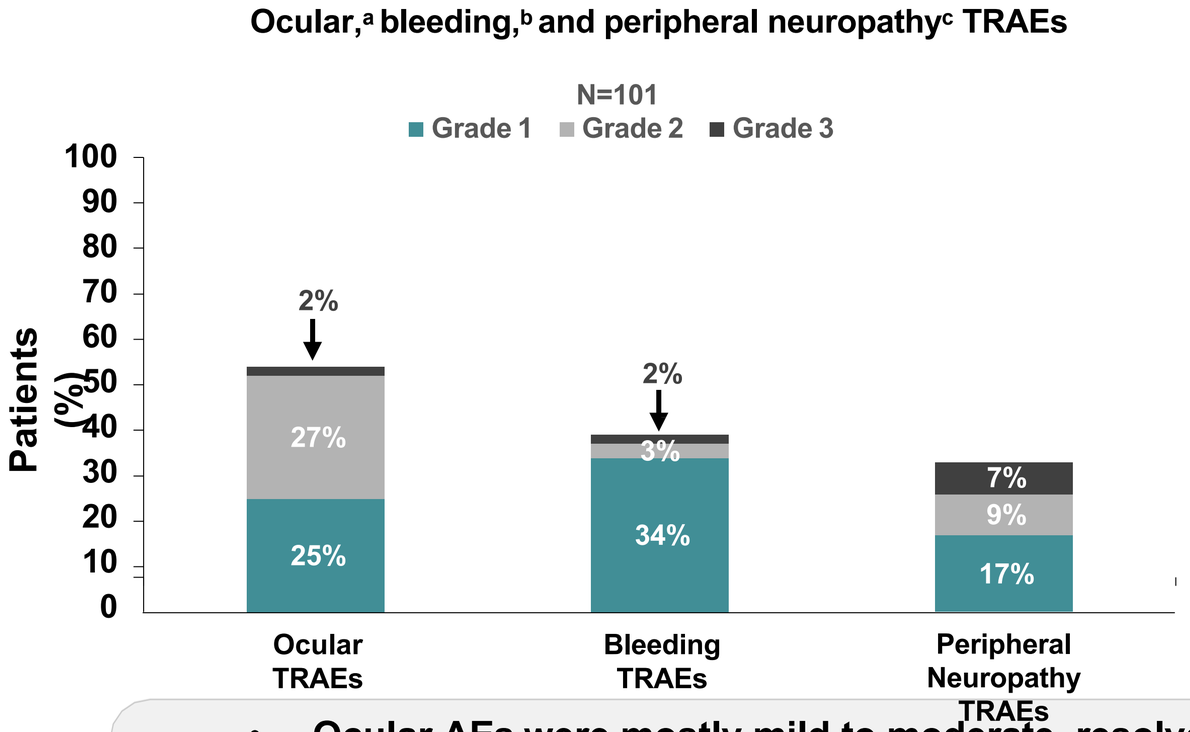


- Most TRAEs were grade 1 or 2 and no new safety signals were reported
- One death due to septic shock was considered by the investigator to be related to therapy[b]

Data cutoff: February 06, 2020. Median duration of follow-up: 10.0 months. Median duration of treatment: 4.2 months (range, 1–16).
[a]Any-grade AEs included if ≥10%. [b]Three treatment-emergent deaths unrelated to therapy included one case of ileus and two with unknown causes. TRAE, treatment-related adverse event.

Coleman RL et al. ESMO 2020. Abstract LBA32.
Coleman RL. *Lancet Oncol.* 2021:S1470-2045(21)00056-5.

Prespecified AEs of Interest of Tisotumab Vedotin



	Ocular	Bleeding	Peripheral Neuropathy
Time to onset (median, months)	1.4	0.3	3.1
Events resolved, %	86	90	21
Time to resolution[d] (median, months)	0.7	0.5	0.6

- Ocular AEs were mostly mild to moderate, resolved, and were manageable with an eye care plan
- Most bleeding events were grade 1 epistaxis (28%) of which majority resolved
- Most peripheral neuropathy events (known MMAE-related toxicity) were grade 1 and manageable with dose modifications; resolution was limited by follow-up period

Data cutoff: February 06, 2020. Median duration of follow-up: 10.0 months. [a]Any ocular SMQ (conjunctival disorders SMQ, corneal disorders SMQ, scleral disorders SMQ, retinal disorders SMQ, periorbital and eyelid disorders SMQ, ocular infections SMQ, optic nerve disorders SMQ, glaucoma SMQ, lacrimal disorders SMQ, and eye disorders SMQ). [b]Hemorrhage SMQ. [c]Peripheral neuropathy SMQ. [d]Assessment limited by the protocol-defined follow-up period for AE of only 30 days after the last dose. AE, adverse event; MMAE, monomethyl auristatin E; SMQ, standardized MedDRA queries; TRAE, treatment-related adverse events.

Coleman RL et al. ESMO 2020. Abstract LBA32.
Coleman RL. *Lancet Oncol.* 2021:S1470-2045(21)00056-5.

