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

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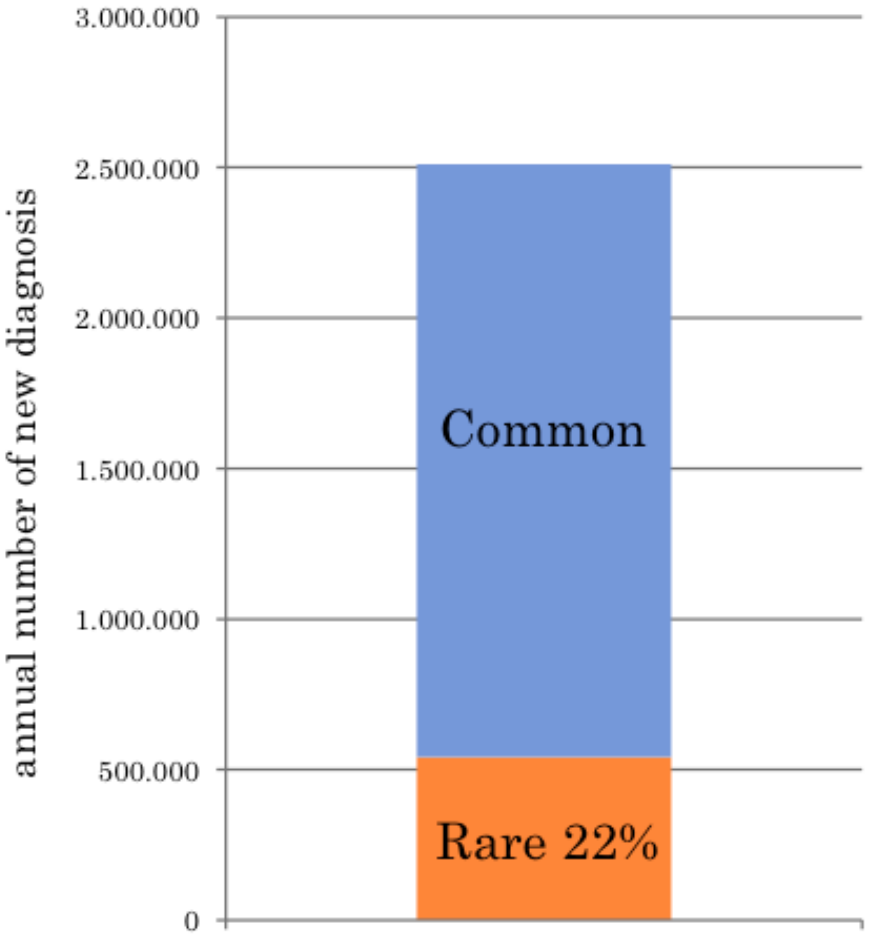
RARE CANCERS: INCIDENCE



