DART: *D*ual *A*nti-CTLA-4 & Anti-PD-1 blockade in *R*are *T*umors

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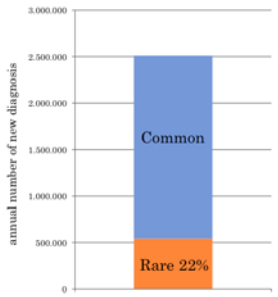
RARE CANCERS: INCIDENCE



186 rare cancers

About 500,000 new cases/year in EU27

22% of all cancer diagnosed/year

Slide: Annalisa Trama, from Paper: Gemma Gatta et al. Eur J of CA 47 (2011) 2493-2511

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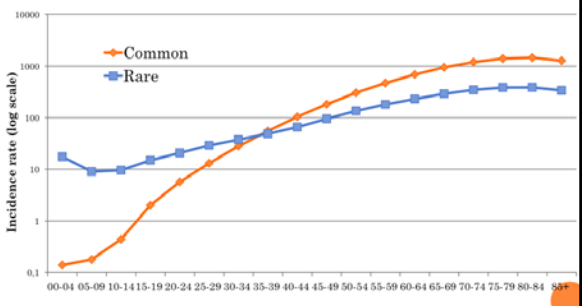
AGE-SPECIFIC INCIDENCE RATES FOR RARE AND COMMON CANCERS IN EU 27



Slide: Annalisa Trama, from Paper: Gemma Gatta et al. Eur J of CA 47 (2011) 2493-2511

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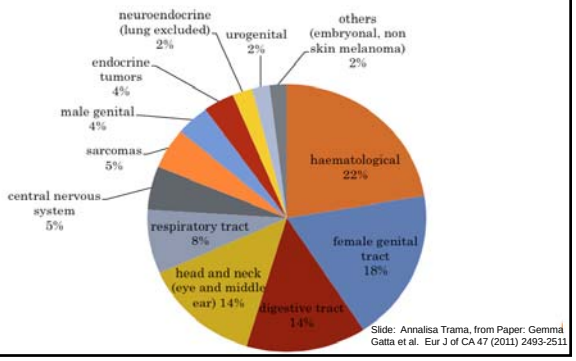
DISTRIBUTION OF MAJOR FAMILIES OF RARE TUMORS WITHIN ALL RARE CANCERS



Slide: Annalisa Trama, from Paper: Gemma Gatta et al. Eur J of CA 47 (2011) 2493-2511

Demographics

- As a group, rare cancers represent almost a quarter of all new cancer cases
  - Individually rare, but collectively a large group
  - Underrepresented in trials
- Rare cancers disproportionately affect younger patients
- Limited treatment options
- Limited clinical trials
  - Market share
  - Regulatory hurdles

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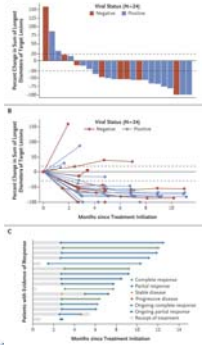
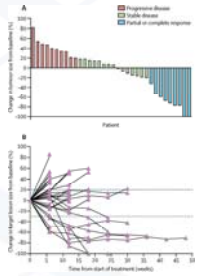
Responses to Immunotherapy in Rare Tumors

Pembrolizumab in Merkel Cell (NEJM 2016)



Nivolumab in Anal Cancer (Lancet Onc 2017)



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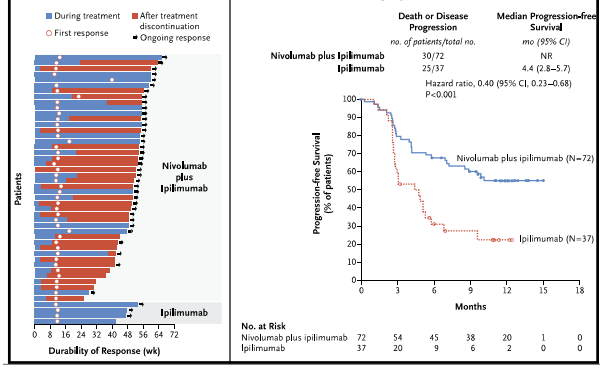
Combinatorial vs Single-Agent Immunotherapy

Postow et al. NEJM 2015



DART: Dual Anti-CTLA-4 & Anti-PD-1 blockade in Rare Tumors

Primary study objective:

- To evaluate the overall response rate (ORR) in patients with advanced rare cancers treated with ipilimumab plus nivolumab combination therapy
  - Primary Endpoint: Overall response rate (ORR) as assessed by traditional RECIST v1.1 measurement criteria will be used.

Secondary objectives:

- To evaluate toxicities in each cohort
- To estimate overall survival, progression-free survival, and immune-related ORR, PFS in each cohort

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SWOG DART Eligibility Overview (cont'd)

- Rare Cancer histologic subtypes (incidence of < 6/100,000 persons/year) with exception of
  - Anal cancer,
  - Lymphoma,
  - Merkel cell carcinoma,
  - Pleural Mesothelioma,
  - Sarcoma (bone & soft tissue),
  - Thymic Carcinoma,
  - Uterine Leiomyosarcoma
- Can enroll directly independent of NCI MATCH

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Rare Tumors Basket Study (2017)

SWOG DART Eligibility Overview (cont'd)

2. Patients with brain metastases must have completed treatment at least 4 weeks prior to registration. Metastatic brain parenchymal disease must have been treated and patient must be off steroids for 14 days prior to study drug administration.
3. Measurable disease by RECIST v1.1.
4. Eligible if received either prior anti-CTLA-4 or other prior anti-PD-1/anti-PD-L1 therapy (not both) provided completed >/= 4 weeks prior to registration.
5. Prior Gr. 3 or higher immune-related AEs on prior immunotherapy not eligible.
6. Patients with controlled HIV, HBV, HCV are eligible.