Tisotumab Vedotin:Management of Ocular Ae's- Care Plan and Mitigation Approaches

Mitigation of ocular AEs during infusion:

-Confirm administration of corticosteroid and vasoconstrictor eye drops before infusion

-Apply cold packs covering the eyes after administration of vasoconstrictor eye drops and leaving/changing pads during infusion

- Keep cold packs on for ~20 min after infusion
- Patient to self-administer corticosteroid eye drops 2x throughout the remainder of the day

Mitigation/assessment of ocular AEs after infusion:

-Use corticosteroid eye drops 3x day for 2-3 days after infusion

-Administer lubricating eye drops for the duration of treatment and 30 days after the last dose

-Monitor for new or worsening ocular signs/ symptoms and promptly refer to eye care provider if warranted

Resources for Healthcare Professionals	
Eye care checklist	tivdakhcp.com/TivdakHCP_Tivdak_Eye_Care_Checklist.pdf
Dosing and administration and eye care guide	tivdakhcp.com/TivdakHCP_Dosing_Administration_and_Eye_Care_Guide.pdf
Resources for Patients	
Important facts	seagendocs.com/Tivdak_Important_Facts.pdf
Eye care guide	tivdakhcp.com/Tivdak_Eye_Care_Guide_for_Patients.pdf
Eye drops tracker	tivdakhcp.com/Eye_Drop_Tracker.pdf
TV wallet card	tivdakhcp.com/Tivdak_Wallet_Card.pdf

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TV: FDA Approval with Black Box Warning

Black Box Warnings:

Ocular toxicity

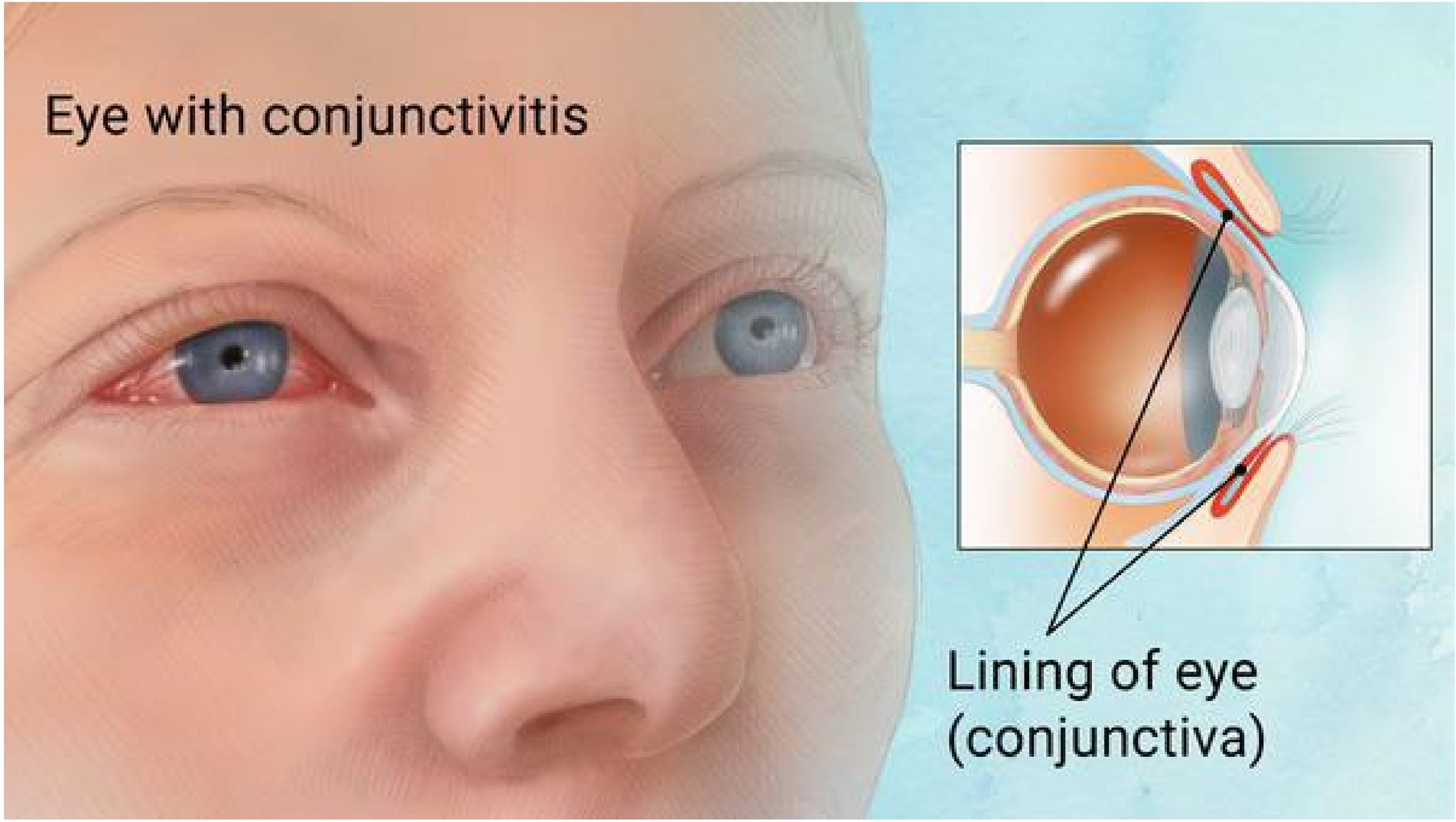
Causes changes in corneal epithelium and conjunctiva resulting in vision changes, including severe vision loss, and corneal ulceration

Conduct ophthalmic examination at baseline, prior to each dose, and as clinically indicated

Adhere to premedication and required eye care before, during, and after infusion

Withhold until improvement and resume, reduce the dose, or permanently discontinue, based on severity

TV: Eye Toxicity



MIRVETUXIMAB SORAVTASINE

FORWARD I

- Platinum-resistant ovarian cancer
- FRα-positive tumor expression
  - Medium (50-74% cells positive)
  - High (≥75% cells positive)
- ECOG performance status 0 or 1
- 1-3 prior therapies

Statistical Assumptions

- Hochberg procedure
- α=0.05 (two-sided), power = 90%

HR=0.58; control arm mPFS 3.5 mos

Mirvetuximab Soravtansine (n=248)