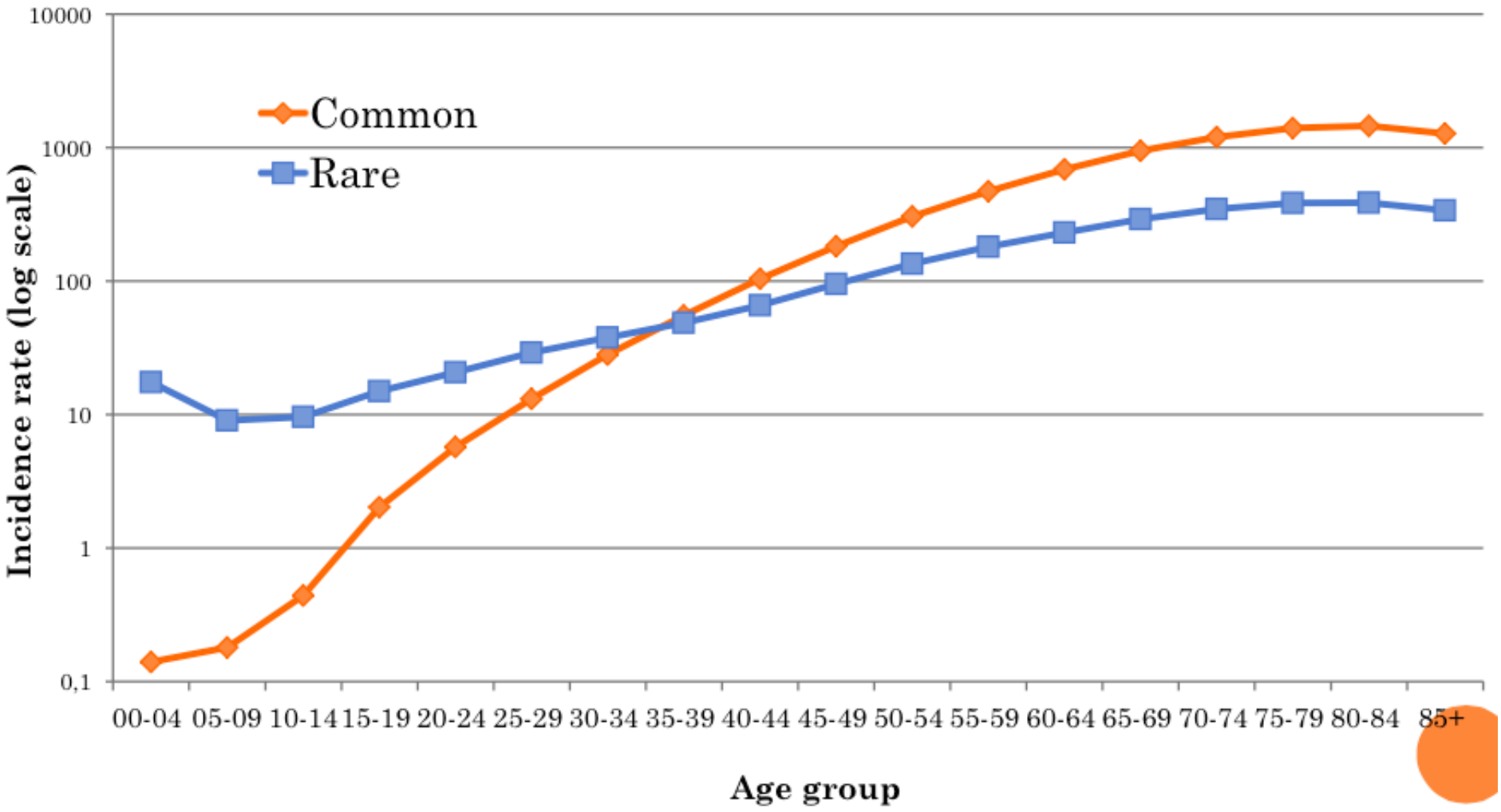
186 rare cancers

About 500,000 new cases/year in EU27

22% of all cancer diagnosed/year

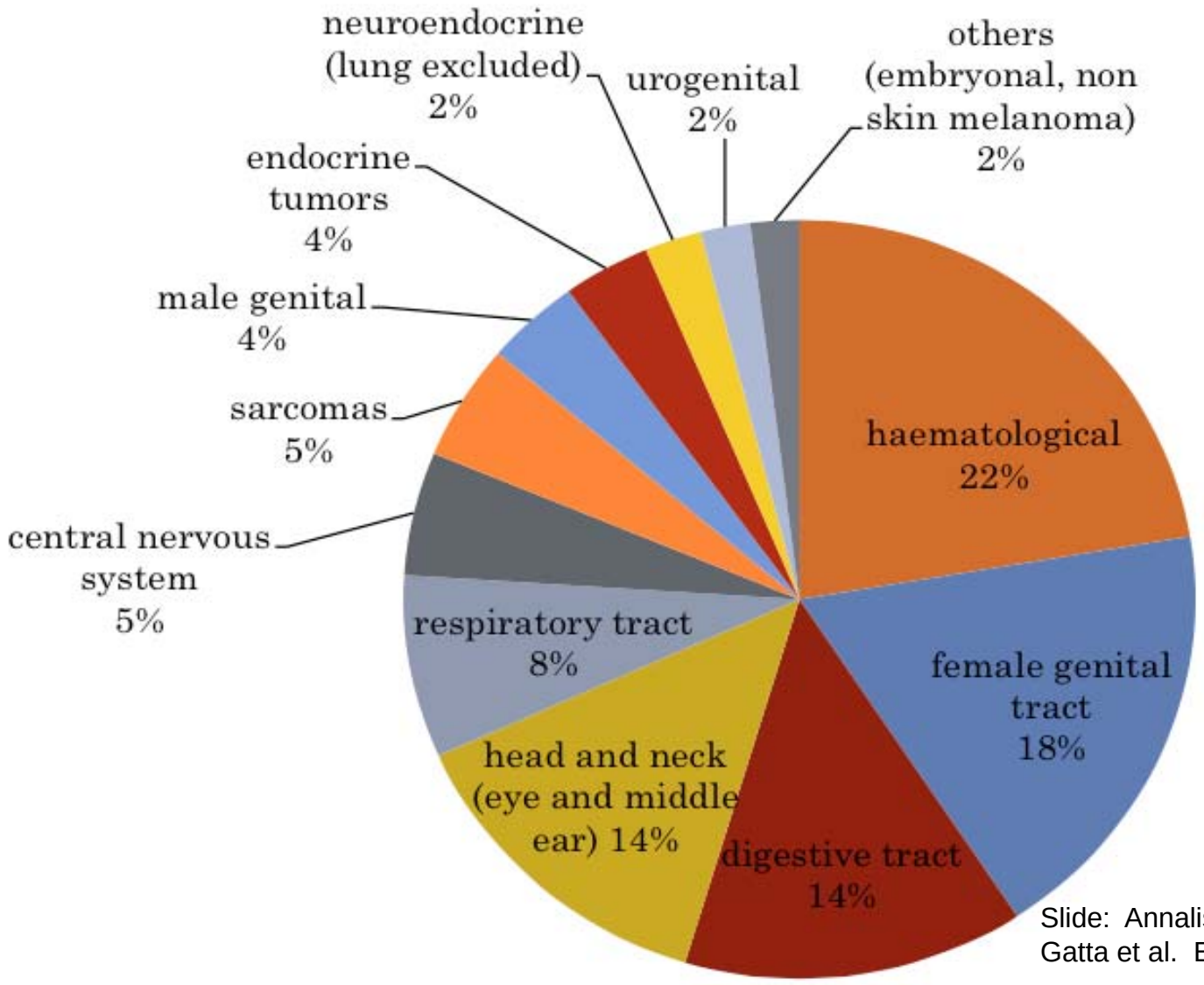
Slide: Annalisa Trama, from Paper: Gemma Gatta et al. Eur J of CA 47 (2011) 2493-2511