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SWOG DART Treatment/ Schema

- Basket study in rare tumors
- Concurrent Combination Immunotherapy:
  Ipilimumab 1 mg/kg IV every 6 weeks and nivolumab 240mg IV (fixed dose) every 2 weeks
  - Nivolumab monotherapy permitted for patients who experience severe immune-related toxicity on combination ipilimumab/nivolumab
- Treatment cycle length: 6 weeks
- Imaging assessments: every 12 weeks

Ipilimumab 1mg/kg IV q6wks

+

Nivolumab 240mg IV q2wks

↓

PD, unacceptable toxicity, or withdrawal of consent

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Statistical Considerations

- **Two Stage Design: 87% power with a one-sided alpha of 13% in each subtype**
  - o First stage: **6 eligible patients** per histologic subtype
    - If no response is observed, accrual to that histologic subtype will be permanently closed.
    - **If ≥ 1 response** is observed, an **additional 10 patients** will be accrued in the second stage.
  - o Second stage: **2 or more responses out of 16** will be considered evidence that the combination regimens warrants further study in the histologic subtype
    - With 16 eligible patients in a histologic subtype, any toxicity with at least a 10% chance of occurring has an 81% chance of being observed at least once.

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DART To Date

DART Activated: 1/13/17; First Patient Treated: 1/30/17

As of **9/1/18**:

- 809 sites approved to enroll through CTSU
- Total enrollment: 525 patients
- 37 Cohorts originally
  - 53 cohorts in upcoming amendment 5

ME1

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Latest Cohort/Accrual Info

- http://www.swogstat.org/accrual/dart.htm

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Slide 14

ME1 Is this true? Not sure how we verified this...
Mayerson, Eddie, 9/8/2017

Upcoming Amendment 5 Revisions

- Hormonal/endocrine blockade allowed as long as prior progression on therapy
- Abnormal TSH, free T4 permitted for patients on thyroid suppression/thyroidectomy for cancer
- B-HCG not required to rule out pregnancy (choriocarcinoma)
- irAE tables to guide management over flowchart
- 16 new cohorts: Gallbladder cancer, small cell ovarian cancer, apocrine cancer, esthenioneuroblastoma, etc.

General Logistical FAQs

- Q. What is the process for enrollment to NOC cohort?
  - A. Email S1609SC@swog.org for approval. If approved, a form will be emailed for upload into RAVE at time of registration.
- Q. What is the turnaround time for NOC approvals?
  - A. Decision usually within 3-4 days. Currently on hold due to protocol revision.
- Q. Ipilimumab dosing is 1 mg/kg. Is this baseline weight or D1 of each cycle?
  - A. Utilize Cycle 1 / Day actual body weight unless there is > 10% change from previous dosing, then re-calculate.
- Q. What is order of administration?
  - A. Nivolumab must be administered prior to ipilimumab

Where to find sites participating in DART….

- www.clinicaltrials.gov:
  - Search for: S1609 or NCT02834013
  - Participating locations are accessible from:
    - The “Contacts and Locations” section of clinicaltrials.gov).
    - “Recruiting” sites are generally updated within 3 days of submission of information to CTSU.

Translational Medicine in DART

	PD-L1 IHC	Immune biomarkers	Germline DNA sequencing	Proteomic immune signature	cDNA sequencing	Tumor DNA/RNA
Performing Lab	CIMACs	CIMACs	Counsyl	Biodesix	Circulogene	MatchBox and CIMACs WES/RNASeq
Sample source	Tumor tissue (FFPE) or unstained slide	Blood in collected in Tempus tubes (one 2cc vial for RNA, another 2cc vial for DNA)	Blood collected in the EDTA tube	Blood collected in the EDTA tube	Blood collected in the EDTA tube	Tumor tissue (FFPE) collected as part of NCI-MATCH
Biomarker Target	PD-L1 protein expression by 28-8 IHC analysis	DNA, RNA sequencing (Nanostring) of tumor tissue and blood	Leukocyte DNA sequencing (Illumina)	Serum proteins	Cell free DNA sequencing (Illumina)	Tumor next-generation sequencing (Ion Torrent)
Specimen Estimate	150 (baseline tissue)	240 (baseline blood)	240 (baseline blood)	240 (baseline blood)	240 (baseline blood)	300 (baseline tissue)
Biomarker output	PD-L1 strata will be grouped <1%, 1-5%, 6-25%, 26-49%, >50%	Immune and Cancer pathway Nanostring (gene expression of 770 genes assaying 24 immune cell types and 500 immune response genes)	Genetic alteration	Predictive signature (good, intermediate, poor group)	Genetic alteration and mutational load	Genetic alteration and mutational load
Statistical Considerations	Binary endpoint by strata	Log-expression	Categorical variable	Categorical variable	Percentile rank of mutational load	Percentile rank of mutational load
Sample time points	Tissue: Baseline	Tissue: baseline Blood: DNA and RNA at three time points	Blood at baseline	Blood: at three time points	Blood: at three time points	Tissue: baseline

TM samples

1. Tissue: pretreatment fresh biopsy or archived tissue (<6 months)
2. Blood: three time points (at baseline, at the first imaging, and at PD)

TM FAQ

- Q. Is a new biopsy required for participation in DART?
  - A. No, archival tissue is allowable. A FFPE tissue block (strongly preferred) or 25-30 unstained slides (minimum 10) will be required.
- Q. What collection vials should be used for blood samples?
  - A. K2 or K3 PLASTIC EDTA vials (any size) are acceptable.
    - Each vial must contain 5 mL blood.

Thank You

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