6 mg/kg (adjusted ideal body weight) once every 3 weeks

2:1 Randomization

Stratification Factors:
FRα expression (medium or high)
Prior therapies (1 and 2, or 3)
Choice of chemotherapy

Investigator's Choice Chemotherapy
Paclitaxel, PLD†, or Topotecan (n=118)

Paclitaxel: 80 mg/m^2 weekly
PLD: 40 mg/m^2 once every 4 weeks
Topotecan: 4 mg/m^2 on Days 1, 8, and 15 every 4 weeks; or 1.25 mg/m^2 on Days 1-5 every 3 weeks

Primary Endpoint

Progression-free survival (PFS; by BIRC*) for ITT and high FRα populations

*BIRC = Blinded Independent Review Committee; analyzed by Hochberg procedure

Secondary Endpoints

Overall response rate (ORR)
Overall survival (OS)
Patient reported outcomes (PRO)

†Pegylated liposomal doxorubicin
ClinicalTrials.gov Identifier: NCT02631876

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SAFETY SUMMARY

	Mirvetuximab soravtansine (n=243*)	IC Chemotherapy (n=109*)
Any TEAE	>99%	98%
Grade 3+ TEAEs	46%	61%
SAEs	28%	28%
Deaths on study drug or within 30 days of last dose	4%	6%
Dose reductions due to related TEAEs	20%	30%
Dose delays due to related TEAEs	29%	28%
Discontinuations due to related TEAEs	5%	8%

***Five and nine patients randomized into the mirvetuximab soravtansine and chemotherapy arms, respectively, did not receive any allocated intervention and were not included in the safety analyses**

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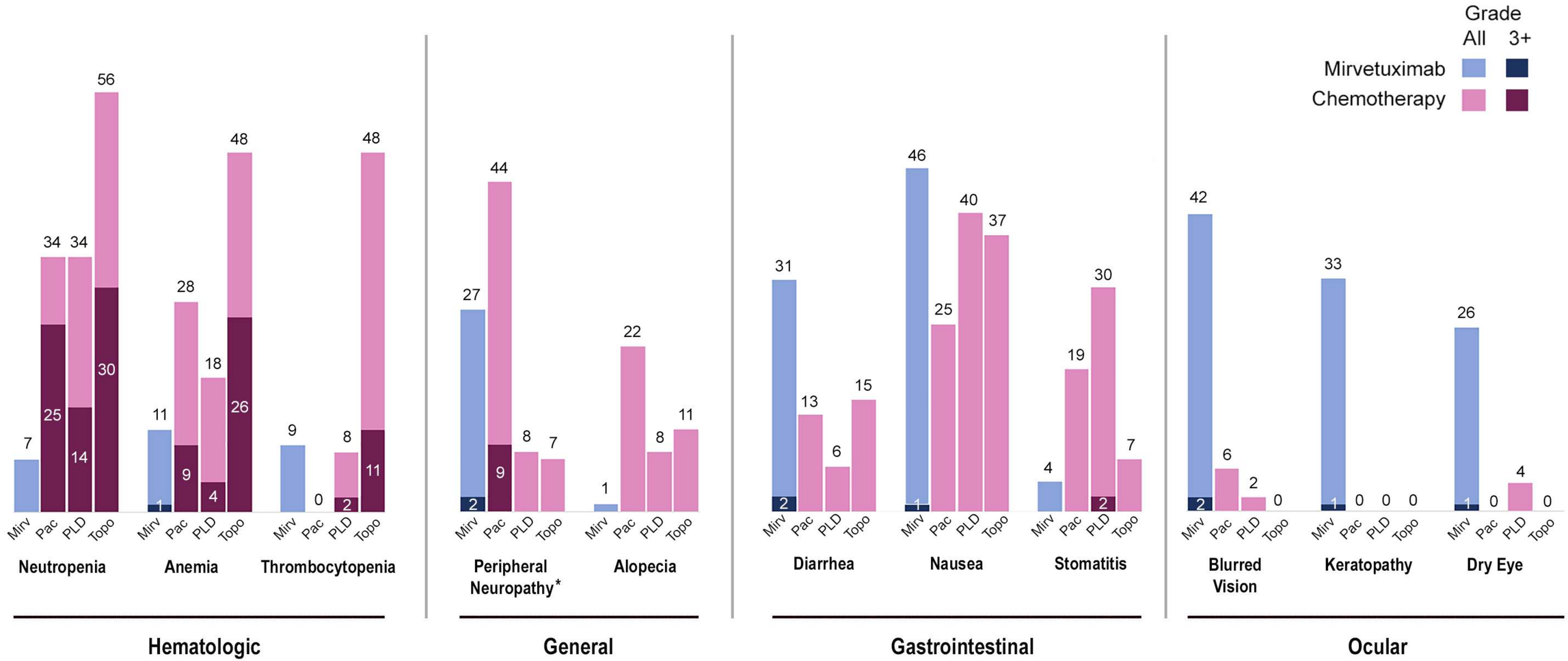
MOST COMMON TREATMENT-RELATED ADVERSE EVENTS (> 20%): DIFFERENTIATED SAFETY PROFILE



*Grade 2+ peripheral neuropathy events were observed in 12% and 28% of patients that received mirvetuximab soravtansine or paclitaxel, respectively.