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

DISTRIBUTION OF MAJOR FAMILIES OF RARE TUMORS WITHIN ALL RARE CANCERS



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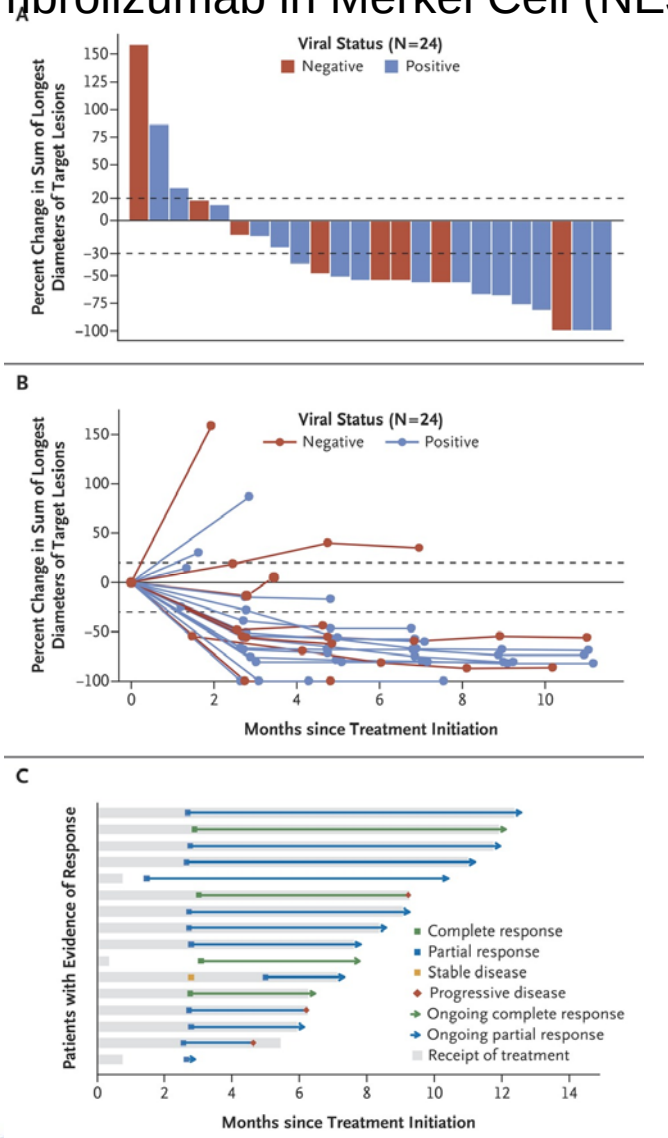
Demographics

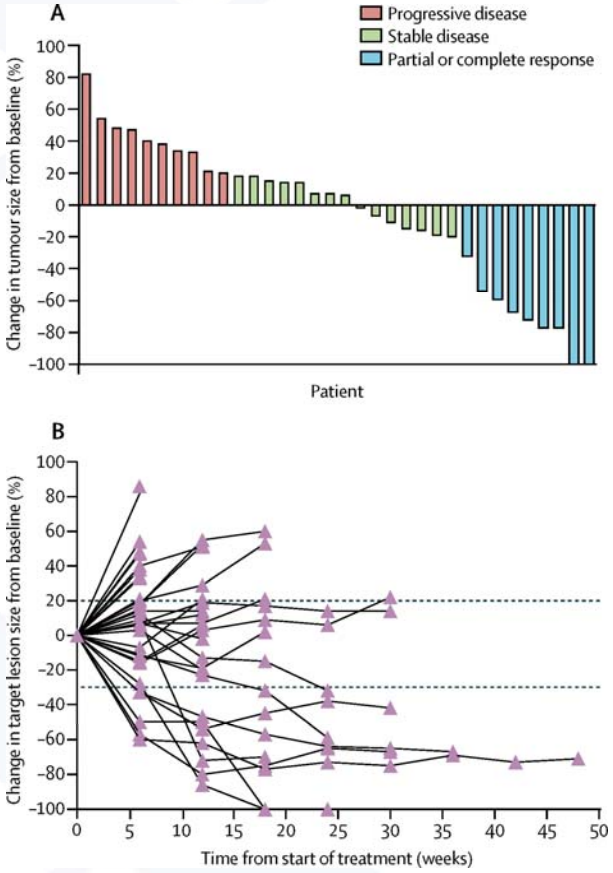
- As a group, rare cancers represent almost a quarter of all new cancer cases
  - Individually rare, but collectively a large group
  - Underrepresented in trials
- Rare cancers disproportionately affect younger patients
- Limited treatment options
- Limited clinical trials
  - Market share
  - Regulatory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

Responses to Immunotherapy in Rare Tumors

Pembrolizumab in Merkel Cell (NEJM 2016)