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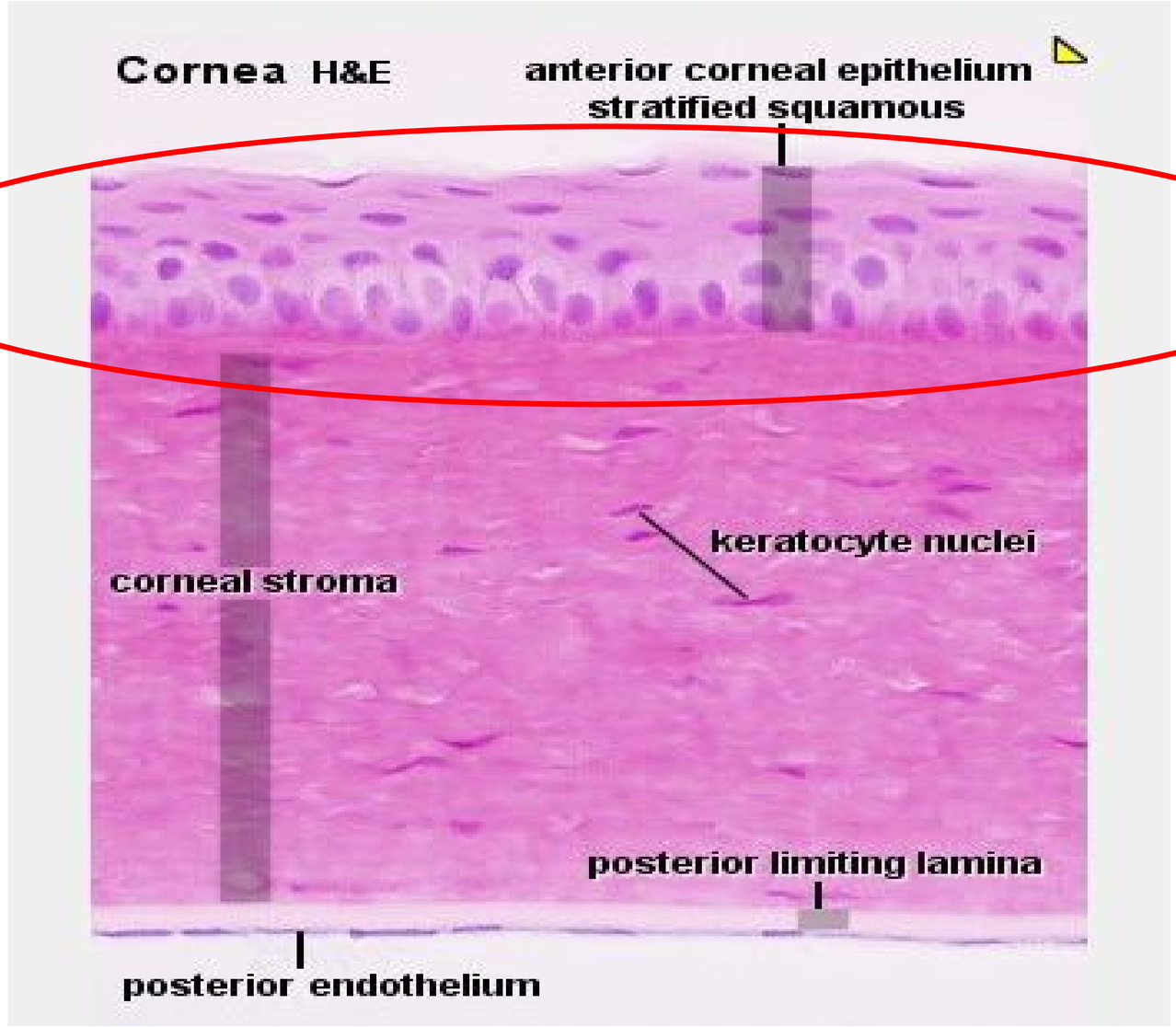
- **Mirvetuximab patients must self-administer corticosteroid eye drops unless the risk outweighs the benefit as determined by the doctor:**
  - 1% prednisolone (Pred Forte® or generic equivalent)
  - Six times daily on Days 1-4 and four times daily on Days 5-8 of each cycle during the study.
    - MIRASOL and SORAYA start on day -1
  - If an individual patients who cannot tolerate the preservative contained in 1% prednisolone, other corticosteroid eye drops may be substituted (e.g. difluprednate 0.05%; Durezol®) and administered on Days 1-8 of each cycle at a frequency prescribed by the ophthalmologist.
- **Lubricating artificial tears:**
  - Mandated for patients randomized to IMGN853. Use of preservative free, lubricating artificial tears on a daily basis (as directed per label and/or physician)
  - Wait at least 15 minutes following steroid eye drop administration before using the lubricating eye drops

Management of ocular adverse events

	Management
Severity (CTCAE Grade)	
Grade 1	• Complete eye exam • Monitor for worsening symptoms • No change in mirvetuximab soravtansine dose or schedule of administration
Grade 2	• Complete eye exam • Weekly symptomatic ocular assessments until symptoms resolve or return to baseline • Hold mirvetuximab soravtansine until improvement to Grade 1 or better
Recommended guidelines	
	• Avoid use of contact lenses • Regular cleaning (baby shampoo, soft cloth) • Warm compress before sleep • Sunglasses in direct sunlight
Prophylactic Measures	
Lubricating eye drops (required)	• Daily administration of preservative-free eye drops (Days 1-21)
Corticosteroid eye drops (expansion cohort)	• 1% prednisolone acetate during active study treatment • Administered six times daily (Days 1-5) • Administered four times daily (Days 6-10)