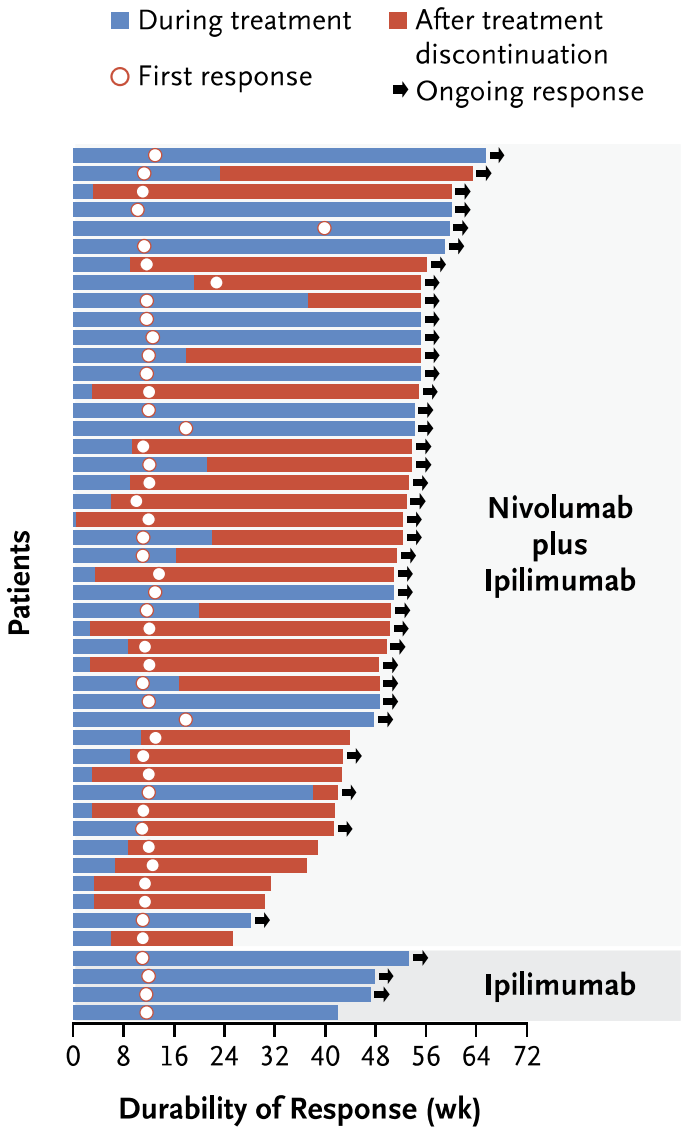


Nivolumab in Anal Cancer (Lancet Onc 2017)



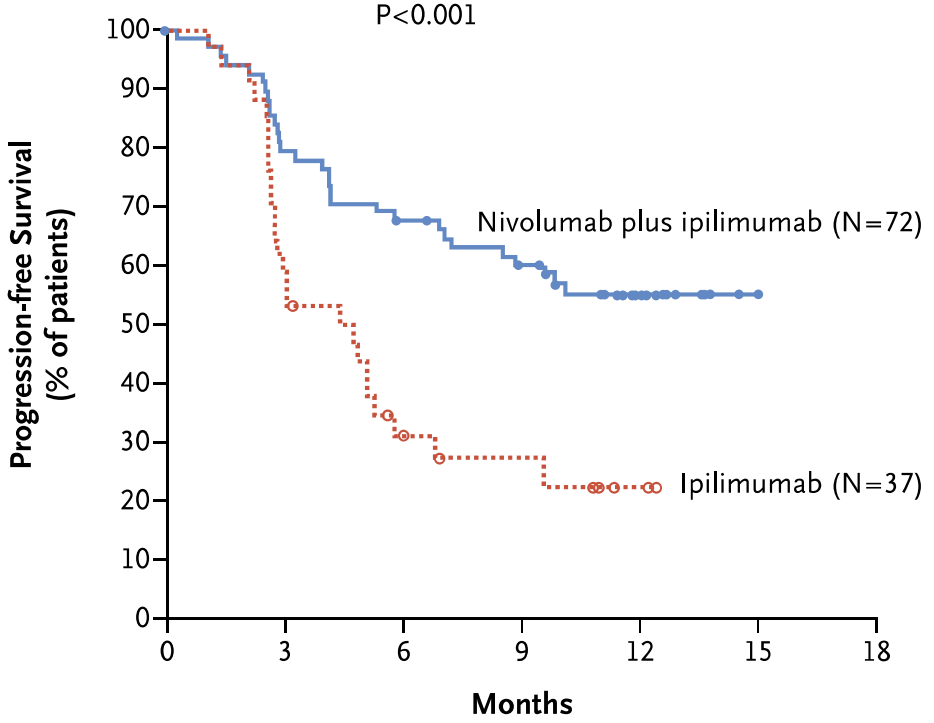
Combinatorial vs Single-Agent Immunotherapy

Postow et al. NEJM 2015



	Death or Disease Progression	Median Progression-free Survival
	no. of patients/total no.	*mo (95% CI)*
Nivolumab plus Ipilimumab	30/72	NR
Ipilimumab	25/37	4.4 (2.8–5.7)