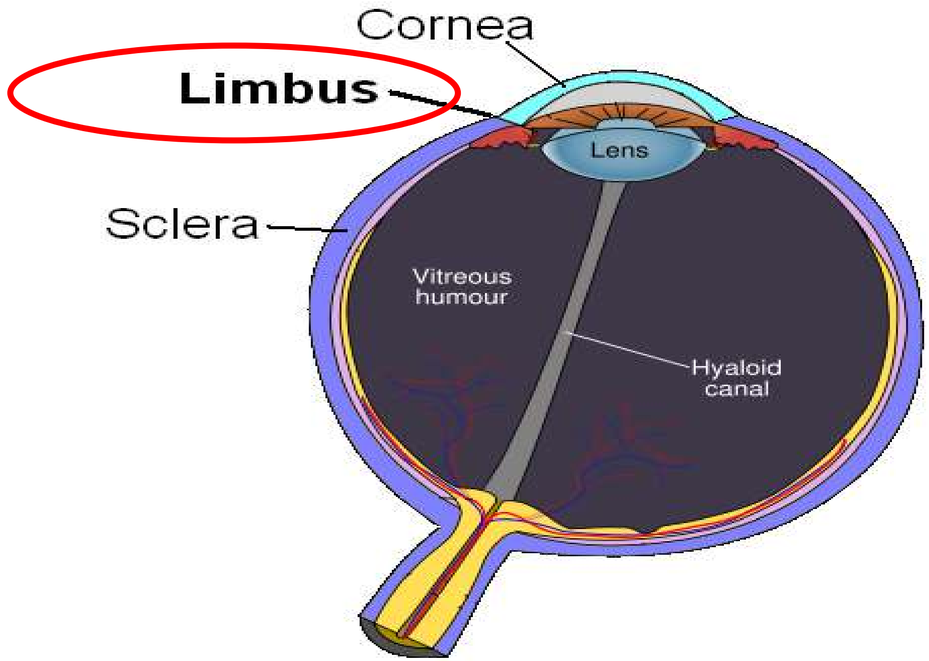
- Moore et al 2018 *Future Oncol* 14:123-136

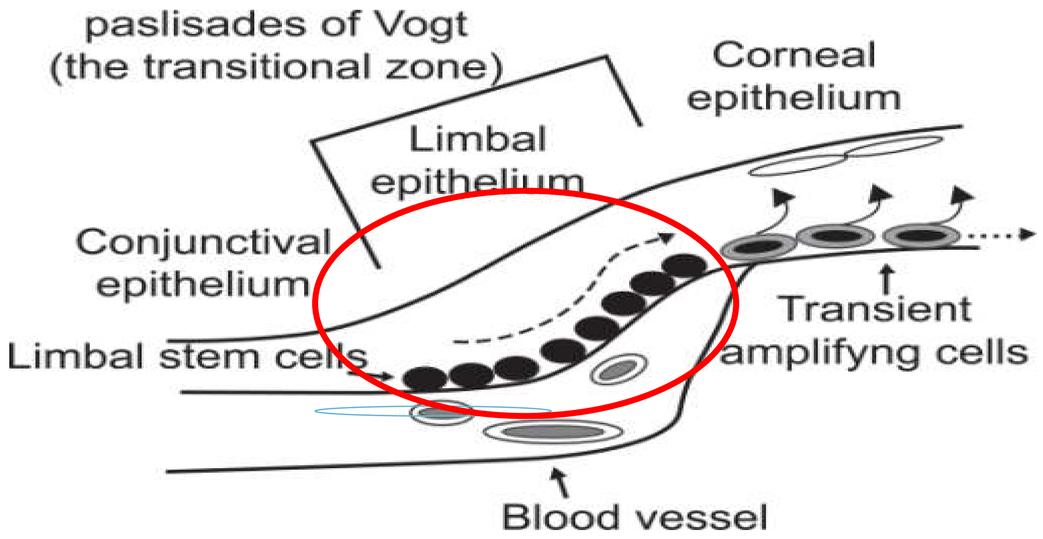
Structure of the Normal Human Cornea: Three *Functional* Layers



Regeneration of the Corneal Epithelium

http://openi.nlm.nih.gov/detailedresult.php?img=2704521_opth-1-373f1&req=4

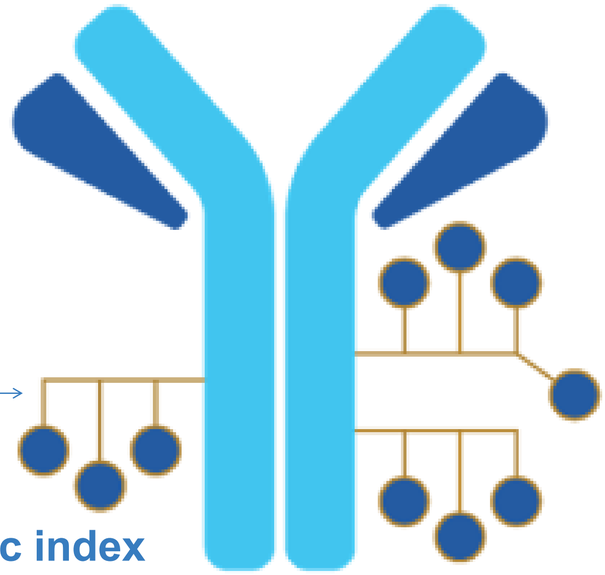




The Limbus provides a reservoir of stem cells for the regeneration corneal epithelium; basal cells through the cornea can proliferate to a limited extent

Upifitimab Rilsodotin (UpRi)

XMT-1536 (upifitamab rilsodotin; UpRi): : A potent NaPi2b Dolaflexin ADC with a high drug-to-antibody ratio and a controlled bystander effect



Dolaflexin
Improved therapeutic index vs other platforms

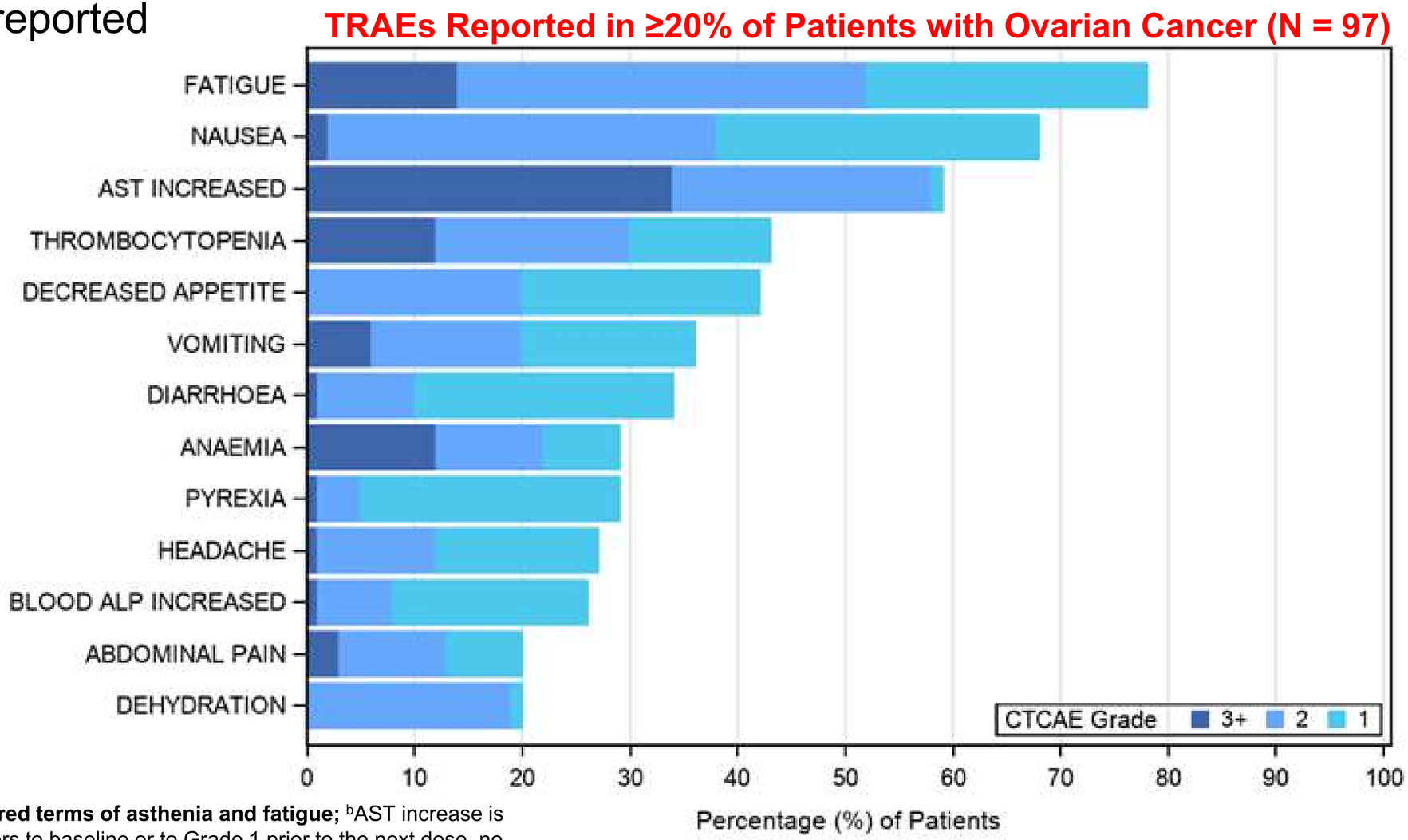
- **Polymer scaffold**
- **High Drug to Antibody Ratio (DAR) ~10-12**
- **Excellent drug like properties**

DolaLock Payload
Efficacy without severe neutropenia, neuropathy, or ocular toxicity

- **Novel auristatin**
- **Controlled bystander effect**
- **Selectively toxic to rapidly dividing cells**
- **Not a PgP substrate**
- **Induces immunogenic cell death**

UpRi Tolerability Profile

- No grade ≥ 3 (severe) TRAEs of neutropenia, peripheral neuropathy, or ocular toxicity have been reported



[a]**Fatigue includes preferred terms of asthenia and fatigue;** [b]AST increase is transient in nature, recovers to baseline or to Grade 1 prior to the next dose, no instances are associated with elevated bilirubin or cases of Hy's law; [c]**Thrombocytopenia includes preferred terms of platelet count decreased and thrombocytopenia. Thrombocytopenia is transient in nature, nadirs at Day 8 and recovers prior to the next dose;** [d]**Anaemia includes preferred terms of anaemia of chronic disease, blood loss anaemia and iron deficiency anaemia**

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Dose modification due to Treatment-Related Adverse Events (TRAEs):