Hazard ratio, 0.40 (95% CI, 0.23–0.68)
P<0.001



No. at Risk

Nivolumab plus ipilimumab	72	54	45	38	20	1	0
Ipilimumab	37	20	9	6	2	0	0

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

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

Rare cancers included in DART

- ✓ **Epithelial tumors of nasal cavity, sinuses, nasopharynx**
  - Squamous cell carcinoma with variants of nasal cavity, sinuses, and nasopharynx and trachea (excluding laryngeal, nasopharyngeal cancer [NPC], and squamous cell carcinoma of the head and neck [SCCHN])
  - Adenocarcinoma and variants of nasal cavity, sinuses, and nasopharynx. Some are related to dust inhalation and have p53, RAS, and p16 changes
- ✓ **Epithelial tumors of major salivary glands**
- ✓ **Salivary gland type tumors of head and neck, lip, esophagus, stomach, trachea and lung, breast and other location**
- ✓ **Undifferentiated carcinoma of gastrointestinal (GI) tract**
- ✓ **Adenocarcinoma with variants of small intestine**
- ✓ **Squamous cell carcinoma with variants of GI tract (stomach small intestine, colon, rectum, pancreas)**
- ✓ **Fibromixoma and low grade mucinous adenocarcinoma (pseudomixoma peritonei) of the appendix and ovary**
- ✓ **Pancreatic tumor including acinar cell carcinoma, mucinous or serous cystadenocarcinoma**
- ✓ **Intrahepatic Cholangiocarcinoma**
- ✓ **Cholangiocarcinoma and extrahepatic bile duct tumors**
- ✓ **Sarcomatoid carcinoma of lung)**
- ✓ **Bronchoalveolar carcinoma lung**
- ✓ **Non epithelia tumors of the ovary**
  - Germ cell tumor of ovary
  - Mullerian mixed tumor and adenosarcoma
- ✓ **Trophoblastic tumor of placenta**
  - Choriocarcinoma of placenta
- ✓ **Transitional cell carcinoma other than renal pelvis uretheral or bladder**
- ✓ **Cell tumor of the testes and extra gonadal tumors**
  - Seminoma and testicular sex cord cancer
  - Non seminomatous tumor
  - Teratoma with malignant transformation
- ✓ **Epithelial tumors of penis - squamous adenocarcinoma cell carcinoma with variants of penis**
- ✓ **Squamous cell carcinoma variants of the genitourinary (GU) system**
- ✓ **Spindle cell type of kidney, pelvis and ureter**
- ✓ **Adenocarcinoma with variants of GU system (excluding prostate cancer)**
- ✓ **Odontogenic malignant tumors**
- ✓ **Endodocrine carcinoma of pancreas and digestive tract**
- ✓ **Neuroendocrine carcinoma including carcinoid of the lung and other sides of other sites**
- ✓ **Pheochromocytoma, malignant**
- ✓ **Paraganglioma**
- ✓ **Carcinomas of pituitary gland, thyroid gland parathyroid gland adrenal cortex**
- ✓ **Dermoid tumors**
- ✓ **Peripheral nerve sheath tumors and NF1 related tumors**
- ✓ **Malignant giant cell tumors**
- ✓ **Chordoma**
- ✓ **Adrenal cortical tumors**
- ✓ **Tumor of unknown primary**
- ✓ **Other**

Rare Tumors Basket Study (2017)

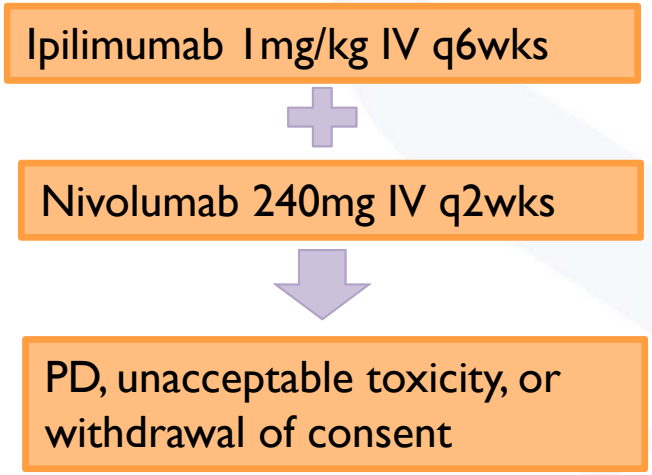
The Cancer Letter 2017

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.

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



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.

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

Slide 14

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

Latest Cohort/Accrual Info

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

UPCOMING DART COHORT CLOSURES AS OF 01-APR-2018 6:10 AM

#	COHORT Name	Up-coming Closure Date	Closure Type
27	Desmoid tumors	04/12/2018	Temporary

CLOSED DART COHORTS AS OF 01-APR-2018 6:10 AM

Closure Type	#	COHORT NAME	TOTAL REGS.	REGS. LAST 12 Month	REGS. LAST 6 Month	REGS. LAST 3 Month	REGS. LAST 30 DAYS	REGS. LAST 7 DAYS	# of ACT. INSTs	# of CURR IRBs
Temporary Close	1	Epithelial tumors of nasal cavity, sinuses, nasopharynx	7	7	5	4	0	0	358	157
Permanent Close	2	Epithelial tumors of major salivary glands	20	19	15	9	5	0		
Temporary Close	3	Salivary gland type tumors of head and neck, lip, esophagus, stomach, trachea and lung, breast and other location	16	16	16	12	0	0		
Permanent Close	7	Fibromixoma and low grade mucinous adenocarcinoma (pseudomixoma peritonei) of the appendix and ovary	10	10	0	0	0	0		
Permanent Close	9	Intrahepatic cholangiocarcinoma	9	7	0	0	0	0		
Permanent Close	10	Extrahepatic cholangiocarcinoma and bile duct tumors	10	9	1	0	0	0		
Permanent Close	13	Non-epithelial tumors of the ovary	23	23	17	12	11	3		
Temporary Close	16	Cell tumor of the testes and extragonadal germ tumors	10	9	9	6	0	0		
Temporary Close	20	Adenocarcinoma with variants of GU system (excluding prostate cancer)	9	9	9	8	2	0		
Temporary Close	22	Endocrine carcinoma of pancreas and digestive tract	10	10	8	4	0	0		
Permanent Close	23	Neuroendocrine carcinoma including carcinoid of the lung	34	33	21	0	0	0		
Temporary Close	26	Carcinomas of pituitary gland, thyroid gland parathyroid gland and adrenal cortex	14	14	11	7	0	0		
Temporary Close	28	Peripheral nerve sheath tumors and NF1-related tumors	8	8	7	5	0	0		
Temporary Close	30	Chordoma	8	8	6	2	0	0		
Permanent Close	32	Tumor of unknown primary (Cancer of Unknown Primary; CuP)	21	18	12	0	0	0		
Permanent Close	34	Adenoid cystic carcinoma	23	18	11	0	0	0		
Temporary Close	35	Vulvar cancer	9	9	9	8	0	0		

DART ACCRUAL REPORT

Status	#	COHORT NAME	TOTAL REGS.	REGS. LAST 12 Month	REGS. LAST 6 Month	REGS. LAST 3 Month	REGS. LAST 30 DAYS	REGS. LAST 7 DAYS	# of ACT. INSTs	# of CURR IRBs
Temporary Close	1	Epithelial tumors of nasal cavity, sinuses, nasopharynx	7	7	5	4	0	0	358	157
Permanent Close	2	Epithelial tumors of major salivary glands	20	19	15	9	5	0		
Temporary Close	3	Salivary gland type tumors of head and neck, lip, esophagus, stomach, trachea and lung, breast and other location	16	16	16	12	0	0		
Open	4	Undifferentiated carcinoma of gastrointestinal (GI) tract	2	2	1	1	1	0		
Open	5	Adenocarcinoma with variants of small intestine	14	13	9	1	1	1		
Open	6	Squamous cell carcinoma with variants of GI tract (stomach small intestine, colon, rectum, pancreas)	5	4	3	3	2	0		
Permanent Close	7	Fibromixoma and low grade mucinous adenocarcinoma (pseudomixoma peritonei) of the appendix and ovary	10	10	0	0	0	0		
Open	8	Rare Pancreatic tumors including acinar cell carcinoma, mucinous cystadenocarcinoma or serous cystadenocarcinoma	7	6	3	2	1	0		
Permanent Close	9	Intrahepatic cholangiocarcinoma	9	7	0	0	0	0		
Permanent Close	10	Extrahepatic cholangiocarcinoma and bile duct tumors	10	9	1	0	0	0		
Open	11	Sarcomatoid carcinoma of lung	3	3	3	2	1	1		
Open	12	Bronchoalveolar carcinoma lung (a.k.a. adenocarcinoma in situ, minimally invasive adenocarcinoma, lepidic predominant adenocarcinoma, or invasive mucinous adenocarcinoma)	3	3	3	3	0	0		
Permanent Close	13	Non-epithelial tumors of the ovary	23	23	17	12	11	3		
Open	14	Trophoblastic tumor	2	2	2	1	0	0		
Open	15	Transitional cell carcinoma other than that of the renal, pelvis, ureter, or bladder	1	1	1	1	0	0		

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

- Metaplastic Breast Cohort
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  - Jourdain Hayward
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