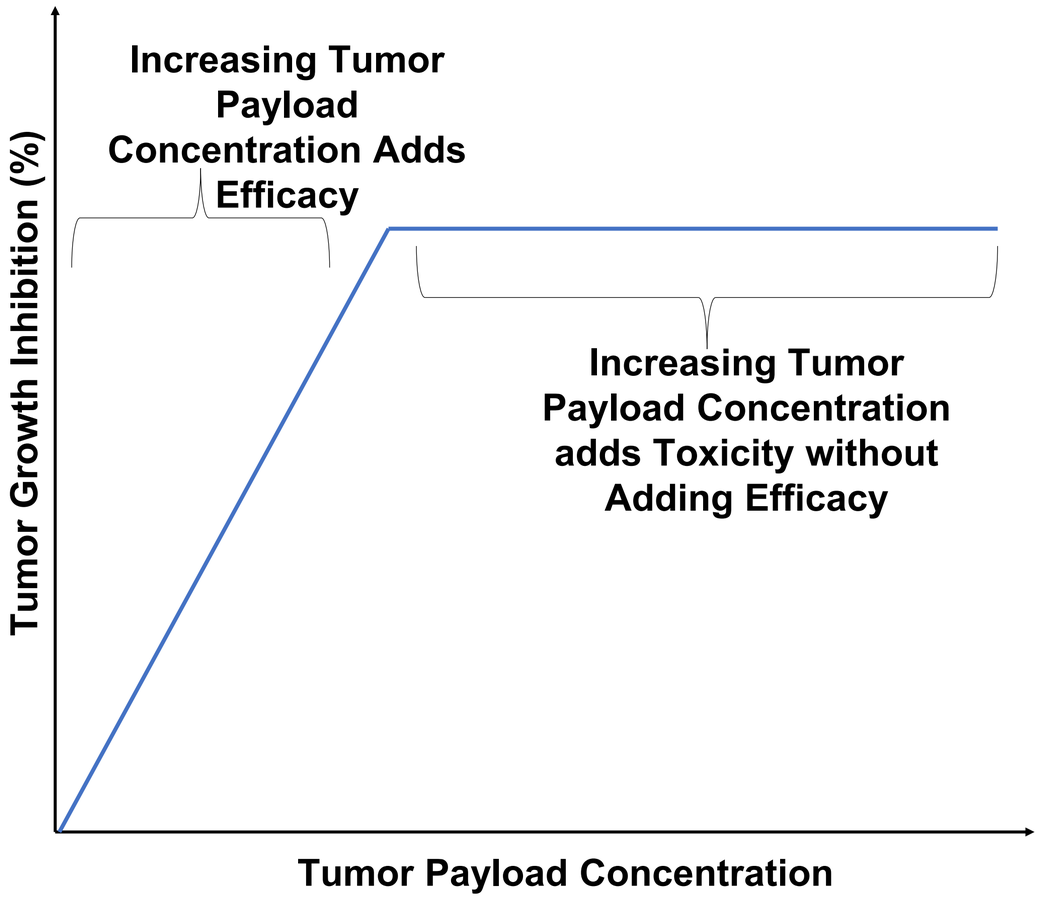
- Of the 97 patients, 43 (44%) had dose delay, reduction, and/or discontinuation due to a TRAE
  - Dose reductions due to TRAEs occurred in 27 (28%) patients
  - Dose delays due to TRAEs occurred in 16 (16%) patients
  - Dose discontinuation (withdrawn) due to TRAEs occurred in 10 (10%) patients

Treatment-Emergent SAEs reported in ≥ 5% of Patients

- Out of 97 patients, 47 (48%) reported Treatment-Emergent SAEs. The most frequent of which were Gastrointestinal Obstruction 7 (7%), 5 (5%) each for Pyrexia, Pneumonitis, and Abdominal Pain
- 22 (23%) of the SAEs were deemed by the investigator to be treatment-related

 Data Cut: June 10, 2021

Correlation of ADC Efficacy and Tumor Payload Concentration



- Further analysis utilizing population PK models confirmed the efficacy and safety findings showing the association between increasing exposure and G3+ adverse events, including pneumonitis
- Preclinically, ADCs have a well-characterized exposure / response relationship
  - ADC efficacy increases with payload tumor concentration up to a plateau
  - Beyond this plateau, additional drug can decrease tolerability without improving efficacy
  - Preclinical data confirm relationship appears regardless of target, payload, linker, or platform

The Dose that Optimizes Therapeutic Index May Not be the Maximum Tolerated Dose

Source: Drug Metab Dispos 47:1146–1155, October 2019

Decreased Grade 3+ Treatment Related AEs with Lower Dose

	Lower Dose 36 mg/m^2	Intermediate Dose ~80 mg	Higher Dose 43 mg/m^2
≥ Grade 3 Fatigue	1 (8%)	6 (13%)	9 (23%)
≥ Grade 3 Increased AST	1 (8%)	16 (35%)	16 (41%)
≥ Grade 3 ILD/Pneumonitis	0 (0%)	0 (0%)	4* (10%)

*** 2 cases of Grade 5 pneumonitis including 1 previously reported; most recent case was in a 75-year-old 4th line recurrent ovarian cancer patient treated at higher dose of 43 mg/m^2 (BSA 1.47 m^2, 105 lb) with past medical history of poor pulmonary reserve: asthma and chronic obstructive pulmonary disease requiring intermittent supplemental oxygen at baseline, coronary artery disease and congestive heart failure**

Data Cut: June 10, 2021

Pre-medications and Supportive Medications UpRi

Recc following premedication regimen prior to the first dose of XMT-1536, and subsequent doses, as appropriate for your individual patients:

- **Corticosteroids –dexamethasone 8mg oral or IV**
- **Antiemetics –NK1 receptor antagonist or 5HT3 receptor antagonist**
- **Antipyretic –NSAIDs preferred (e.g., ibuprofen 400mg oral), Acetominophen (limit to 2 grams/day)**
- **Consider scheduled NSAIDs, antiemetics, and/or dexamethasone on days 2-5 for nausea/vomiting/pyrexia, in addition to standard PRN prophylaxis**
- **Consider scheduling the patients for intravenous (IV) fluids and IV antiemetics on Day 8 of each cycle**
- **Early dose reduction for tolerability is an option**

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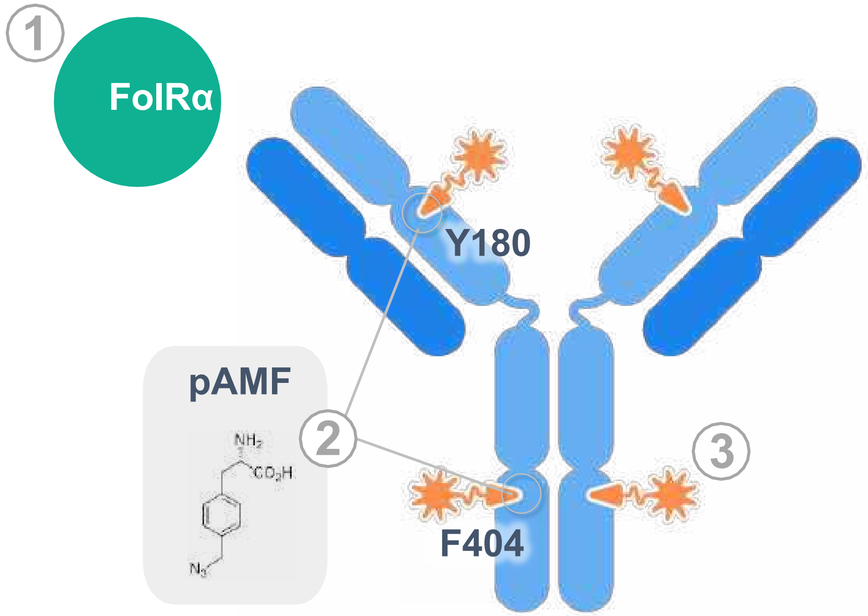
STRO-002 Highly optimized ADC designed to drive efficient tumor responses across a broad range of target antigen levels



STRO-002 is a homogeneous antibody drug conjugate (ADC) with a drug-antibody ratio (DAR) of 4, targeting folate-receptor alpha (FolRα)

1. **FolRα is overexpressed in certain cancers including ovarian cancer and endometrial cancer**
2. **Precisely positioned non-natural amino acids, p-azidomethyl-L-phenylalanine (pAMF), at positions Y180 and F404 on the heavy chain**
3. **Stable protease-cleavable linkers, with rapid clearance of toxic catabolite after release and cell killing**
4. **Warhead is hemiasterlin-derivative[1] with potentially dual mechanism against the tumor – tubulin-inhibitor cytotoxin, less sensitive to P-gp transport and induces immunogenic response upon cell death[2]**

[1] Sutro-proprietary tubulin-targeting 3-aminophenol hemiasterlin warhead, SC209
[2] Based on STRO-002 pre-clinical models showing immune stimulation at site of tumor upon cell death

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•Emerging Safety Profile is Manageable – 85.5% of TEAEs were Grade 1-2
•No new safety signals were observed, including the absence of keratopathy

STRO 002

Dose Expansion

Most Common G3+ TEAEs (≥2 Subjects) by Dose

	4.3 mg/Kg (N=23)			5.2 mg/Kg (N=20)			Total (N=43)		
	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Subjects reporting at least 1 event	**13 (57)**	**4 (17)**	**0**	**8 (40)**	**8 (40)**	**1 (5)**	**21 (48)**	**12 (28)**	**1 (2)**
Neutropenia [(1)]	10 (44)	4 (17)	0	6 (30)	8 (40)	1 (5)	16 (37)	12 (28)	1 (2)
Febrile Neutropenia	*1 (2)*	*0*	*0*	*0*	*0*	*1 (5)*	*1 (2)*	*0*	*1 (2)*
White blood cell count decreased	4 (17)	1 (4)	0	1 (5)	2 (10)	0	5 (12)	3 (7)	0
Anemia	1 (4)	0	0	3 (15)	0	0	4 (9)	0	0
Arthralgia	4 (17)	0	0	0	0	0	4 (9)	0	0
Diarrhea	2 (9)	0	0	0	1 (5)	0	2 (5)	1 (2)	0
Platelet count decreased	2 (9)	0	0	1 (5)	0	0	3 (7)	0	0
Thrombocytopenia	0	0	0	2 (10)	0	0	2 (8)	0	0
Vomiting	0	0	0	2 (10)	0	0	2 (8)	0	0
Fatigue	2 (9)	0	0	0	0	0	2 (8)	0	0
Activated partial thromboplastin time prolonged	2 (9)	0	0	0	0	0	2 (8)	0	0
Hyponatremia	2 (9)	0	0	0	0	0	2 (8)	0	0
Neuralgia	2 (9)	0	0	0	0	0	2 (8)	0	0
Acute kidney injury	0	0	0	2 (10)	0	0	2 (8)	0	0

Asymptomatic neutropenia was the leading TEAE, resulting in treatment delay or dose reduction

- Neutropenia resolved with **1 week delay ± G-CSF**, in the majority of cases
- **Febrile neutropenia is rare**
  - One Grade 5 event at the 5.2 mg/kg dose cohort
  - One Grade 3 event at the 4.3 mg/kg dose cohort
- **Protocol was updated** to require dose reduction for Grade 4 neutropenia
- **Dose reductions ameliorated neutropenia**
- **Safety profile will be optimized with G-CSF prophylaxis in pivotal study**

(1) Neutropenia included the following preferred terms: neutropenia, febrile neutropenia, and neutrophil count decreased.

Note: Data as of Nov. 8, 2021.

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Conclusions

- ADCs allow more precise delivery of chemotherapy to cancer cells, which should improve effectiveness relative to toxicity.
- Antibody drug conjugates have their own unique toxicities/adverse events
- TV already approved and others on the horizon so understanding toxicities and incorporating supportive measures are key
- Eye care plans required for both TV and Mirvetuximab but different
- UpRi- GI anti-emetics, IVF hydration are key
- STRO-002- Neutropenia and arthralgias noted

Thank You

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